24 July 2025
EMA/264858/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zurzuvae

International non-proprietary name: zuranolone

Procedure No. EMEA/H/C/006488/0000

Note

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

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List of abbreviations

%CV	percent coefficient of variation (SD/mean x 100)
AAG	α_1-acid glycoprotein
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
ADT	antidepressant therapy
AE	adverse event
ALT	alanine aminotransferase
AmCuAg	amino cupric silver
API	Active Pharmaceutical Ingredient
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
$AUC_{0\text{-}12h}$	area under the concentration-time curve from 0 to 12 hours after dose administration
$AUC_{0\text{-}24h}$	area under the concentration-time curve from 0 to 24 hours after dose administration
$AUC_{0\text{-}48h}$	area under the concentration-time curve from 0 to 48 hours after dose administration
$AUC_{0\text{-}last}$	area under the concentration-time curve from time 0 to the time of the last measurable concentration
$AUC_{0\text{-}t}$	area under the concentration-time curve from time 0 to time *t*
AUC∞	area under the concentration-time curve from time 0 to infinity
AUC_{inf}	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BCRP	breast cancer resistance protein
BCS	biopharmaceutical classification system
BIMF	Barkin Index of Maternal Functioning
BLA	basolateral amygdala
BMI	body mass index
BPD	bipolar disorder
BSEP	bile salt export pump
C_{avg}	average concentration
CDP	chlordiazepoxide
CEP	certificate of Suitability of the EP
CFU	Colony Forming Units
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression – Severity Scale
cGMP	current Good Manufacturing Practice
CHO	Chinese hamster ovary

CI	confidence interval
CL	clearance
CL/F	apparent plasma clearance
CLP	clinical pharmacology
CLR	renal clearance
CLss/F	apparent plasma clearance at steady state
CMA	critical material attributes
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration(s) at steady state
$C_{max,u}$	maximum observed unbound concentration(s)
CNS	central nervous system
CoA	certificate of analysis
COVID-19	coronavirus disease 2019
CPP	critical process parameters
CQA	critical quality attributes
C-QTc	concentration-corrected QT interval
CRCDS	Cognitive Research Corporation Driving Simulator
CRF	case report form
CRL	Charles River Laboratories, Inc.
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CUS	chronic unpredictable stress
CV	cardiovascular / coefficient of variation
CYP	cytochrome P450 (enzyme family)
DDI	drug-drug interaction
DN	dose-normalised
DRF	dose range-finding
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5^{th} edition
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
EEG	electroencephalography/ electroencephalogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPDS	Edinburgh Postnatal Depression Scale
ER	exposure-response
ETD	essential tremor disorder
EU	European Union
EXM	experimental medicine

F1	first generation
F_{abs}	absolute bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
Frel	relative bioavailability
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid type A receptor
$GABA_B$	γ-aminobutyric acid type B receptor
GCP	Good Clinical Practice
GD	gestation day
GEE	generalised estimating equation
GLP	Good Laboratory Practice
GM	geometric mean
GMR	geometric mean ratio
GOF	goodness of fit
HAM-A	Hamilton Anxiety Rating Scale
HAMD-17	17-item Hamilton Rating Scale for Depression
HAP	human abuse potential
HDPE	high density polyethylene
HEK	human embryonic kidney
hERG	human ether-à-go-go-related gene
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
HSA	human serum albumin
IC_{20}	concentration resulting in 20% inhibition
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IIV	interindividual variability
$I_{maxu,inlet}$	maximum unbound plasma concentration of the interacting drug at the hepatic inlet
IND	investigational new drug
INN	International Non-proprietary Name
IP	intraperitoneal(ly)/ investigational product
IPC	in-process control
IPSC	inhibitory postsynaptic current
IR	infrared
IS	internal standard
ISR	incurred sample reanalysis
IU	International Unit

IV	intravenous(ly)
Ki	inhibitor constant
kp	breast milk/plasma partition coefficient
LC-MS	liquid chromatography-mass spectrometry
LC-MS/MS	liquid chromatography with tandem mass spectrometric detection
LD	lactation day
LDPE	low density polyethylene
LFT	liver function test
LLDPE	double linear low-density polyethylene
LLOQ	lower limit of quantification
Log D_{ow}	octanol:water distribution coefficient
LS	least squares
MADRS	Montgomery-Åsberg Depression Rating Scale
MAH	Marketing Authorisation holder
MATE	multidrug and toxin extrusion transporter
MDD	major depressive disorder
MDE	major depressive episode
MDR1	multidrug resistance protein 1
MEC	molecular extinction coefficient
MED	minimum effective dose
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimal important difference
MMRM	mixed effects model for repeated measures
MOA	mechanism of action
mRNA	messenger ribonucleic acid
MRP-2	multidrug resistance protein-2
MS	mass spectrometry
MTT	3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2H-tetrazolium bromide
MTT1	mean transit time - first chain
MTT2	mean transit time - second chain
NA	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NAS	neuroactive steroid
ND	not detected / not determined
NE	not estimable / not evaluated
NLT	not less than
NMR	nuclear magnetic resonance
NMT	not more than
NOAEL	no observed adverse effect level

NR	not reported
NTR1	number transit compartments - first chain
NTR2	number transit compartments - second chain
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
OECD	Organization for Economic Co-operation and Development
OOS	out of specifications
PAM	positive allosteric modulator
P_{app}	apparent permeability coefficient
PAPS	3'-phosphoadenosine-5'-phosphosulphate
PBT	persistent, bioaccumulative and toxic
PCS	potentially clinically significant
PCTFE	polychlorotrifluoroethylene
PD	pharmacodynamic
PDA	photo diode array
PE	polyethylene
PEC_{SW}	predicted environmental concentration in surface water
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopoeia
PHQ-9	9-item Patient Health Questionnaire
PL	Package Leaflet
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PND	postnatal day
PopPK	population pharmacokinetic(s)
PP	polypropylene
PPD	postpartum depression
PRO	patient reported outcome
PSD	particle size distribution
PSG	polysomnography
PT	preferred term
PVC	polyvinyl chloride
Q25	25th percentile
Q75	75th percentile
QC	quality control
QD	once daily
QT	interval between the start of the Q wave and of the T wave, which indicates the time for ventricular repolarisation

QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's correction
$R_{AUC0\text{-}12h}$	accumulation ratio =ratio of $AUC_{0\text{-}12h}$ on Day 5 to Day 1 $AUC_{0\text{-}12h}$
$R_{AUC0\text{-}24h}$	accumulation ratio =ratio of $AUC_{0\text{-}24h}$ on Day 28 to Day 1 $AUC_{0\text{-}24h}$
$R_{AUClast}$	accumulation ratio =ratio of AUC_{0last} on final day of dosing to Day 1 AUC_{last}
RH	relative humidity
RID	relative infant dose
RMP	risk management plan
RRT	relative retention time
S9	microsomal liver preparations
SAP	statistical analysis plan
SD	standard deviation
SDLP	standard deviation of lateral positioning
SE	status epilepticus
SEM	standard error of mean
SNRI	serotonin-norepinephrine reuptake inhibitor
SOC	system organ class
SmPC	Summary of Product Characteristics
SSRI	selective serotonin reuptake inhibitor
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TGA	thermo-gravimetric analysis
TK	toxicokinetic(s)
T_{max}/t_{max}	time of maximum observed concentration
TQT	thorough QT
TRPV1	transient receptor potential cation channel subfamily V member 1
TSE	transmissible spongiform encephalopathy
TCAM	transit compartment absorption model
UHPLC	ultra-high performance liquid chromatography
UK	United Kingdom
ULN	upper limit of normal
US	United States
USP/NF	United States Pharmacopeia/National Formulary
UV	ultraviolet
V/F	apparent volume of distribution
V1/F	apparent central volume of distribution
V2/F	apparent peripheral volume of distribution
VPC	visual predictive check
WT	wildtype

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Netherlands B.V. submitted on 22 July 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Zurzuvae, 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 25 January 2024.

The applicant applied for the following indication:

Zurzuvae is indicated for the treatment of postpartum depression (PPD) 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 applicant's 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/0019/2023 on the agreement of a paediatric investigation plan (PIP) and on the granting of a (product-specific) waiver and on the granting of a deferral.

At the time of submission of the application, the PIP P/0019/2023 was not yet completed as some measures were deferred.

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 zuranolone 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 of zuranolone for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
15 December 2022	EMA/SA/0000110975	*Kerstin Wickström, Rune Kjeken*

The scientific advice pertained to the following quality aspects:

- The proposed approach for the routine commercial manufacture of the finished product

1.7. Steps taken for the assessment of the product

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

Rapporteur: Paulo Paixão Co-Rapporteur: Peter Mol

The application was received by the EMA on	22 July 2024
The procedure started on	15 August 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 November 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 November 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 March 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	8 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 May 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 May 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 June 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 July 2025

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zurzuvae on	24 July 2025
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)	24 July 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Postpartum Depression (PPD) is the occurrence of a Major Depressive Episode (MDE) with peripartum onset (during the course of pregnancy or up to 4 weeks after delivery), with a MDE as defined by the DSM-5 being characterised by the presence of 5 or more of the following symptoms: depressed mood, diminished interest or pleasure, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive guilt, diminished ability to concentrate, and recurrent thoughts of death (suicidal ideation or attempt) that have been present during the same 2-week period and represent a change from previous functioning; with at least one of the symptoms being either depressed mood or loss of interest or pleasure (DSM-5).

2.1.2. Epidemiology

PPD is identified as one of the most common complications of pregnancy and childbirth [O'Hara and Wisner 2014]. The estimated prevalence of PPD symptoms in the EU is 12.4% of women with a recent live birth [Dekel 2019] with estimates ranging from 4.7% [Dekel 2019] to 19.9% [Clavenna 2017]. Among the women with PPD symptoms, it is estimated that 21% meet DSM criteria for PPD [Cena 2021].

Based on 3,885,585 live births in the EU in 2022 [Eurostat 2022], a PPD symptom prevalence of 12.4% [Dekel 2019] would translate to 481,813 women with PPD symptoms in 2022 in the EU. PPD can have devastating consequences for the woman and her family [Fihrer 2009; Verbeek 2012]. Mental health conditions are one of the leading causes of pregnancy-related death [Davis 2019]. The societal burden of PPD is significant, with contributions from increased risk of death due to any cause [Hagatulah 2024], an increased risk for suicidal behaviours [Yu 2024], and suicide [Savitz 2011], maternal morbidity, child morbidity associated with impaired mother-infant bonding, infant malnutrition during the first year of life, and loss of work days for the mother due to depression [Accortt 2015; Gavin 2005; Parsons 2012; Slomian 2019].

Limited evidence on the natural course of PPD is currently present in literature.

2.1.3. Biologic features, aetiology

Physiological fluctuations in neuroactive steroid (NAS) during pregnancy and the peri-partum period are associated with changes in GABAergic signalling which, in susceptible women, may result in dysregulated neural network responses and the development of PPD.

2.1.4. Clinical presentation, diagnosis

The natural course of PPD is typically characterised by symptom onset during pregnancy or within 4 weeks of parturition, with resolution of PPD by 3 months. Two longitudinal studies (1 US sample [Campbell and Cohn 1997] and one Norway sample [Glavin 2010]) suggest that prevalence of PPD after an initial diagnosis is approximately 30% to 50% at 3 months and approximately 30% at 6 months. Based on the same studies, the applicant concludes that 50%-70% of patients recover spontaneously in 3-6 months. However, this does not fit with the duration of symptoms seen in the study population with severe PPD (study 217-PPD-301), where the mean duration of symptoms was 5 months, and patients were included up to 12 months postpartum. In addition, generally a major depressive episode in MDD is not considered to be self-limiting, in particular in severe cases. Although it remains a matter of debate whether depression with peripartum onset is distinct from major depressive episodes without peripartum onset, diagnosis, clinical features, and treatment approaches of PPD are comparable to those of a major depressive episode without peripartum onset. Rapid onset in the improvement of depressive symptoms is an important outcome, especially because PPD patients are considered a vulnerable population, and depressive symptoms have adverse consequences for both mother and infant.

2.1.5. Management

First-line treatment recommendations comprise cautious use of oral antidepressant therapy (ADTs) for moderate to severe PPD [Kittel-Schneider 2022]. This approach is based primarily on research in the general major depressive disorder (MDD) population rather than extensive studies in PPD [Austin 2013], and high-quality data to support the efficacy of MDD-approved ADTs in PPD are limited [Brown 2021].

Most pharmacological classes of ADTs used to treat PPD act through monoaminergic mechanisms (e.g., selective serotonin reuptake inhibitor (SSRIs) and serotonin-norepinephrine reuptake inhibitor (SNRIs)). These agents may take 4 to 6 weeks for the onset of antidepressant effects and evidence suggests that this may be even more prolonged in PPD than MDD [Hendrick 2000]. The requirement for chronic dosing with all these agents carries risk of ongoing adverse effects that range from troublesome to potentially life threatening. Common and persistent side effects associated with approved antidepressants include gastrointestinal symptoms, sleep disturbances, weight gain, and sexual dysfunction [Clayton 2002; Fava 2000; Papakostas 2008]. More serious effects can rarely occur, such as serotonin syndrome or hepatic failure. Nonadherence rates are high with ADTs; combined with perceived stigma around treatment and potential for concerns around impact on breastfeeding, these therapies, with their relatively slow onset of symptomatic relief, have not been optimal for PPD [Clayton 2002; Fava 2000; Goodman 2009; Papakostas 2008; Sansone and Sansone 2012].

There has been limited progress with specific treatments for PPD. Still, some patients benefit from active treatment. The timing of treatment is relevant, since the mother-child interaction may be disturbed with PPD.

Zulresso (brexanolone, IV administration in hospital) [2019] and Zurzuvae (zuranolone, oral use) [2023], both PAMs of GABAA receptors, are the only products currently approved for the treatment of PPD, and only in the US. Elsewhere there are not specific treatments for PPD.

2.2. About the product

Zuranolone is an orally bioavailable, synthetic neuroactive steroid (NAS) with rapid antidepressant effects. The mechanism of action in the treatment of PPD is not fully understood, but like the endogenous NAS, allopregnanolone, zuranolone is considered a potent positive allosteric modulation of the $GABA_A$ receptor. Zuranolone enhances GABA activity at synaptic and extrasynaptic receptors and has been shown to increase cell surface expression of $GABA_A$ receptors in *in vitro* studies. Extrasynaptic δ-subunit-containing $GABA_A$ receptors mediate tonic inhibitory currents that play a critical role in controlling network activity in the brain, including synchronisation within and across neural networks. Brain network activity is regulated via a balance of inhibitory (e.g., GABAergic) and excitatory (e.g., glutamatergic) signalling inputs. Zuranolone may exert antidepressant effects by enhancing GABAergic inhibition, and normalization of dysregulated brain network function. Based on the presented non-clinical data, there is limited evidence for a more tonic versus phasic inhibition.

Zuranolone has minimal off-target activity and has PK characteristics that support once-daily oral administration.

2.3. Type of application and aspects on development

Zuranolone is approved for the treatment of PPD in adults in the US under the brand name Zurzuvae (August 2023).

Clinical development program

Zuranolone (also known as BIIB125 and SAGE-217) was initially developed by Sage Therapeutics, Inc. (hereafter referred to as Sage) and has been under development globally by Sage and Biogen Inc. (hereafter referred to as Biogen), as a treatment for PPD and MDD.

Shionogi & Co. Ltd. (hereafter referred to as Shionogi) has been developing zuranolone as a treatment for MDD in Japan.

The zuranolone clinical development programme comprises 33 completed and 3 ongoing clinical studies (Studies 2122A3734, 2207A3736, and 217-CLP-118) as of the data cut-off date of 3 February 2024 for this submission, and includes 5119 unique participants, 3992 of whom were exposed to zuranolone. A listing of the clinical studies in the zuranolone clinical development programme is provided in 2.6.1 Tabular overview of clinical studies.

Early clinical studies of zuranolone in healthy participants evaluated single and multiple ascending doses and characterised the PK and PD (via electroencephalographic target engagement). These studies, in conjunction with the preclinical toxicology data, demonstrated appropriate safety, PK, and engagement of expected neuronal systems, and supported further development of zuranolone using a once daily 14-day dosing regimen.

Subsequent Phase 2 and 3 studies were conducted for evaluation in PPD, MDD, essential tremor, bipolar disorder, and Parkinson's disease. The studies in PPD were appropriately powered, well-controlled, double-blind, PC, parallel group trials that also accounted for zuranolone's short term, non-chronic dosing.

Most of the studies were conducted in the US, with a few exceptions. Studies conducted outside the US include a small number of patients enrolled in Study 217-PPD-301 in European countries (Spain and the UK), a clinical pharmacology study and efficacy studies in MDD conducted in Japan by Shionogi (a development partner for zuranolone) and selected clinical pharmacology studies conducted in Canada.

The two PPD clinical trials Study 217-PPD-201 and 217-PPD-301 utilised a 14-day, once-daily dosing regimen, including starting doses of zuranolone 30 mg (ProFill) [Study 217-PPD-201B] and 50 mg (Autofill) [Study 217-PPD-301], although dose reduction to improve tolerability (20 mg and 40 mg, respectively for Studies 217-PPD-201B and 217-PPD-301) was allowed in both studies.

Assessments conducted early in the treatment course (e.g., Day 3 and Day 8) were included to evaluate the rapid-acting characteristics of zuranolone treatment and time course of response. Additionally, 4 or more weeks of follow-up were included to evaluate durability of the treatment effect and the off-treatment safety profile, providing data for a minimum total of 6 weeks in each PPD efficacy study. Importantly, chronically administered ADTs have generally required studies with 6- to 8-week treatment periods in order to capture the delayed onset of efficacy typical of these agents.

In addition, a suite of clinical pharmacology studies evaluating the PD, PK, and safety of zuranolone in healthy participants and special populations was conducted.

Some portion of the target patient population for zuranolone will be currently treated with oral antidepressants when they begin treatment with zuranolone. Thus, in the 2 PPD efficacy studies, both participants with no current treatment (monotherapy) and participants on stable, chronically administered antidepressants (add-on) were allowed to enrol in the studies.

Scientific advice

Scientific Advice for the treatment of PPD was sought with the National Authority of Medicines and Health Products (INFARMED, Portugal) in 2021, The Spanish Agency of Medicines and Medical Devices (AEMPS, Spain) in 2022, and Medical Products Agency (MPA, Sweden) in 2022.

The main aspects of the advices concerned the adequacy of the two phase 3 studies (217-PPD-201B and 217-PPD-301) to support an indication for the treatment of PPD; and the adequacy of the clinical pharmacology package to characterize the PK and PD profile of zuranolone. In general, the NCAs considered that two convincing studies could suffice to support an indication of PPD. However, several concerns were raised with respect to the studies, including:

- To what extent is PPD a different medical disorder from major depressive disorder (MDD) and, thus, should be handled differently with respect to clinical study requirements;
- The sufficiency of a two-week treatment regimen to treat a PPD episode;
- The lack of an active comparator arm;
- The use of concomitant antidepressant therapy. There should be convincing evidence that the safety and efficacy profile are comparable in the add-on and monotherapy groups;
- It is questioned whether the length of the 4-week follow-up is sufficient to establish a durable response;
- The extrapolation from US to EU patients may be challenging in case no or very few EU patients are included, which is the case for both studies.

Furthermore, the adequacy of the clinical safety database partly relies on how well the MDD population can be extrapolated to the PPD population, considering there are longer term safety data from the MDD population.

The scientific advices were in general followed, except for some clinical aspects: the insufficient justification of the two-week treatment regimen, the short duration of study with 45 days of follow-up only; the need to discriminate PPD from MDD, the lack of two studies and a significant number of patients, given the reported frequency of severe PPD worldwide. Further, although concomitant

antidepressant therapy was discussed by the applicant, uncertainties with regard to the efficacy of combined treatment with zuranolone, needed to be clarified (refer to efficacy section).

Per the EMA guideline on treatment of depression (EMA/CHMP/185423/2010 Rev. 3) it is recommended to obtain scientific advice with regards to the most appropriate measurement timepoints and trial duration. In addition, the AEMPS recommended the applicant to ask for scientific advice in light of a "pan-European perspective". The applicant received scientific advice on the development of zuranolone for the treatment of postpartum depression from the CHMP in 2022 (EMA/SA/0000110975) pertained to Quality aspects: Process Performance Qualification strategy for commercial manufacturing of zuranolone. An acceptable validation strategy has been proposed in line with the received CHMP advice presented. The applicant did not request scientific advice from the EMA for the clinical data package for PPD.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard gelatin capsules containing 20 mg, 25 mg or 30 mg of zuranolone active substance.

Other ingredients are:

Capsule content: croscarmellose sodium (E468), mannitol (E421), microcrystalline cellulose (E460), silica colloidal anhydrous (E551), sodium stearyl fumarate.

Capsule shell: gelatin (E441), red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172).

Capsule print (black ink): ammonium hydroxide (E527), black iron oxide (E172), propylene glycol (E1520), shellac glaze (E904).

The product is available in: high-density polyethylene (HDPE) bottles with child resistant, foil induction-sealed polypropylene closures (20 mg, 25 mg, 30 mg), OR polyvinyl chloride (PVC) laminated polychlorotrifluoroethylene (PCTFE) aluminium blister (20 mg and 25 mg).

2.4.2. Active substance

2.4.2.1. General information

The chemical name of zuranolone is 1-[2-[(3*R*,5*R*,8*R*,9*R*,10*S*,13*S*,14*S*,17*S*)-3-hydroxy-3,13-dimethyl-2,4,5,6,7,8,9,10,11,12,14,15,16,17-tetra-deca-hydro-1H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl]pyrazole-4-carbonitrile, corresponding to the molecular formula $C_{25}H_{35}N_3O_2$. It has a relative molecular mass of 409.57 and the following structure:

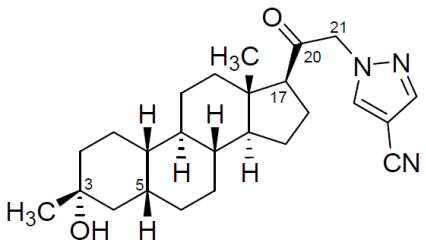


Figure 1: Active substance structure

The chemical structure of zuranolone was elucidated by a combination of elemental analysis, IR, NMR, MS, UV-Vis, and single crystal x-ray diffraction.

The solid state properties of the active substance were measured by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), dynamic vapor sorption (DVS) for hygroscopicity.

The active substance is a white to off-white solid. It is soluble in most organic solvents and practically insoluble in aqueous buffers and n-heptane. The active substance is non-hygroscopic and photostable.

Zuranolone exhibits stereoisomerism due to the presence of 8 chiral centres. A test for chiral purity is not included in the specification of the active substance. However, the specifications of materials used in the synthesis of the active substance ensure adequate control.

Polymorphism has been observed for the active substance. One form is the most thermodynamically stable and was selected to be used in the formulation. Polymorphism is not controlled in the active substance specification, since it was demonstrated that the manufacturing process consistently provides the desired form. In addition, polymorphic form is controlled as an in-process control in the manufacturing process.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at two manufacturing sites. Satisfactory GMP documentation has been provided.

Zuranolone is synthesized in five main steps, including a micronization step, using well defined starting materials with acceptable specifications.

Detailed description of the manufacturing process has been provided. Reprocessing procedures have been established, and the provided information is considered satisfactory.

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

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

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

During the procedure, a Major Objection (MO) has been raised in relation to the control of benzene, as it may be present as contaminant in the solvents used in the synthesis. The applicant was requested to implement a test for benzene in the active substance or in the intermediate specification or otherwise provide a justification supported by data. The applicant provided evidence to support that any potential benzene carryover in the active substance is well below the proposed limit. The provided justification was deemed acceptable. However, analytical data demonstrating that benzene is below the acceptable limit in the active substance or in the intermediate have not been provided during the procedure and should be provided post-approval (REC001). The applicant committed to provide analytical data on benzene levels for at least three active substance consecutive batches. The applicant has adequately addressed the question.

The active substance is packaged in low-density polyethylene (LDPE) bags, which comply with Commission Regulation (EU) 10/2011, as amended.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identity (FTIR, HPLC-UV), assay (HPLC-UV), impurities (HPLC-CAD, HPLC-UV, LC-MS), residual solvents (GC-HS), water content (Ph. Eur.), residue on ignition (Ph. Eur.), particle size distribution (laser diffraction), elemental impurities (IPC-MS), microbial purity (Ph. Eur.).

The active substance specification parameters and limits are in line with relevant guidelines and are acceptable. No impurities are present at higher levels than the ICH qualification threshold.

Omission of testing for polymorphism and chiral purity has been properly justified and found acceptable, as previously described.

The particle size distribution is considered relevant for the active substance, and it is controlled within the active substance specification.

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

Batch analysis data of at least 3 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from 4 pilot scale batches of active substance stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) were provided. Following a MO, supportive stability data have been provided for 2 additional batches manufactured at one site. These batches were stored for up to 9 and 12 months under long term conditions and for up to 6 months under accelerated conditions. This was found acceptable and in line with ICH guidelines.

The following parameters were tested: appearance, assay, specified impurities, unspecified and total Impurities, water content, polymorphism and microbiological quality.

The analytical methods used were the same as for release and were considered stability indicating. At long term and accelerated conditions all tested parameters were within the specifications and no specific trend was observed.

In addition, XRPD results demonstrated that the desired polymorphic form is stable up to 24 months of storage at 25 °C/ 60% RH and up to 6 months of storage at 40 °C/ 75% RH.

Photostability testing following the ICH guideline Q1B was performed on 1 batch and demonstrated that the active substance is stable when exposed to UV and visible light.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored below 25 °C in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product consists of hard capsules containing 20 mg, 25 mg or 30 mg of zuranolone and have the following appearance:

20 mg: size 1 hard gelatin capsules with a light-orange cap and an ivory to light-yellow body, printed with "S 217 20mg" in black ink.

25 mg: size 1 hard gelatin capsules with a light-orange cap and a light-orange body, printed with "S 217 25mg" in black ink.

30 mg: size 1 hard gelatin capsules with an orange cap and a light-orange body, printed with "S 217 30mg" in black ink.

All excipients are compendial excipients, except for capsules shells ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of the development for the finished product was to generate an oral immediate release formulation. The quality target product profile (QTPP) was defined and is outlined in Table 1.

Table 1. Quality Target Product Profile (QTPP) of Zurzuvae hard capsules

Product Profile	Design Requirement
Route of administration	Oral
Strengths	20 mg, 25 mg, and 30 mg
Size	Size 1 capsule
Container closure system/ Packaging configuration	White, high-density polyethylene (HDPE) bottles with child resistant cap and 28-count blister cards with push through aluminum lidding
Pharmacokinetic characteristics	Immediate release
Excipients	Globally acceptable, provide acceptable product stability, safety, and performance
Quality Attributes	Acceptable appearance, assay, content uniformity, dissolution, water content, microbial limits, degradation products and stability. Physically and chemically stable at room temperature, with a minimum shelf life of 36 months.

Zuranolone active substance is classified as a Biopharmaceutical Classification System (BCS) Class 2 compound (low solubility, high permeability).

The formulation development studies have been properly described.

The proposed product has fast dissolution rates in the proposed QC dissolution method. Initially the proposed QC dissolution was not found acceptable and a MO has been raised. In response, the applicant has adequately justified with sufficient level of detail the type and concentration of surfactant used. Also, the applicant has adequately justified the proposed rotation speed. The QC dissolution method is considered acceptable.

The discriminatory power of the dissolution method has been demonstrated. A bioequivalence study has not been performed, which was considered acceptable as not required.

In addition, since the applicant has conducted clinical studies using the 20 and 30 mg strengths, a biowaiver has been proposed for the 25 mg strength. The applicant has performed in-vitro dissolution comparison. Considering the provided data, the biowaiver was found acceptable.

During manufacturing process development, the applicant optimised the manufacturing process. A risk assessment for the manufacturing process was performed to identify any risks associated with each quality attribute of the finished product. The process parameters for each manufacturing step that were identified as medium or high risks were evaluated during process development and re-assessed based on the results and appropriate control strategies were set to mitigate the risks. Critical process parameters have been adequately identified.

The primary packaging of the 20 mg, 25 mg, 30 mg strengths is HDPE bottle with child resistant, foil induction-sealed polypropylene closures. The 20 mg and 25 mg strengths can also be packed in PVC-laminated PCTFE aluminium blister. The materials comply with Ph.Eur. and EC requirements. The choice of the container closure systems 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 site and satisfactory information with respect to GMP documentation has been provided.

The manufacturing process consists in the following main steps: blending, milling, de-lumping, and re-blending. The final blend is then encapsulated in hard gelatin capsules by an automatic process. The bulk capsules are packed in double linear low-density polyethylene (LLDPE) or polyethylene (PE) bags. Finally, the capsules are packed in the proposed blisters or HDPE bottles. The manufacturing process of the finished product is considered standard.

Appropriate information on the containers and storage conditions used for holding of the bulk intermediates have been provided upon request.

Critical steps and IPC have been identified and considered acceptable. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Process validation protocols have been provided and found acceptable.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance, identity (HPLC-UV & HPLC-PDA), assay (HPLC-UV), degradation products (HPLC-UV), content uniformity (HPLC-UV), water content (Ph. Eur.), dissolution (HPLC-UV), microbiological quality (Ph. Eur.).

The specifications for the control of the finished product contain the typical tests for this type of pharmaceutical form and the limits have been adequately justified. A justification for not including a test for disintegration was provided and found acceptable.

The dissolution test acceptance criteria were initially found not acceptable since the dissolution method was initially considered not acceptable, and a MO has been raised. Since the applicant has adequately addressed the MO related to the dissolution method, the applicant was able to justify the dissolution limits.

The specification limits for each individual and total degradation products were tightened in line with batch analysis results and stability data. Degradation products are controlled in line with ICH Q3B guidance and there are no degradation products present at levels higher than the qualification threshold.

The absence of a specification test for polymorphism has been properly justified. It was demonstrated that polymorphic form does not change upon active substance storage and finished product manufacture.

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 in the finished product specification. The information on the control of elemental impurities is satisfactory.

Following a MO, a comprehensive risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with 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) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the additional information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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 identity, assay and impurities testing has been presented.

Batch analysis results are provided for at least 3 primary batches per strength (20 mg, 30 mg) and additional data from 2 supportive 25 mg batches 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

HDPE bottles (20 mg, 25 mg, 30 mg)

Stability data from 3 primary batches for each of the 20 mg and 30 mg strengths of finished product stored for up to 48 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition, supportive stability data from 1 primary batch of the 25 mg strength of finished product stored for up to 24 months under long term conditions and for up to 6 months under accelerated conditions were provided.

PVC laminated PCTFE aluminium blister (20 mg and 25 mg)

Stability data from 3 primary batches for the 20 mg strength of finished product stored for up to 48 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Supportive stability data from 1 primary batch of the 25 mg strength of finished product stored for up to 24 months under long term conditions and for up to 6 months under accelerated conditions were provided. In addition, supportive stability data were

provided for 3 primary batches for the 30 mg strength for up to 48 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH), which will not be marketed. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Results (HDPE bottle & blister)

Samples were tested for appearance, assay, degradation products, dissolution, water content, and microbial counts. The analytical procedures used are stability indicating.

All tested parameters meet the acceptance criteria. These findings demonstrate that the selected packaging configurations effectively maintain the stability and quality of the finished product. In addition, the water content release and shelf-life specification limits have been tightened during the procedure according to batch data.

In addition, 1 batch per each strength (20 mg and 30 mg) packaged in both primary packaging were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results show that the finished product is not sensitive to light when stored in bottles or in blisters.

Bulk stability

The applicant proposed a bulk holding time of 36 months for the bulk capsules packed in LLDPE or PE bags placed in high-density polyethylene (HDPE) drums and stored at 20°C to 25°C. The design of the bulk stability studies followed the principles outlined in the *EMA Quality of medicines questions & answers: Part 2, Stability - Stability issues of pharmaceutical bulk products use in manufacture of the finished product*. All measured quality attributes have remained within specification throughout the study period. No trends have been observed, demonstrating the robustness of the bulk product under the actual storage conditions in its intended container closure systems.

Regarding the shipping qualification studies, although accelerated condition bulk hold studies were not conducted, supporting data from "in-use" stability studies demonstrate the robustness of the zuranolone capsule formulation under significantly more challenging conditions.

Furthermore, an additional shipping qualification study, which employed the validated bulk packaging system, has also been performed. This study used thermostatically controlled electric/battery powered shipping containers or temperature-controlled trucks maintained at 2-25 °C to ensure continued protection from temperature excursions during transport. Although relative humidity was not directly measured during shipping, the physical integrity and moisture barrier properties of the packaging mitigate potential risk to product quality.

Based on available stability data, the proposed shelf-life of 4 years at the proposed storage condition of "Store below 25°C" as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

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 in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the assessment there were a number of quality MOs raised. These concerned the control of benzene in the active substance specification, active substance shelf-life specification limits and additional required stability data related to the second manufacturer, the development of the dissolution method and relative FP specification limits, the proposed biowaiver for the 25 mg strength and the evaluation of potential nitrosamine impurities in the finished product. To resolve these MOs, the applicant provided evidence supporting that any potential benzene carryover in the active substance is below the proposed limit. The shelf-life specification limits for assay, related substance and water content have been revised, as requested, and supportive information has been provided to justify omission of PSD parameter and omission of specified impurities from the shelf-life specification. Also, supportive stability data has been provided for the active substance manufactured at the second manufacturer. With respect to the dissolution method the applicant has adequately justified the presence of the surfactant, its concentration, and the increased rotation speed. The specification limits for dissolution have not been tightened, however this was considered justified in line with batch data and justified dissolution method. Regarding the proposed biowaiver for the 25 mg strength, the applicant provided in vitro dissolution data which showed similar dissolution between the three strengths and the biowaiver was considered acceptable. Finally, the applicant provided a revised risk assessment with further evidence to support the omission of testing for nitrosamines in the finished product.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant committed to provide analytical data on benzene levels for at least three active substance consecutive batches by 2 months following EC decision. This point is put forward and agreed as recommendation for future quality development (REC001).

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 SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

REC001: The applicant should provide analytical data on benzene levels for at least three consecutive active substance batches by 2 months following EC decision (30 November 2025).

2.5. Non-clinical aspects

2.5.1. Introduction

Zuranolone is an orally bioavailable, synthetic neuroactive steroid (NAS) with rapid antidepressant effects. Like the endogenous NAS, allopregnanolone, zuranolone exhibits potent positive allosteric modulation of the $GABA_A$ receptor. Zuranolone enhances GABA activity at synaptic and extrasynaptic receptors and has also been shown to increase cell surface expression of $GABA_A$ receptors in *in vitro*

studies. Extrasynaptic delta subunit-containing $GABA_A$ receptors mediate tonic inhibitory currents that play a critical role in controlling network activity in the brain, including synchronization within and across neural networks. Brain network activity is regulated via a balance of inhibitory (e.g., GABAergic) and excitatory (e.g., glutamatergic) signalling inputs. Abnormalities in brain network activity have been associated with symptoms of depression. Physiological fluctuations in NAS during pregnancy and the peri-partum period are associated with changes in GABAergic signalling which, in susceptible women, may result in dysregulated neural network responses and the development of Postpartum depression (PPD). Zuranolone may exert antidepressant effects by enhancing GABAergic inhibition, in particular tonic inhibition, and may provide a mechanism to normalise function in brain networks in regions dysregulated during a major depressive episode (MDE).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Zuranolone is a $GABA_A$ receptor positive allosteric modulator (PAM) that potentiates both synaptic (γ subunit-containing) and extrasynaptic (δ subunit containing) $GABA_A$ receptors which is being developed for the treatment of PPD and major depressive disorder (MDD) indications. Zuranolone demonstrated predictable pharmacodynamic activity, including anticonvulsant, anxiolytic-like, and sedative effects, across a broad range of rodent models consistent with its mechanism of action as a $GABA_A$ receptor PAM. In addition, zuranolone modulated network oscillations in multiple frequency bands, including the θ and β frequency ranges as measured by electroencephalography, consistent with observations in humans.

Zuranolone demonstrated activity at synaptic and extrasynaptic $GABA_A$ receptors and significantly enhanced both phasic and tonic currents after acute administration as recorded from rat brain slide preparations. Additionally, zuranolone administration suggested an increase in $GABA_A$ receptor surface expression.

Zuranolone exhibited dose-related anticonvulsant, electroencephalographic, anxiolytic-like, and sedative effects consistent with the $GABA_A$ receptor PAM mechanism in rodent models and demonstrated activity in a rat model of oral dyskinesia and status epilepticus, unlike benzodiazepines. Electroencephalography (EEG) studies with zuranolone indicated effects in multiple frequency bands, including β-frequency and θ-frequency; the effects on the θ-frequency in particular are different from what has been reported for benzodiazepines.

Administration of $GABA_A$ receptor PAMs can lead to dose-dependent motor impairment and loss of coordination, reflecting the sedative effects expected from strong GABAA receptor potentiation. In line with this, nonclinical data demonstrated dose-related motor effects. However, no impairment was observed at clinically relevant exposure levels. Conversely, clinical findings confirmed that zuranolone may impact psychomotor performance and driving ability. The proposed warnings in section 4.4 of the SmPC, as well as the corresponding sections of the Package Leaflet, adequately address these potential risks.

2.5.2.2. Secondary pharmacodynamic studies

Off-target binding and activity of zuranolone was evaluated in various assays against more than 100 targets at a concentration of 10 μM (4096 ng/mL) in most studies. Significant effects were defined as effects differed ≥50% from baseline and included binding to sigma and glycine receptors at

concentrations much higher than observed in the clinic. No data is presented for these receptors at lower concentrations. Furthermore, zuranolone inhibited TRPV1 function at concentrations much higher than observed in the clinic. Zuranolone did not demonstrate significant effects on the nuclear hormone receptors. The applicant states that results between 25% and 50% are indicative of weak to moderate effects and should be confirmed by further testing (e.g., in Study SSN-616). Zuranolone exhibited significant (87-89%) and reproducible binding to sigma 2 receptor at 10 µM, a concentration well exceeding the maximum clinical exposure. The applicant did not provide sigma 2 binding and functional data with zuranolone at lower, clinically relevant concentrations or adequately justify not presenting such data. Nonetheless, the available nonclinical safety data do not indicate adverse effects that would support sigma 2-mediated toxicity, and no functional consequences have been observed. The literature cited further supports the absence of known safety concerns related to sigma 2 receptor modulation in early clinical development of other compounds.

Based on a human plasma protein binding value of ≥99.5%, the applicant calculated that an unbound concentration of 10 or 12 µM (4096 to 4915 ng/mL) represents a zuranolone plasma concentration equivalent to 819,200 to 983,000 ng/mL. However, the % zuranolone binding to plasma proteins was evaluated over a concentration range of 30-500 ng/mL (Study SSN-02733) and the % plasma binding at 30-500 ng/mL versus 819,200-983,000 ng/mL zuranolone cannot be assumed to be similar. However, even in disregard of plasma binding, these receptor/cell-based effects were noted at concentrations significantly higher than the clinically relevant plasma concentration of 94.5 ng/mL.

2.5.2.3. Safety pharmacology programme

Central Nervous System (CNS) safety pharmacology-related effects of zuranolone included decreased activity, ataxia, hypersensitivity to touch and/or sound, and impaired righting reflex. Reversible, transient neurobehavioural effects were noted in the FOB at 4 to 8 hours postdose. These effects were observed at 3-fold the mean human C_{max} exposure at 50 mg.

The IC_{50} for inhibition of the hERG channel was > 3 µM, which is approximately 2080-fold the mean human C_{max} exposure at 50 mg. Assessment of CV function in dogs indicated that zuranolone had minor effects on blood pressure and heart rate, but no effects on QTc at exposures 7.1-fold the mean human C_{max} exposure at 50 mg.

Administration of zuranolone to rats was associated with minor, reversible changes in indices of pulmonary function consistent with its primary mechanism of action ($GABA_A$ receptor modulator). These minor effects were seen at 3-fold the mean human C_{max} exposure at 50 mg.

2.5.2.4. Pharmacodynamic drug interactions

In PD drug interaction evaluations, zuranolone showed the potential for positive interaction with the $GABA_A$ receptor modulators diazepam and pentobarbital, and the potential for negative interaction with propofol using patch-clamp techniques. *In vivo*, zuranolone and diazepam demonstrated the potential for positive interaction when co-administered in two rodent seizure models. Given zuranolone's outpatient use and the controlled setting of propofol administration, the potential interaction is manageable within standard anaesthetic practice. Co-administration of CNS depressants with anaesthetics is common and routinely accounted for by clinicians.

2.5.3. Pharmacokinetics

Nonclinical PK testing in mice, rats, and/or dogs demonstrated a low to moderate rate of clearance, a moderate volume of distribution indicative of uptake into tissues, generally dose linear PK with no substantial accumulation with repeat dosing, high protein binding in plasma with no preferential partitioning to the cellular component of blood, rapid and high distribution to the brain, extensive metabolism, and excretion by both renal and hepatobiliary routes.

In clinical studies, zuranolone demonstrated oral bioavailability and dose-linear PK with no obvious sex-related differences, minor accumulation with repeat dosing, high protein binding, extensive metabolism, and excretion via the renal and hepatobiliary routes. In general, the nonclinical PK of zuranolone is consistent with observations in humans, with the exception of gender differences in Rat studies. The effect of gender on zuranolone oral exposure was assessed in male and female Sprague Dawley rats in Study SSN-01240. Across the evaluated dose range of 1 to 10 mg/kg, female rats showed a 6- to 10-fold higher mean AUC_{last} value and a 2 to 4-fold higher mean C_{max} value, compared to males. These exposure differences can be attributed to a higher clearance rate of zuranolone in male rats. A concomitant increase in t½ was observed in females. In the 3-month study (Study SSN-01403), while male rats received doses that were approximately 5- to 6-fold higher than female rats on a mg/kg/day basis, systemic exposure (in terms of AUC_{last} and C_{max} values) to zuranolone was similar between genders in each treatment group (low- to high-dose levels). Cytochrome P450 phenotyping in humans suggests that CYP3A is responsible for a significant fraction of metabolism. It is plausible that rat CYP3A18, which is most closely analogous to CYP3A5 in humans [Hammer 2021], predominates clearance in the species. CYP3A18 is known to have higher expression (up to 25x in liver [Robertson 1998]) in males than in females, which would result in the observed sex difference in rat oral exposure. Since the underlying cause is based on normal physiology, no adjustment to exposure safety margins is required.

The distribution of zuranolone in the placenta and excretion in milk was not provided.

Although metabolism was extensive in humans, rats, and dogs, there were some differences in the biotransformations observed. Zuranolone was metabolised in mice, rats, dogs, and humans with no plasma human metabolites present at greater than 10% of total drug-related material. All human metabolites detected at greater than 1% of drug, were also detected in rat or dog plasma. Mouse metabolites were formed from single or multiple oxidations of the steroid rings, the cyano-pyrazole moiety and/or the C3-methyl group, and dehydrogenation of the steroid rings and sulfation reactions. The dog metabolite profile was the result of the similar biotransformations observed in mice as well as additional metabolites generated from N dealkylation and glucuronidation reactions. Rats and humans exhibited the greatest number of metabolites, with the majority of the metabolites derived from the same biotransformations present in mice and dogs: single or multiple oxidations on the steroid rings and/the cyano pyrazole moiety, dehydrogenation of the steroid rings, sulfation, N dealkylation and glucuronidation, with additional metabolites generated by epimerization of the C3-methyl, elimination of the C3-alcohol to produce the available olefins, and reduction of the C20 ketone. In all species, the majority of the metabolites were the result of multiple biotransformation reactions.

Human studies identified CYP3A4 as the primary enzyme responsible for zuranolone's metabolism. *In vitro* studies suggest minimal risk of drug-drug interactions through CYP inhibition or induction, with no significant time- or metabolism-dependent inhibition observed. Minor inhibition of enzymes such as CYP2C8, CYP2B6, and CYP2D6 by certain metabolites was noted, but these effects were not clinically relevant based on [I]/Ki ratios. Induction studies suggested some potential for CYP3A4 and CYP2B6 induction, but the levels required for such effects were far above clinically observed concentrations, indicating a low risk of clinically significant interactions. Zuranolone was evaluated for the potential to interact with drug transporters *in vitro* and no significant interaction was found. In the context of

expected clinical plasma levels and plasma protein binding, zuranolone does not show the potential to cause a DDI via inhibition or induction of CYP enzymes or drug transporters.

Zuranolone metabolites M125 (SGE-07672), M117 (SGE-02369), M135 (SGE 03632), and M136 (SGE-03633) were evaluated for their potential to inhibit CYP enzymes and, taking into account physiologic parameters and anticipated clinical concentrations, these metabolites are not likely to precipitate a DDI.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single dose toxicity studies were conducted in the mice (CByB6F1-Tg(HRAS)2Jic Wild Type [rasH2]), Sprague-Dawley rats and Beagle dogs. Toxicokinetic parameters were assessed in rats and dogs.

In mice, doses up to 1000 mg/Kg zuranolone were tested by oral gavage. In rats, zuranolone was administered by oral gavage at i) doses up to 20 mg/Kg, ii) doses up to 40 and 10 mg/Kg in male and females, respectively; and iii) doses up to 35 and 5 mg/Kg in male and females, respectively. The observed maximum nonlethal dose in mice (male and female) is 300 mg/kg. In rats, the maximum nonlethal dose levels are 20-40 mg/Kg in males and 4-6 mg/Kg in males and females. Different levels of systemic exposure to zuranolone were identified between sexes in rats. Based on the available TK values, the AUC and C_{max} in males dosed 20 mg/Kg zuranolone are 5710 ng.h/mL and 453 ng/mL, respectively, and in females dosed 7.5 mg/Kg zuranolone are 7640 ng.h/mL and 641 ng/mL, respectively. Therefore, the selected dose levels cover an identical range of systemic exposures male and female rats. Across single oral administration studies in rodents, sedation was the primary and dose-limiting treatment-related effect, consistent with the anticipated pharmacological activity of zuranolone.

A set of three single dose studies were also conducted in Beagle dogs, with zuranolone administered once by oral gavage at doses up to 2.5 mg/Kg in two studies and doses up to 3.0 mg/Kg in a third study. No mortalities were observed in the dose range tested. Clinical findings observed in dogs were also consistent with a dose-dependent sedation which is an expected pharmacologic effect of zuranolone. Systemic exposures to zuranolone were similar between sexes (within 2-fold) across all dose levels tested.

With respect to toxicological assessment, sedation is the main safety concern in single dose toxicity studies, which is an anticipated exaggerated pharmacological effect of zuranolone via the $GABA_A$ receptor.

2.5.4.2. Repeat dose toxicity

Good laboratory practice (GLP) repeat dose toxicity studies up to 28 days, 6 months and 9 months duration were conducted in mice, Sprague Dawley rats and Beagle dogs.

Across the repeated oral administration studies of zuranolone to mice, rats and dogs, sedation was the primary and dose-limiting treatment-related effect, consistent with the anticipated exaggerated pharmacological activity of zuranolone via the $GABA_A$ receptor. The severity and duration of sedation showed a dose-response relationship with evidence of tolerance occurring with continued systemic exposure. In general, the dose-dependent sedation-related clinical signs in pivotal toxicity studies included, but were not limited to, ataxia, decreased activity, impaired equilibrium, and tremors. At higher exposures associated with severe sedation, laboured respiration, prostrate body position,

transient decreased body temperature, pedalling, twitches, and salivation were noted in one or both species.

In CByB6F1-Tg(HRAS)2Jic wild-type [rasH2] mice, once-daily oral gavage administration of zuranolone was tolerated up to 100 mg/kg for 28 days, corresponding to safety margins of 3- and 14-fold, based on the systemic exposure (AUC and C_{max}, respectively) at the dose established for clinical use (50mg/day, AUC 1218 ng.h/mL and C_{max} 94.5 ng/mL). Liver findings consisted in a non-dose related decreased liver weights were noted in male mice. Microscopic findings were limited to a slight decrease (minimal to mild) in the amount of cytoplasmic vacuolation in hepatocytes of animals in all zuranolone-treated groups, which was morphologically consistent with decreased glycogen storage. According to the applicant position, the decreased glycogen was considered to be related to decreased food consumption and a non-adverse effect.

A GLP study to evaluate the potential repeated dose toxicity of zuranolone administered orally for 14 days, including a 14-day recovery period, was conducted in Sprague Dawley rats. Zuranolone was administered once daily at dose levels of 0, 3, 10, or 22.5 mg/kg/day to males and 0, 1, 3, or 8 mg/kg/day to females. Liver was identified as a potential target organ of toxicity. Increased liver weight (mean absolute and relative) was observed in females at the highest dose tested, 8 mg/kg/day. This finding was not clearly correlated to any microscopic finding, although females at this dose level had a higher incidence of minimal hepatocellular vacuolation, correlated with slight increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (1.1-1.4 and 1.8-fold increase in serum level of AST and ALT, respectively). The liver weight differences were not evident following completion of the recovery period. Hepatocellular vacuolation was observed in all dosed group females (1, 3, and 8 mg/kg/day) and in males from the intermediate dose (10 mg/kg/day). The NOAEL was considered to be 22.5 mg/kg/day for males and 3 mg/kg/day for females. The systemic exposures at the NOAEL in females ($AUC_{0\text{-}24h}$ of 5270 ng·h/mL and C_{max} 392 ng/mL on Day 14) are approximately 4-fold above the expected exposures in humans following daily administration of zuranolone 50 mg.

Moreover, GLP studies addressing the potential toxicity of zuranolone when administered daily for a minimum of 90 consecutive days, and 182 consecutive days, including recovery periods of 28-day, were also conducted in Sprague Dawley rats.

Zuranolone was administered at 0, 0.8, 2.5, 8, or 30 mg/kg/day to males and at 0, 0.15, 0.5, 1.5, or 5 mg/kg/day to females in the 3-month study. Zuranolone-related changes in liver weight (absolute liver weight and/or liver to final brain weight at the primary necropsy) were noted in males dosed 2.5, 8, and 30 mg/kg/day and females dosed 1.5 and 5 mg/kg/day. No microscopic correlate was identified for these organ weight changes. In females, no liver findings were noted at 0.5 mg/Kg, at systemic exposures ($AUC_{0\text{-}24h}$ of 1230 ng·h/mL and plasma C_{max} 79.3 ng/mL on Day 90) approximately identical to that reached in patients (AUC 1218 ng·h/mL and C_{max} 94.5 ng/mL) following daily administration of zuranolone 50 mg. Based on study results, the NOAEL was considered to be 30 mg/kg/day for males and 1.5 mg/kg/day for females. Systemic Exposures at the NOAEL in females (AUC_{last} 3190 ng·h/mL and mean C_{max} 218 ng/mL) are approximately 2.6 and 2.3-fold above the expected exposures in humans. In addition, zuranolone was administered at doses up to 30 mg/kg/day and 5 mg/kg/day to male and female rats, respectively, in the 6-month duration study. No liver or other potential target organs were identified, and the NOAEL was considered to be 10 mg/kg/day and 5 mg/kg/day for males and females, respectively. The systemic exposures at the NOAEL in females (AUC_{last} 7590 ng·h/mL and C_{max} 564 ng/mL) are approximately 6-fold above the expected exposures in humans.

A GLP 14-days duration study was conducted in dogs to evaluate the potential for repeated dose toxicity, followed by a 14-day recovery period. Zuranolone was administered via oral gavage at dose levels of 0, 0.4, 1, or 2.5 mg/kg/day once daily for 14 days. A transient decrease in core body

temperature and increase in heart rate (shortening of the RR interval of the ECG) were noted in the 1 and 2.5 mg/kg/day group. For a few dogs, this increase was characterised as sinus tachycardia. The increase in heart rate was accompanied by a physiologically appropriate shortening of the PR and QT intervals. There was no zuranolone-related effect on the QT or QTc intervals or QRS duration. The proposed NOAEL was 2.5 mg/kg/day, the highest dose level tested in this study. However, it is suggested to consider a lower NOAEL at 0.4 mg/Kg due to cardiac findings noted at 1.0 and 2.5 mg/Kg. The corresponding systemic exposures ($AUC_{0\text{-}24h}$ and C_{max} on Day 14) for males and females combined were 1690 ng·h/mL and 118 ng/mL, respectively, leading to lower safety margins, 1.4-fold and 1.2-fold, based on clinical exposure (AUC and C_{max}) following daily administration of 50 mg zuranolone.

In the 3-month GLP study in Beagle dogs, zuranolone was administered via oral gavage at dose levels of 0.06, 0.2, 0.6, or 2 mg/kg/day once daily for a minimum of 90 consecutive days, including a 28-day recovery period. Changes in electrocardiogram (ECG) parameters were noted at ≥ 0.6 mg/kg/day (shortened PR, RR, and QT intervals), which were associated with dose-dependent increases in heart rate (33% in 0.6 mg/kg/day males; 43% and 25% in 2 mg/kg/day males and females, respectively) on Day 1. The serial collection of ECGs (Days 1, 28, and 86) demonstrated a decrease in the magnitude of change for heart rate for both the 0.6 and 2 mg/kg/day group males and females. By Day 86, heart rate remained slightly elevated only for the 2 mg/kg/day group males. When considering plasma exposure levels of zuranolone, the heart rate response did not correlate proportionally with dose over the course of the study. Specifically, exposure levels (AUC_{last}) increased marginally for females from Study Day 1 through Study Day 90 (4320, 5130, and 6860 ng·h/mL on Study Days 0, 30, and 90, respectively); however, heart rate continued to decrease towards acclimation period values for the 2 mg/kg/day dose group during this time. Based on the results of this study, the NOAEL was considered to be 0.6 mg/kg/day with associated AUC_{last} values and C_{max} values of 1980 ng·h/mL and 165 ng/mL, respectively, on Day 90. The corresponding safety margins are 1.6-fold and 1.7-fold above the expected exposures in humans.

An additional GLP study was conducted to evaluate the potential toxicity in dogs when zuranolone was administered at dose levels up to 2.5 mg/kg/day once daily for 273 days, including a 28-day recovery period. No zuranolone-related abnormalities in rhythm or waveform ECG morphology or effects on heart rate, RR interval, PR interval, QRS duration, QT interval, or QTc interval were observed at any dose level in the 9-month study, which is in line with cardiovascular safety pharmacology assessment. The NOAEL was considered to be 1.2 mg/kg/day (AUC_t 6400 ng·h/mL and C_{max} 409 ng/mL for sexes combined on Day 272), and the corresponding systemic exposures at the NOAEL are approximately 5.3 to and 4.3-fold above the expected exposures in humans.

The adverse clinical signs/early mortality noted in individual animals in the 3-month and 9-month dog studies appears consistent with an acute withdrawal-type response following prolonged administration at high dose levels to dogs: i) at the highest dose tested (2 mg/kg/day) in the 3-month study, a single male was found dead on Day 61 prior to dosing. This animal had received 59 total doses. During the 10 days prior to death (Days 52 to 61), transient clinical signs, including tonic convulsions and periods of prolonged sedation, were noted for this animal; ii) at the highest dose tested (2.5 mg/kg/day) in the 9-month study, mortality was observed in a female on Day 30. This animal received its last dose on Day 29, and was observed to have tonic and clonic convulsions prior to dosing on Day 30. Another single female animal was found dead on Day 276 during the recovery period (4 days after receiving its last dose).

The potential toxicity of zuranolone when administered in an episodic (cyclical) dose design to Beagle dogs, has been addressed in two regimens: Regimen 1 (each cycle consisted of 14 days of dosing followed by a 42-day nondosing period, except for Cycle 6 that had a minimum 14-day nondosing period prior to necropsy), and Regimen 2 (each cycle consisted of 14 days of dosing followed by a 21-

day nondosing period, except for Cycle 6 that had a minimum 14-day nondosing period prior to necropsy). In both regimens, zuranolone was orally administered to Beagle dogs at dosage levels of 1.2 and 2.5 mg/kg/day. The anticipated dose-dependent sedation and corresponding clinical observations were comparable among treatment Regimens 1 and 2, and were almost exclusively limited to the periods of dosing during each cycle, with the greatest incidence and severity noted at 2.5 mg/kg/day. The NOAEL 1.2 mg/kg/day corresponded to a mean AUC_t value of 4210 ng·h/mL and a mean C_{max} value of 321 ng/mL for males and females combined (Regimen 1) on Day 12 (similar values were obtained for animals assigned to Regimen 2 and dosed at 1.2 mg/kg/day).

2.5.4.3. Genotoxicity

The genotoxic potential of zuranolone has been assessed *in vitro* and *in vivo* in line with ICH S2 (R1).

The *in vitro* mutagenic potential of zuranolone was evaluated in 2 GLP bacterial reverse mutation assays using the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* tester strain WP2 *uvrA* (1 assay using rat S9 and 1 assay using human liver S9 with PAPS). The clastogenic potential of zuranolone was assessed *in vitro* and *in vivo*, in a GLP chromosome aberration assay using CHO cells and in a micronucleus assay in rats.

Zuranolone was not mutagenic in the bacterial reverse mutation assay. Moreover, zuranolone was not clastogenic *in vitro* in the mammalian chromosome aberration test, or *in vivo* in a micronucleus assay in rats, at doses up to 30 mg/kg.

2.5.4.4. Carcinogenicity

The carcinogenic potential of zuranolone was assessed in a 6-month GLP study conducted in CByB6F1-Tg(HRAS)2Jic (hemizygous) [rasH2] mice, and in 104-Week GLP study Sprague Dawley Rats.

Zuranolone was administered via oral gavage at dose levels of 10, 30, or 100 mg/kg/day once daily for up to 26 weeks in mice, and at dose levels of 2, 6, or 20 mg/kg/day in male rats and 0.2, 0.6, and 1.5 mg/kg/day in female rats once daily for up to 92 weeks.

Zuranolone did not produce any evidence of carcinogenic effects in the CByB6F1-Tg(HRAS)2Jic (hemizygous) [RasH2] mouse model system. The high dose, 100 mg/kg/day of zuranolone, produced the highest exposures, corresponding to an $AUC_{0\text{-}24h}$ of 5070 ng·h/mL and a C_{max} of 1100 ng/mL on Day 182, and associated safety margins 4.2- and 12-fold higher, based on the systemic exposure in humans following daily administration of zuranolone 50mg/day.

Moreover, zuranolone did not produce any evidence of an oncogenic effect in Sprague-Dawley rats. The highest dose levels, 20 mg/kg/day for males ($AUC_{0\text{-}24h}$ values of 6430 ng·h/mL and C_{max} values of 457 ng/mL) and 1.5 mg/kg/day for females ($AUC_{0\text{-}24h}$ values of 4560 ng·h/mL and C_{max} values of 307 ng/mL) lead to safety factors 5.3 and 4.8 for males, and 3.7 and 3.2 for females, based on AUC and C_{max}, respectively, at the clinical human dose.

2.5.4.5. Reproductive and developmental toxicity

Fertility and Early Embryonic Development

Potential adverse effects of zuranolone on fertility and early embryonic development have been addressed in two GLP studies conducted in Sprague Dawley rats: i) zuranolone was administered to female Sprague Dawley rats via oral gavage at dose levels of 1, 3, or 10 mg/kg/day once daily beginning 15 days before cohabitation through GD 7; ii) zuranolone was administered to male Sprague

Dawley rats via oral gavage at dose levels of 3, 10, or 30 mg/kg/day once daily beginning 28 days before cohabitation and continuing until male euthanasia (51 to 52 days of treatment).

In the pivotal fertility and early embryonic development study in female rats, the 10 mg/kg/day dose level was associated with mortality and increased incidences of hyperreactivity, twitches, ungroomed coat, chromodacryorrhea, mild dehydration (based on skin turgor), ataxia, gasping, and urine-stained abdominal fur. The 3 mg/kg/day dose level was also associated with increased incidences of hyperreactivity (nonadverse, pharmacology-related). Sedation, an extension of the expected pharmacologic activity of zuranolone, was observed at ≥ 3 mg/kg/day at dose-dependent severities. On the basis of these data, the maternal NOAEL was 3 mg/kg/day.

With respect to the assessment of fertility and reproductive function, the 10 mg/kg/day dose was associated with a significant increase in the number of rats exhibiting transient persistent dioestrus during the first 10 days of dosing, and a reduction in the number of oestrous stages during the dosing period. There were no zuranolone-related effects on mating, fertility, or ovarian and uterine parameters, and there were no gross maternal abnormalities detected at necropsy examinations. As a result, the proposed NOAEL for fertility and reproductive function in female rats is 10 mg/kg/day. However, based on zuranolone-related transient effects noted on oestrous cycling, we would suggest to consider a lower NOAEL at 3 mg mg/kg/day, with associated AUC_t and C_{max} of 5150 ng·h/mL and 480 ng/mL, respectively. The corresponding Safety Margins are 4.2 and 5-fold, respectively, based on systemic exposure at the clinical dose 50 mg/day.

In addition to effects noted in female rats, microscopic findings showing hypertrophy of corpora lutea in the ovaries were also observed in the transgenic mice, CByB6F1-Tg(HRAS)2Jic (hemizygous) [rasH2], dosed at ≥ 30 mg/kg (safety margin 3.6 based on systemic exposure) in the 26-week carcinogenicity study.

In the pivotal fertility study conducted in males, mortality was observed in 2 animals in the 30 mg/kg/day dose group during treatment. Administration of ≥ 10 mg/kg/day was associated with increased incidences of observations of hyperreactivity, impaired righting reflex, rales, and cold to touch as well as dose dependent incidences of sedation, an extension of the expected pharmacologic action of zuranolone. Body weight gain and food consumption were reduced at 30 mg/kg/day during the dosing period. On the basis of these data, the NOAEL in males for parental toxicity is 10 mg/kg/day, leading to safety margins of 3.7- fold, based on systemic exposure. In male rats, there were no zuranolone-related effects on mating and fertility or sperm parameters at the end of the dosing or recovery periods. There were no zuranolone-related effects on any ovarian or uterine parameter in the untreated females that were mated with treated males. Therefore, the NOAEL for fertility and reproductive function was 30 mg/kg/day in male rats leading to safety margins approximately 2.9-fold (AUC) and 4.8-fold (C_{max}) greater than the systemic exposure in humans. Notwithstanding this information is not relevant for the intended target population/therapeutic indication under assessment.

Embryo-foetal development

Embryo-foetal development GLP studies were conducted in pregnant Sprague Dawley rats Crl:CD1(ICR) mice and rabbits.

Zuranolone was administered to rats by oral gavage at dose levels of 2.5, 7.5, or 22.5 mg/kg/day once daily from GDs 6 through 17, and to rabbits at dose levels of 25, 125, or 500 mg/kg/day once daily from GDs 7 through 19. The corresponding TK parameters were determined in pregnant animals.

In the pivotal rat embryo-foetal development study, maternal effects of zuranolone included mortality (22.5 mg/kg/day, high dose), reduced mean body weight gain (≥ 7.5 mg/kg/day), as well as decreased food consumption and dose-dependent observations of sedation (≥ 2.5 mg/kg/day). Gravid

uterine weights were significantly reduced, and post-implantation loss was increased at 22.5 mg/kg/day, reflecting increased numbers of early resorptions in this group.

Concerning the assessment of developmental parameters, foetal body weights were significantly reduced (8% to 9% below control) at 22.5 mg/kg/day. The numbers of litters and foetuses with any external, visceral, and skeletal malformations and variations were increased in the 22.5 mg/kg/day dose group. Malformations were noted in 10 foetuses in the 22.5 mg/kg/day group and included exencephaly (1 foetus), absent tail (2 littermates), short thread like-tail and/or malformation of the sacral and caudal vertebrae (2 littermates), umbilical hernia and depressed eye bulges (1 foetus), absent or small lens of the eye (2 littermates), and vertebral/rib malformations (3 foetuses in 2 litters). Additionally, the average numbers of ossified bones of the hindlimbs (tarsals, metatarsals, and phalanges) were reduced as compared to control. The overall increase in malformed foetuses at 22.5 mg/kg/day was attributed to effects of zuranolone. A low incidence of malformations was observed at 7.5 mg/kg/day (1 foetus with a malformed forelimb and umbilical hernia; 2 foetuses with rib/vertebral malformations), and at 2.5 mg/kg/day (1 foetus with depressed eye bulges).

The NOAEL for maternal toxicity was considered to be 2.5 mg/kg/day, with associated AUC_{last} and C_{max} values of 3710 ng·h/mL and 281 ng/mL, respectively, on GD 17. The proposed developmental NOAEL was 7.5 mg/kg/day, associated to maternal AUC_{last} and C_{max} values of 9380 ng·h/mL and 656 ng/mL, respectively, on GD 17. The relevance of the occurrence of individual malformations in rats, at the lower and intermediate dose, was adequately discussed by the applicant. However, we would suggest to consider a lower NOAEL of 2.5 mg/kg/day for the developmental toxicity. The corresponding safety margins based on systemic exposures (AUC and C_{max}) are approximately 3.0-fold higher than the clinical mean AUC of 1218 ng·h/mL and steady-state C_{max} of 94.5 ng/mL observed in humans dosed 50 mg/day zuranolone.

Pregnant female Crl:CD1(ICR) mice were dosed via oral gavage once daily during GD 6–15. Sedation (a manifestation of exaggerated pharmacologic activity of SAGE-217) was noted throughout the dosing period (GD 6–15) at all dose levels, with severity increasing with increasing dose. At the high dose, there was a decrease in body weight gain of the dams. Foetuses in the mid and high dose groups had lower mean body weights (around 5 and 17% lower than controls respectively), which coincided with incomplete ossification at the high dose, and cleft palate at the mid dose (2 foetuses out of 2 litters) and the high dose (10 foetuses out of 3 litters). These effects are likely related to the lower foetal body weights, since the cleft palates were seen in the foetuses with the lowest weight. Clinical relevance cannot be excluded. The NOEAL is set at the low dose. This results in a safety margin of 1.9 at the NOAEL, and an exposure margin of 5 at the LOAEL.

In the pivotal embryo-foetal development study in rabbits, zuranolone-related early mortality was noted at 500 mg/kg/day (high dose). Sedation and associated clinical observations were noted at ≥ 25 mg/kg/day at dose-dependent severities and incidences. Mean maternal body weight gains were reduced at ≥ 125 mg/kg/day for the overall dose period. Based on these results, the NOAEL for maternal toxicity was considered to be 25 mg/kg/day, leading to systemic exposures (AUC and C_{max} values 663 ng·h/mL and 39.1 ng/mL, respectively) associated to lower safety margins (values <1).

Mean foetal body weights were reduced in the 500 mg/kg/day dose group. There were no zuranolone-related effects on ovarian or uterine parameters at any dose level, and no foetal external, visceral, or skeletal abnormalities. Therefore, the NOAEL for developmental toxicity was 125 mg/kg/day, which was associated with AUC_{last} values of 395 and 663 ng·h/mL and C_{max} values of 19.8 and 39.1 ng/mL in pregnant rabbits on GD 7 and 19, respectively. Safety margins based on systemic exposure values at the NOAEL were lower than 1 (0.5 and 0.4 based on AUC and C_{max}, respectively in DG19) for the embryo foetal study conducted in rabbits.

Prenatal and postnatal development, including maternal function

The potential effects of zuranolone on female Sprague Dawley rats, consequent to exposure during gestation, parturition, and lactation, as well the potential effects on offspring survival, physical development, behaviour, and reproductive performance were assessed. Zuranolone was administered by oral gavage at dose levels of 1, 4, or 10 mg/kg/day once daily from GD 6 through LD 20. In addition, the TK characteristics of zuranolone were determined in the pregnant and lactating females and plasma concentrations of zuranolone were determined in the pups.

In the pivotal perinatal/postnatal development study in rats, evidence of maternal toxicity was observed as early mortality and reduction of mean food consumption at ≥ 4 mg/kg/day (mid and high dose groups) during the gestation and/or lactation periods. As a result of the extent of mortality and total litter loss in the 10 mg/kg/day dose group, the surviving animals in the dose group were terminated on LD 8 to 10. There were no zuranolone-related maternal abnormalities detected at necropsy at ≤ 10 mg/kg/day (high dose). The number of pups found dead, euthanised, or presumed cannibalised was increased at 4 mg/kg/day on PND 1 to 4, resulting in a significant reduction in the viability index. Pup weights were significantly reduced at 4 mg/kg/day on PNDs 4, 10, and 14 (~ 94% of controls). Postweaning, there was no zuranolone-related mortality or clinical signs in the F1 generation at ≤ 4 mg/kg/day. Mean body weights were significantly reduced at 4 mg/kg/day in the F1 males from PND 22 to 71, and mean food consumption was transiently reduced in the F1 males from PND 22 to 43. There were no zuranolone-related effects on sexual maturation, neurobehavioral assessments (motor activity, acoustic startle response and habituation, learning, and memory), or any reproductive endpoints, including oestrous cycles or ovarian and uterine examinations in the F1 males or females at ≤ 4 mg/kg/day. Plasma zuranolone-concentrations in PND 4 and PND 10 pups at 2 and/or 4 hours postdose were approximately 0.6% to 0.7% and 0.3% to 0.5%, respectively, of the dam plasma concentrations, on average, at both dose levels (1 and 4 mg/kg/day).

The maternal NOAEL for general toxicity was 1 mg/kg/day. The NOAEL for growth and development in the offspring was 1 mg/kg/day (maternal exposures on GD 17: AUC_t of 2420 ng·h/mL and C_{max} of 223 ng/mL). The corresponding safety margins are approximately 2.0-fold (AUC) and 2.4-fold (C_{max}) greater than the clinical mean AUC of 1218 ng·h/mL and steady-state C_{max} of 94.5 ng/mL at the proposed clinical dose of 50 mg day zuranolone.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

In a GLP 7-week juvenile toxicity study, zuranolone was administered orally to juvenile rats from PND 22 through PND 71, followed by a 6 weeks recovery phase. The dose levels in male rats were 3, 10, or 30 mg/kg/day from PND 22 through scheduled euthanasia. Female rats were administered 3, 10, or 30 mg/kg/day from PND 22 to PND 35, then dose levels were adjusted (due to tolerability) to 1, 3, or 10 mg/kg/day from PND 36 through scheduled euthanasia.

In the 30 mg/kg/day dose group there were 12 males (of 81) found dead or euthanised due to adverse clinical signs within the first 4 days of dose administration, with no zuranolone-related deaths occurring after PND 25. In addition, there were 24 females (of 81) found dead or euthanized due to adverse clinical signs between PND 22 and 35; there were no zuranolone related deaths on or after PND 36, when the dose levels were reduced. Sedation, an expected pharmacologic effect occurred in a dose-dependent manner in all dose groups.

There were no zuranolone-related effects on male sexual maturation, ophthalmology, acoustic startle response and habituation, learning and memory, reproductive function, bone lengths or density, or clinical or anatomic pathology parameters in either sex at any dose level.

The mean age of vaginal patency was statistically significantly higher in females at 30/10 mg/kg/day (35.8 days *vs*. 32.5 days in controls). In addition, the mean body weight on the day of sexual maturity was statistically significantly increased at 30/10 mg/kg/day (134.9 g *vs*.118.5 g in controls).

Motor activity at 30 mg/kg/day on PND 54 ± 2 (during treatment, prior to daily dosing) was increased in males in the number of fine movements. In females, motor activity on PND 54 ± 2 was increased in ambulation at 30/10 mg/kg/day and in fine movements at 10/3 and 30/10 mg/kg/day. Motor activity was comparable to controls during the recovery period.

The NOAEL in juvenile male and female rats was identified as 10 and 3/1 mg/kg/day, respectively, corresponding to male AUC_t of 3740 ng·h/mL and C_{max} of 506 ng/mL and female AUC_t of 2610 ng·h/mL and C_{max} of 240 ng/mL. These values are approximately 3.1- and 2.1-fold (AUC, males and females, respectively) and 5.4- and 2.5-fold (C_{max}, males and females, respectively) greater than the clinical mean AUC of 1218 ng·h/mL and steady-state C_{max} of 94.5 ng/mL observed in humans following administration at the proposed clinical dose of zuranolone 50 mg daily.

The potential for zuranolone to cause neurodegeneration was assessed in a single dose study conducted in PND 7 Crl:CD(SD) Sprague Dawley rats. A single dose of zuranolone administered by oral gavage to male and female juvenile rats on PND 7 resulted in sedation and sedation-related clinical observations at 2.5 and 7.5 mg/kg in a dose-dependent manner for up to 4 hours postdose.

The level of neuronal disintegration in all structures in the brain observed at 2.5 mg/kg zuranolone was similar to the level seen in the water and vehicle controls. However, increased apoptotic neurodegeneration relative to controls was observed in one area of the brain (subiculum) in both males and females at 7.5 mg/kg zuranolone. Therefore, the occurrence of neurological degeneration effects can be expected at systemic exposures 5.6-fold [(based on AUC in PND7 rats (6815 ng.h/mL) *vs.* AUC in humans (1218 ng.h/mL)] or 6.4-fold [(based on C_{max} at PND7 rats (605 ng/mL) *vs*. 94.4 ng/mL in humans] higher than the systemic exposure in humans.

At the NOEL of 2.5 mg/kg, the mean $AUC_{0\text{-}24h}$ (1730 ng·h/mL) and the mean C_{max} was 201 ng/mL (combined males and females), leading to the corresponding safety margins of 1.4 and 2.1-fold, respectively.

According to the applicant position, the region affected was small and variations in staining were noted between levels of the subiculum, highlighting the challenges of interpreting the AmCuAg stain due to its high inherent background and the differentiation of pathologic cell death from normal neuronal apoptosis that occurs in multiple brain structures in early life (i.e., PND 8). Therefore, the ultimate biologic significance of this level of neuronal disintegration within the subiculum was considered unclear given the plasticity of the developing brain.

2.5.4.6. Toxicokinetic data

Toxicokinetics assessment has been addressed within the scope of the corresponding toxicological studies.

2.5.4.7. Local tolerance

No stand-alone local tolerance studies were conducted with zuranolone.

2.5.4.8. Other toxicity studies

Dependence

Five *in vivo* GLP studies were conducted to investigate the abuse and physical dependence potential of zuranolone.

Zuranolone was evaluated in 2 drug discrimination studies in male and female rats to determine whether zuranolone may have interoceptive effects similar to those of midazolam, a benzodiazepine and positive modulator of $GABA_A$ receptors. The reinforcing properties of zuranolone were evaluated in an intravenous self-administration study in cocaine-trained female rats. Finally, zuranolone was evaluated in 2 physical dependence studies in male and female rats to establish whether zuranolone induces a withdrawal syndrome following abrupt discontinuation after 28 days of oral administration.

Zuranolone produced dose-dependent generalisation to the discriminative stimulus effects similar to those of midazolam, with full generalisation occurring at doses that produced a zuranolone plasma C_{max} of 219 ng/mL in male rats and 499 ng/mL in female rats (*i.e.,* 2.3 to 5.3-fold higher than the clinical mean steady state C_{max} of 94.5 ng/mL at the proposed clinical dose of 50 mg/day), that also reduced response rate in the drug discrimination task.

Evaluation of zuranolone in an IV self-administration study assessed the reinforcing properties of zuranolone in female rats to determine whether self-administration behaviour was maintained when zuranolone was substituted for cocaine. The dose range evaluated in this study produced plasma concentrations ranging from 1.1- to 3.2-fold over the clinical mean steady state C_{max} value (94.5 ng/mL) on Day 1 of substitution, suggesting that the zuranolone plasma concentrations that are at or exceed the clinically relevant plasma concentration (94.5 ng/mL) did not maintain robust self-administration in animals with a previous history of cocaine self-administration, indicating that zuranolone has minimal to no reinforcing properties. In addition, the mid and high dose of zuranolone produced some clinical observations of unsteady gait, altered activity, and subdued behaviour in some animals after some substitution sessions, suggesting that evaluation of a higher dose may be associated with a reduction in lever pressing. In contrast, midazolam produced comparable response to the cocaine group during the last 2 substitution sessions indicating that the current experimental parameters were sensitive to the reinforcing properties of $GABA_A$ receptor positive modulation. Together, these results indicate that zuranolone has minimal to no reinforcing properties.

The potential drug dependence and withdrawal effects of zuranolone were examined in male and female rat studies. The abrupt discontinuation of any tested dose of zuranolone in male rats did not induce meaningful changes in physiological, neurobehavioral, and locomotor activity parameters, suggesting that there were no withdrawal-related phenotypes associated with C_{max} plasma concentrations up to 410 ng/mL (Day 28). In contrast, discontinuation of chlordiazepoxide (CDP) induced a withdrawal syndrome in both sexes consistent with that of benzodiazepines.

In female rats, discontinuation of repeated zuranolone administration at 0.5 and 1.5 mg/kg/day did not induce meaningful changes in the measured parameters at doses associated with C_{max} plasma concentrations up to 325 ng/mL (Day 28). Upon discontinuation of zuranolone 5 mg/kg/day (a dose associated with a C_{max} of 696 ng/mL in Day 28), female rats showed a transiently reduced food consumption and body weight loss. These animals also spent significantly more time in the arena margins, showed increased defecation, had fewer escape attempts, and had lower arousal on specific days during the 7-day discontinuation period.

Taken together, these data indicate no withdrawal syndrome in female or male rats at zuranolone plasma concentrations that are up to approximately 3.4- to 4.3-fold higher than the clinical mean steady state C_{max} of 94.5 ng/mL at the proposed clinical dose of 50 mg/day zuranolone, respectively.

Mild withdrawal signs were observed in female rats following discontinuation of zuranolone at a plasma concentration that is approximately 7.4-fold higher than the clinical mean steady state C_{max} of 94.5 ng/mL. However, these withdrawal signs were less marked than those associated with CDP

discontinuation, which induced a withdrawal syndrome in female rats consistent with that of benzodiazepines.

Studies on impurities

In silico analyses for mutagenic potential were conducted for impurities, process intermediates, and degradation products.

Based on computational hazard assessment of potential genotoxicity, 9 potential impurities were further evaluated for mutagenic potential in standard GLP Ames bacterial mutagenicity studies in the presence and absence of metabolic activation. No evidence of mutagenic potential was observed for the following 6 impurities: SGE-1559, SGE-2748, SGE-2749, SGE-1932, SGE-7382, and SGE-7390; therefore, all are considered Class 5 compounds. Three impurities, SGE-2747, SGE-6334, and SGE-2054, were predicted positive for mutagenicity by *in silico* analysis and were experimentally confirmed positive by standard GLP Ames assay. All 3 impurities are considered Class 2 compounds. SGE-6334 and SGE-2747 are controlled in the proposed regulatory starting material SGE-1936 in accordance with Option 2 and Option 3, respectively, of the ICH M7(R2) *Guidance on Assessment and Control of DNA reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic risk*. SGE-2054 is controlled in the DS at a proposed temporary specification of 3.0 µg/day or 60 ppm (see Quality part).

Phototoxicity studies

Studies to investigate the phototoxic potential of zuranolone were not conducted. Zuranolone does not absorb light between 250 and 700 nm although some limited absorption occurs between 200 and 250 nm, with maximal absorption at approximately 214 nm. Between 290 nm and 700 nm, zuranolone does not have a MEC greater than 1000 L mol-1cm-1. Therefore, zuranolone was judged not to have a potential for phototoxicity, in line with the Guideline ICH S10 on *Photosafety Evaluation of Pharmaceuticals*.

2.5.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) provided by the applicant follows the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00, Rev. 1, 2024).

An ERA Phase I was conducted to consider the environmental risk for Zurzuvae 20mg, 25mg and 30mg, hard capsules. The MAA is for use in the treatment of postpartum depression (PPD) as a rapid-acting short course oral treatment at a maximum daily dose of 50 mg, to be taken for a maximum of 14 days.

Relevant endpoints, methods used and results obtained were discussed and study results are summarised in *Table 2* below.

Table 2. Summary of main study results

Substance (INN/Invented Name): zuranolone			
CAS-number (if available): 1632051-40-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	log K_{OW} = 4.3 at pH 7 (neutral form at pH <10)	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log K_{OW} = 4.3 at pH 7 (neutral form at pH <10)	not B

PBT-statement:	The compound is considered to be not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{sw, refined}$	0.00166 refined based on prevalence and treatment regimen	µg/L	≥ 0.01 threshold: N
Other concerns (e.g., chemical class)	EAS concern to be determined		(N)

The applicant provided an experimental log K_{ow} study with zuranolone, on log Dow following OECD Guideline 123, slow-stirring method. This study was carried out under the principles established by the OECD, in compliance with the Good Laboratory Practice (GLP) conditions, and the study report was provided.

The log K_{ow} value for Zuranolone was below 4.5 (4.3 at pH 7). Zuranolone has a pKa of 14.6-16.8 and is expected to be neutral at pH values <10. Based on the pKa value and ionisation state of zuranolone, log K_{ow} values at pH 5 and pH 9 are also expected to be 4.3. Therefore, no further assessment of PBT/vPvB was required.

According to the Guideline EMEA/CHMP/SWP/4447/00 rev 1, 2024 for PECsurfacewater calculation in Phase 1, the applicant may use the Fpen default value of 0.01 or a refined the F_{pen} value to calculate PEC_{sw}.

Since the default PEC_{sw} of 0.21 µg/L exceeds the action limit of 0.01 µg/L, a refined value PECsw was calculated. Fpen was refined based on based on prevalence and treatment regiment, taking the worst-case treatment period and worst-case number of treatment repetitions per year into consideration.

The MAA for Zuranolone for the treatment of Postpartum depression (PPD) is for a short course of oral therapy lasting a maximum of 14 days. Since women will not experience more than one full-term pregnancy per year, they will receive a maximum of one course of treatment of Zuranolone.

F_{pen} was refined based on the prevalence of postpartum depression and the treatment regime for the worst-case scenario, resulting in the refined F_{pen} value of 0.00166, which is below the Phase I trigger value of 0.01 µg/L.

Zuranolone has a structure similar to that of steroid hormones, therefore the compound was potentially an EAS. Based on the limited EAS-related effects observed in the mammalian studies in the non-clinical dossier, it could be concluded that zuranolone is not an EAS.

Appropriate disposal of unused pharmaceuticals is considered essential to reduce the environment's exposure. The applicant applied precautionary and safety measures to reduce the risk to the environment and enhance environmental protection on SmPC and PL, according to the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 Rev.1, 2024).

Conclusions on ERA:

$PEC_{surfacewater}$ for zuranolone is below the action limit of 0.01 µg/L. Therefore, zuranolone is not expected to pose a risk to the environment.

A bioaccumulation potential is not indicated based on the log K_{OW} <4.5. Zuranalone is not a PBT or vPvB substance.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The non-clinical pharmacology programme consisted of a series of *in vitro* and *in vivo* studies to characterise target engagement and mechanism of action of zuranolone. The ability of zuranolone to potentiate GABA currents was studied using electrophysiological recordings from cells heterologously expressing different synaptic and extrasynaptic human GABAA receptor subtypes. The effects of zuranolone on phasic (synaptic-mediated) and tonic (extrasynaptic mediated) GABA currents in neurons was assessed using electrophysiological recordings from rodent brain slice preparations. PD target engagement was also studied in rodent models of anticonvulsant, electroencephalographic, anxiolytic-like, and sedative activity consistent with the GABAA receptor PAM mechanism.

Zuranolone was shown to be a $GABA_A$ receptor PAM that potentiates both synaptic (γ subunit-containing) and extrasynaptic (δ subunit containing) $GABA_A$ receptors which is being developed for the treatment of PPD and MDD indications. Zuranolone demonstrated predictable pharmacodynamic activity, including anticonvulsant, anxiolytic-like, and sedative effects, across a broad range of rodent models consistent with its mechanism of action as a $GABA_A$ receptor PAM. In addition, zuranolone modulated network oscillations in multiple frequency bands, including the θ and β frequency ranges as measured by electroencephalography, consistent with observations in humans. Zuranolone demonstrated activity at synaptic and extrasynaptic $GABA_A$ receptors and significantly enhanced both phasic and tonic currents after acute administration as recorded from rat brain slide preparations. Additionally, zuranolone administration suggested an increase in $GABA_A$ receptor surface expression.

Zuranolone exhibited dose-related anticonvulsant, electroencephalographic, anxiolytic-like, and sedative effects consistent with the $GABA_A$ receptor PAM mechanism in rodent models and demonstrated activity in a rat model of oral dyskinesia and status epilepticus, unlike benzodiazepines. EEG studies with zuranolone indicated effects in multiple frequency bands, including β-frequency and θ-frequency; the effects on the θ-frequency in particular are different from what has been reported for benzodiazepines.

Administration of GABAA receptor PAMs can lead to dose-dependent motor impairment and loss of coordination, reflecting the sedative effects expected from strong GABAA receptor potentiation. In line with this, nonclinical data demonstrated dose-related motor effects. However, no impairment was observed at clinically relevant exposure levels. Conversely, clinical findings confirmed that zuranolone may impact psychomotor performance and driving ability. The proposed warnings in section 4.4 of the SmPC, as well as the corresponding sections of the Package Leaflet, adequately address these potential risks.

Reference is also made to SGE-516 (also a NAS GABAA receptor PAM, the Applicant claims a similar primary pharmacology and *in vivo* target engagement profile as zuranolone), which demonstrated antidepressant activity (e.g., altered functional connectivity and decreased θ frequency oscillations) in genetic mouse models of PPD and CUS-induced depression.

Off-target binding and activity of zuranolone was evaluated in various assays against more than 100 targets at a concentration of 10 μM (4096 ng/mL) in most studies. Significant effects were defined as effects differed ≥ 50% from baseline and included binding to sigma and glycine receptors at concentrations much higher than observed in the clinic. No data is presented for these receptors at lower concentrations. Furthermore, zuranolone inhibited TRPV1 function at concentrations much higher than observed in the clinic. Zuranolone did not demonstrate significant effects on the nuclear hormone receptors. Zuranolone exhibited significant (87-89%) and reproducible binding to sigma 2 receptor at 10 μM, a concentration well exceeding the maximum clinical exposure. The Applicant did not provide

sigma 2 binding and functional data with zuranolone at lower, clinically relevant concentrations or adequately justify not presenting such data. Nonetheless, the available nonclinical safety data do not indicate adverse effects that would support sigma 2-mediated toxicity, and no functional consequences have been observed. The literature cited further supports the absence of known safety concerns related to sigma 2 receptor modulation in early clinical development of other compounds.

Although no data is available of sigma-2 receptor binding at clinically relevant zuranolone concentrations and it cannot be excluded that the MoA of zuranolone involves sigma-2 receptor modulation, this lack of knowledge does not impact the benefit/risk evaluation of zuranolone.

Based on a human plasma protein binding value of ≥ 99.5%, the applicant calculated that an unbound concentration of 10 or 12 µM (4096 to 4915 ng/mL) represents a zuranolone plasma concentration equivalent to 819,200 to 983,000 ng/mL. However, the % zuranolone binding to plasma proteins was evaluated over a concentration range of 30-500 ng/mL (Study SSN-02733) and the % plasma binding at 30-500 ng/mL versus 819,200-983,000 ng/mL zuranolone cannot be assumed to be similar. However, even in disregard of plasma binding, these receptor/cell-based effects were noted at concentrations significantly higher than the clinically relevant plasma concentration of 94.5 ng/mL.

Central nervous system (CNS) safety pharmacology-related effects of zuranolone included decreased activity, ataxia, hypersensitivity to touch and/or sound, and impaired righting reflex. Reversible, transient neurobehavioural effects were noted in the FOB at 4 to 8 hours postdose. These effects were observed at 3-fold the mean human C_{max} exposure at 50 mg. These neurobehavioral effects, including some at clinically relevant exposure, are considered target-related and in line with the primary MOA of zuranolone.

The non-clinical study to evaluate the potential of zuranolone to inhibit hERG channel-mediated potassium currents showed some shortcomings, including regression analysis based on too few datapoints, inclusion of datapoints that failed to meet the acceptance criterion for recovery following application, and extrapolation of free plasma concentration (similar as done in secondary pharmacology studies). Nevertheless, at the highest concentration evaluated (3 µM) no significant hERG channel inhibition was observed (23%), while this was sufficiently higher than the clinical Cmax. Furthermore, assessment of CV function in dogs indicated that zuranolone had minor effects on blood pressure and heart rate, while no effects on QTc at exposures was noted at levels up to 7.1-fold the mean human Cmax exposure at 50 mg. The lack of effect of zuranolone on QTc interval was confirmed in the clinic (Study 217-CLP-112). Thus, zuranolone is unlikely to have a pharmacologically adverse effect on the cardiovascular system from a non-clinical perspective. Administration of zuranolone to rats was associated with minor, reversible changes in indices of pulmonary function consistent with its primary mechanism of action ($GABA_A$ receptor modulator). These minor effects were seen at 3-fold the mean human C_{max} exposure at 50 mg.

In PD drug interaction evaluations, zuranolone showed the potential for positive interaction with the $GABA_A$ receptor modulators diazepam and pentobarbital, and the potential for negative interaction with propofol using patch-clamp techniques. *In vivo*, zuranolone and diazepam demonstrated the potential for positive interaction when co-administered in two rodent seizure models. Given zuranolone's outpatient use and the controlled setting of propofol administration, the potential interaction is manageable within standard anaesthetic practice. Co-administration of CNS depressants with anaesthetics is common and routinely accounted for by clinicians.

Pharmacokinetics

Nonclinical PK testing in mice, rats, and/or dogs demonstrated a low to moderate rate of clearance, a moderate volume of distribution indicative of uptake into tissues, generally dose linear PK with no

substantial accumulation with repeat dosing, high protein binding in plasma with no preferential partitioning to the cellular component of blood, rapid and high distribution to the brain, extensive metabolism, and excretion by both renal and hepatobiliary routes. In clinical studies, zuranolone demonstrated oral bioavailability and dose-linear PK with no obvious sex-related differences, minor accumulation with repeat dosing, high protein binding, extensive metabolism, and excretion via the renal and hepatobiliary routes. In general, the nonclinical PK of zuranolone is consistent with observations in humans, with the exception of gender differences in Rat studies. The effect of gender on zuranolone oral exposure was assessed in male and female Sprague Dawley rats in Study SSN-01240. Across the evaluated dose range of 1 to 10 mg/kg, female rats showed a 6- to 10-fold higher mean AUC_{last} value and a 2 to 4-fold higher mean C_{max} value, compared to males. These exposure differences can be attributed to a higher clearance rate of zuranolone in male rats. A concomitant increase in t½ was observed in females. In the 3-month study (Study SSN-01403), while male rats received doses that were approximately 5- to 6-fold higher than female rats on a mg/kg/day basis, systemic exposure (in terms of AUC_{last} and C_{max} values) to zuranolone was similar between genders in each treatment group (low- to high-dose levels). Cytochrome P450 phenotyping in humans suggests that CYP3A is responsible for a significant fraction of metabolism. It is plausible that rat CYP3A18, which is most closely analogous to CYP3A5 in humans [Hammer 2021], predominates clearance in the species. CYP3A18 is known to have higher expression (up to 25x in liver [Robertson 1998]) in males than in females, which would result in the observed sex difference in rat oral exposure. Since the underlying cause is based on normal physiology, no adjustment to exposure safety margins is required.

The distribution of zuranolone in the placenta and excretion in milk were not provided.

Although metabolism was extensive in humans, rats, and dogs, there were some differences in the biotransformations observed. Zuranolone was metabolised in mice, rats, dogs, and humans with no plasma human metabolites present at greater than 10% of total drug-related material. All human metabolites detected at greater than 1% of drug, were also detected in rat or dog plasma. Mouse metabolites were formed from single or multiple oxidations of the steroid rings, the cyano-pyrazole moiety and/or the C3-methyl group, and dehydrogenation of the steroid rings and sulfation reactions. The dog metabolite profile was the result of the similar biotransformations observed in mice as well as additional metabolites generated from N dealkylation and glucuronidation reactions. Rats and humans exhibited the greatest number of metabolites, with the majority of the metabolites derived from the same biotransformations present in mice and dogs: single or multiple oxidations on the steroid rings and/the cyano-pyrazole moiety, dehydrogenation of the steroid rings, sulfation, N dealkylation and glucuronidation, with additional metabolites generated by epimerization of the C3-methyl, elimination of the C3-alcohol to produce the available olefins, and reduction of the C20 ketone. In all species, the majority of the metabolites were the result of multiple biotransformations reactions.

Human studies identified CYP3A4 as the primary enzyme responsible for zuranolone's metabolism. *In vitro* studies suggest minimal risk of drug-drug interactions through CYP inhibition or induction, with no significant time- or metabolism-dependent inhibition observed. Minor inhibition of enzymes such as CYP2C8, CYP2B6, and CYP2D6 by certain metabolites was noted, but these effects were not clinically relevant based on [I]/Ki ratios. Induction studies suggested some potential for CYP3A4 and CYP2B6 induction, but the levels required for such effects were far above clinically observed concentrations, indicating a low risk of clinically significant interactions. Zuranolone was evaluated for the potential to interact with drug transporters *in vitro* and no significant interaction was found. In the context of expected clinical plasma levels and plasma protein binding, zuranolone does not show the potential to cause a DDI via inhibition or induction of CYP enzymes or drug transporters.

Zuranolone metabolites M125 (SGE-07672), M117 (SGE-02369), M135 (SGE 03632), and M136 (SGE-03633) were evaluated for their potential to inhibit CYP enzymes and, taking into account physiologic

parameters and anticipated clinical concentrations, these metabolites are not likely to precipitate a DDI.

Toxicology

The non-clinical safety profile of zuranolone has been addressed in a complete set of toxicological studies.

The toxicological assessment is based on in single and repeated dose oral (gavage) toxicity studies in rats and dogs, *in vitro* and *in vivo* genotoxicity tests, reproduction and developmental toxicity studies in rabbits and/or rats, juvenile toxicity studies using rats, carcinogenicity studies in rats and transgenic mice, and studies to assess abuse liability and dependence potential.

Across all toxicological studies, sedation was the primary and dose-limiting treatment-related effect, consistent with the anticipated exaggerated pharmacological activity of zuranolone via the $GABA_A$ receptor. The severity and duration of sedation showed a dose-response relationship with evidence of tolerance occurring with continued systemic exposure. In general, the dose-dependent sedation-related clinical signs in pivotal toxicity studies included, but were not limited to, ataxia, decreased activity, impaired equilibrium, and tremors. At higher exposures associated with severe sedation, laboured respiration, prostrate body position, transient decreased body temperature, pedalling, twitches, and salivation were noted in one or both species.

In addition to expected effects related to the exaggerated pharmacological activity of zuranolone, the main potential safety findings were identified in repeat dose studies and reproductive and developmental studies conducted in Sprague Dawley rats.

Single dose toxicity studies were performed in rats in dogs. These all resulted in sedation and accompanying effects. Since zuranolone is not meant for single use, these studies are not considered as pivotal to the assessment.

Repeated dose toxicity was performed in mice, rats and dogs. The mouse study is a preliminary study for the transgenic mouse carcinogenicity study. Doses of up to 200 mg/kg/day, the highest dose tested, were well tolerated for 4 weeks. Target organ was the liver. Rats were dosed up to 6 months, with doses up to 30 mg/kg/day in males and 5 mg/kg/day in females. These disparate dose ranges were selected due to sex differences and to align exposure between male and female dose groups. Pharmacology mediated sedation and accompanying effects were seen in males at exposure multiples of around 4 in males and 6.5 in females. After 3 months of dosing there was an increase in liver weight, and after 6 months of dosing also an increase in thyroid weight at the high dose in both sexes. There were no histopathological findings related to this increased weight, and therefore it is not considered adverse or of relevance for humans. In dogs, a 3-month and a 9-month pivotal study was performed with doses up to 2.5 mg/kg/ml, resulting in exposures of 9.4-fold the clinical exposure. In the 3-month study, also ECGs were included. Sedation was seen at exposures below the clinical exposure, and tremors were seen at about 5.5-fold the clinical exposure. Higher doses were not achievable due to the sedative effect, but is considered sufficient. The adverse clinical signs/early mortality noted in individual animals in the 3-month and 9-month dog studies appears consistent with an acute withdrawal-type response following prolonged administration at high dose levels to dogs: i) at the highest dose tested (2 mg/kg/day) in the 3-month study, a single male was found dead on Day 61 prior to dosing. This animal had received 59 total doses. During the 10 days prior to death (Days 52 to 61), transient clinical signs, including tonic convulsions and periods of prolonged sedation, were noted for this animal; ii) at the highest dose tested (2.5 mg/kg/day) in the 9-month study, mortality was observed in a female on Day 30. This animal received its last dose on Day 29, and was observed to have tonic and clonic convulsions prior to dosing on Day 30. Another single female animal was found

dead on Day 276 during the recovery period (4 days after receiving its last dose). Overall, the repeated dose studies are considered adequate to inform on risk for patients.

A complete assessment of reproductive and developmental toxicity program has been conducted.

Fertility in male rats, doses 0, 3, 10, 30 mg/kg/day: sedation from 10 mg/kg/day with reduced body weight gain and food consumption, and therefore less mating. No direct effect on male fertility, up to an AUC 3540 ng.h/ml which is 2.9-fold the human exposure. The exposure margin is low, but no concern is raised. Fertility in female rats, doses 0, 1, 3, 10 mg/kg/day: sedation from 3 mg/kg/day with reduced body weight gain and food consumption, but no effect on mating. No effect on female fertility up to AUC 11.000 ng.h/ml which is 9-fold the human exposure.

EFD in rats, doses 0, 2.5, 8.5, 22.5 mg/kg/day: Sedation at all doses, severe at 22.5 dose with reduced body weight gain and food consumption. Reduced foetal weight at the high dose. The number of foetuses with visceral malformations was increased at the high dose only (2 from 1 litter). The number of foetuses with skeletal malformations is increased in the mid dose (3 from 2 litters) and high dose (6 from 5 litters). The applicant argues that the malformations in the mid dose are not treatment-related, since there is no dose response. Although this might be the case for most individual malformations because of low incidence, there is clearly a dose response for the total of skeletal malformations. The effect on the foetuses could be related to the PD effect in the dams, but a direct effect of zuranolone cannot be excluded. The NOAEL for foetal toxicity is therefore the low dose of 2.5 mg/kg/day and not the mid dose of 7.5 mg/kg/day as suggested by the applicant. AUC at 2.5: 3710 ng.h/ml, and AUC at 7.5: 9380 ng.h/ml. This corresponds to a safety margin of 3 at the NOAEL and an exposure margin of 7.7 at the LOAEL.

An additional EFD study in mice was submitted at D120. Sedation was noted throughout the dosing period (GD 6–15) at all dose levels, with severity increasing with increasing dose. At the high dose, there was a decrease in body weight gain of the dams. Fetuses in the mid and high dose groups had lower mean body weights (around 5 and 17% lower than controls respectively), which coincided with incomplete ossification at the high dose, and cleft palate at the mid dose (2 foetuses out of 2 litters) and the high dose (10 foetuses out of 3 litters). These effects are likely related to the lower foetal body weights, since the cleft palates were seen in the foetuses with the lowest weight. Clinical relevance cannot be excluded. Although the incidence of effects is low in the mid dose, there is clearly a dose-related effect, which cannot be ignored. The NOEAL is therefore set at the low dose instead of the mid dose as suggested by the applicant. This results in a safety margin of 1.9 at the NOAEL, and an exposure margin of 5 at the LOAEL.

Overall, with the available data from the previous round, there is evidence from 2 species in EFD studies, mouse and rat, that there is a risk for skeletal malformations. The applicant argues that a risk in the first trimester of pregnancy is low, since no adverse findings were seen in the FEED study. However, the outcome of the EFD studies are still relevant for the later stage of the human first trimester and beginning of second trimester. It cannot be excluded that women may become pregnant again whilst taking zuranolone. The risk is mitigated by the advice to women of childbearing potential to use contraception, and a contraindication during pregnancy. In a juvenile rat study with a single dose at PND 7, which corresponds to brain development at the end of the third trimester in humans, apoptotic neurodegeneration in one area of the brain (subiculum) in both males and females was seen. The safety margin is low (1.4-fold at NOEAL). This risk is sufficiently mitigated by the change in indication, which now only includes women after childbirth.

EFD in rabbits, doses 0, 25, 125, 500 mg/kg/day: Sedation at all doses, severe at the high dose with reduced body weight gain and food consumption. There were no effects on the foetus, therefore the NOAEL is the high dose. However, the exposures to zuranolone were very low and did not increase with increasing dose. The highest exposure was in the mid-dose group with an AUC of 663 ng.h/ml,

which is far below the clinical exposure. Rabbit does not appear to be an appropriate species to test the reproductive toxicity of zuranolone and these results do not mitigate the risk identified in the rat study.

PPND in rats, doses 0, 1, 4, 10 mg/kg/day: Sedation at all doses, moderate from the mid dose. Slight reduction in body weight gain. There were litter losses at the mid and high doses resulting in a reduced viability index. After delivery, there was an increase in pup mortality from the mid dose, with no pups surviving in the high dose at LD20. Pup weight was lower at these doses, and they didn't appear to be nursing well. Body weight of the F1 generation (mid dose) remained lower until the end of the study, however there was no effect on the subsequent reproductive potential of F1. The NOAEL for postnatal development was the low dose of 1, resulting in an AUC of 2420 ng.h/ml, 2-fold higher than clinical exposure, which is low. The cause of pup mortality is not completely clear, it could be due to sedation of the pups which caused them not to nurse, or due to another direct effect from the zuranolone exposure in utero. Transfer to milk is not measured in animals. Data from a clinical lactation study indicate that zuranolone is present in low levels in human breast milk. The calculated maximum daily relative infant dose (RID) was <1% when calculated using mean concentration in human breast milk. Since the risk for the newborn is unknown it is recommended to not breastfeed, unless the benefits of breastfeeding outweigh the potential risk (see Clinical section on lactation study).

The juvenile toxicity study in rats from PND 22 to 71 has been provided and summarized above. The safety profile is consistent with that observed in adult animals.

The primary pharmacological mode of action for zuranolone is through the positive allosteric modulation of GABAa receptors, a receptor system with documented abuse potential. Therefore, the abuse potential was investigated. In a study with cocaine-trained rats, there appeared to be no abuse potential of zuranolone. Likewise, no withdrawal symptoms were seen in rats at doses up to 4.3-fold higher than human exposure based on C_{max}, and only slight withdrawal in the high dose group at 7.4-fold the human exposure. It is concluded that the nonclinical in vitro and in vivo abuse potential data collected suggest that the abuse potential of zuranolone is likely less than or, at most, similar to that of benzodiazepines. Zuranolone is not genotoxic. Carcinogenicity was studied in mouse and rat. In both species the exposure was limited (around 4-fold human exposure in mouse and 4 to 5-fold in rats) but higher doses were not achievable due to pharmacological effects of sedation. At these exposures, no increase in tumour incidence was observed in either species, as compared to control groups. Carcinogenic risk of zuranolone is low, and not relevant for the current indication as the duration of treatment is short term.

Ecotoxicology/environmental risk assessment:

Zuranolone refined PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. As such, zuranolone is not expected to pose a risk to the environment.

However, while zuranolone targets GABAA receptors, it has a structure similar to steroid hormones and could potentially be an endocrine active substance (EAS). For EAS the action limit does not apply, and a Phase II risk assessment should always be performed. It is therefore necessary to determine if zuranolone is a potential EAS. The Applicant investigated the potential for zuranolone to be endocrine active using screening-level receptor transactivation studies with twenty nuclear receptors, including oestrogen (α and β), androgen and progesterone receptors. Zuranolone was tested at concentrations

up to 10 µM and did not activate any of the receptors above a threshold of a 5-fold increase in luminescence, which was considered pharmacologically inconsequential.

The applicant was requested to provide additional information to conclude that Zuranolone is not a potential EAS, for example by demonstrating the absence of reproductive effects using the available mammalian studies on reproductive toxicity and repeated dose toxicity from the non-clinical part of the dossier. The applicant summarised the mammalian studies. In female rates, a transient effect on estrus cycling was shown in the first 10 days of dosing. In transgenic mice, which are not intact animals for EAS assessment, hyperplasia was shown in the mammary glands and in corpora lutea. Based on these limited effects, zuranolone is not considered to exhibit EAS properties. Therefore, a further assessment was not warranted.

2.5.7. Conclusion on the non-clinical aspects

Zuranolone, a $GABA_A$ receptor PAM under development for PPD and MDD, exhibits a predictable pharmacodynamic profile with anticonvulsant, anxiolytic-like, and sedative effects in rodent models. Its mechanism of action involves potentiation of both synaptic and extrasynaptic $GABA_A$ receptors, leading to enhanced phasic and tonic currents. The compound also affects network oscillations in multiple frequency bands, including the θ and β ranges, with distinct effects compared to benzodiazepines. Safety pharmacology evaluations indicated minor, reversible CNS effects and negligible impact on cardiovascular and pulmonary functions at therapeutic exposure levels. Notably, zuranolone showed potential positive interactions with diazepam and pentobarbital, while exhibiting a negative interaction with propofol. Overall, zuranolone demonstrates a favourable pharmacodynamic profile for the clinical treatment of PPD and MDD.

The nonclinical pharmacokinetic (PK) data for zuranolone in mice, rats, dogs, and humans demonstrate consistent properties, including dose-linear PK, extensive tissue distribution (especially to the brain), high protein binding, and metabolism leading to elimination via renal and hepatobiliary routes. While biotransformation pathways differed among species, most metabolites were shared, indicating good translational relevance.

In humans, CYP3A4 is the primary enzyme for zuranolone metabolism, with minimal risk of drug-drug interactions (DDIs) via inhibition or induction of CYP enzymes or transporters. Although some metabolites showed minor inhibition of certain enzymes, these effects were not clinically significant.

The non-clinical safety profile of zuranolone has been addressed in a complete set of toxicological studies. Data is adequate to support the use of zuranolone in the treatment of postpartum depression, according to the recommended dose of zuranolone, 50 mg once daily, for 14 days. The main toxicology findings are related to sedation of zuranolone and therefore PD-related.

The refined $PEC_{surfacewater}$ for zuranolone is below the action limit of 0.01 µg/L and zuranolone is not a PBT nor a vPvB substance as the log K_{ow} does not exceed 4.5.

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.

Table 3. **Tabular overview of clinical studies**

Type of Study	Study Identifier	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Participants Dosed	Healthy Participants or Diagnosis	Duration of Treatment	Study Status[a]; Type of Report
5.3.1 Reports of Biopharmaceutic Studies								
5.3.1.2 Comparative BA and Bioequivalence Study Reports								
Relative BA and Food Effect	217-CLP-103	To assess the safety and tolerability of zuranolone capsules in healthy participants	Phase 1, randomized, open-label, four-period, two-sequence, crossover relative BA study	Period 1: Single 30-mg dose of zuranolone ProFill capsules or a single 30-mg dose of zuranolone oral solution on Day 1, administered in the fasting state. Period 2: Participants crossover to the dose form that they did not receive in Period 1, a single 30-mg dose of zuranolone oral solution or a single 30-mg dose of zuranolone ProFill capsules administered in the fasting state. Period 3: Single 30-mg dose of zuranolone ProFill capsules administered with a high-fat meal on Day 15. Period 4: Single 30-mg dose of zuranolone ProFill capsules administered with a standard meal on Day 22.	21	Healthy male and female participants, aged 18 to 55 years (inclusive)	Four single 30-mg doses of zuranolone over a 4-week period (one dose each week)	Complete; Full
Relative BA and Food Effect	217-CLP-109	To evaluate the relative BA of zuranolone 30 mg administered as an auto-filled capsule (Automated Capsule) compared to zuranolone 30 mg administered as a manually filled capsule (ProFill Capsule) under fasted and fed conditions	Phase 1, open-label, nonrandomized, parallel-group, 5-treatment study to assess the relative BA of the Autofill capsule compared with ProFill capsule and food effect of zuranolone PK	Single dose of zuranolone Automated capsules 30 mg or zuranolone ProFill capsules 30 mg administered orally with food or in the fasted state	60 (12 per treatment group)	Healthy male and female participants, aged 18 to 55 years (inclusive)	Single dose	Complete; Full
5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials								
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies								
Metabolism	SSN-03938	Metabolite profiling and identification in plasma, urine, and faeces (single dose)	—	zuranolone	8	Healthy male participants aged 19 to 55 years (inclusive)	Single dose in Study 217-CLP-105	Completed; Full
Metabolism	SSN-03843	Metabolite profiling and identification in plasma (single dose)	—	zuranolone	8	Healthy male participants aged 19 to 55 years (inclusive)	Single dose in Study 217-CLP-105	Completed; Full
Metabolism	SSN-02180	Metabolite profiling and identification in plasma	—	zuranolone	48	Healthy male and female participants, aged 18 to 55 years (inclusive)	Cohort 1 through Cohort 3: 7 days (Study 217-CLP-102)	Completed; Full
Metabolism	SSN-03660	Metabolite profiling and identification in plasma and urine (single dose)	—	zuranolone	8	Healthy male participants aged 19 to 55 years (inclusive)	Single dose in Study 217-CLP-105	Completed; Full

Metabolism	SSN-03661	Metabolite profiling and identification in plasma, urine, and faeces (single dose)	—	zuranolone	8	Healthy male participants aged 19 to 55 years (inclusive)	Single dose in Study 217-CLP-105	Completed; Full
Metabolism	SSN-03760	Metabolite profiling and identification in plasma (single dose)	—	zuranolone	8	Healthy male participants aged 19 to 55 years (inclusive)	Single dose in Study 217-CLP-105	Completed; Full
Metabolism	SSN-03219	Metabolite profiling and identification in plasma and urine (single dose)	—	zuranolone	8	Healthy male participants aged 19 to 55 years (inclusive)	Single dose in Study 217-CLP-105	Completed; Full
Metabolism	SSN-03234	Metabolite profiling and identification in urine	—	zuranolone	8	Healthy male participants aged 19 to 55 years (inclusive)	Single dose in Study 217-CLP-105	Completed; Full
5.3.3 Reports of Human Pharmacokinetic (PK) Studies								
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports								
PK and Safety	217-CLP-101	To determine the MTD of zuranolone oral solution in healthy participants aged 18 to 55 years	Phase 1, 4-part study Part 1: Randomized, double-blind, placebo-controlled SAD design in fasted participants Part 2: Open-label food effect Part 3: Randomized, double-blind, placebo-controlled, 2-period crossover using EEG in fasted participants	Single doses of zuranolone oral solution Part 1: 9 cohorts of 8 participants (6 active: 2 placebo) received single doses of 0.25, 0.75, 2.0, 5.5, 11, 22, 44, and 66 mg, followed by 55 mg for Cohort 9 after reaching stopping criteria (sedation) at 66 mg Part 2: 4 participants from Part 1 received a single dose of 22 mg (50% of MTD) under fed conditions Part 3: Cohort A. 8 participants received a single dose of 22 mg (50% of MTD)	94	Parts 1-3: Healthy male and female participants; aged 18 to 55 years (inclusive) Part 4 only: Participants with ET who were otherwise healthy, aged 18 to 75 years (inclusive)	All participants: single dose zuranolone Food effect cohort: additional single dose zuranolone in a fed condition EEG cohorts: single doses zuranolone and placebo	Complete; Full
			Part 4: single open-label dose in fed participants	Cohort B 7 participants received a single dose of 55 mg (MTD) Part 4: 6 participants received a single dose of 55 mg (MTD)				
Safety, PK, and DDI	217-CLP-102	To determine the safety and tolerability of multiple doses of zuranolone oral solution in healthy volunteers aged 18 to 55 years	Phase 1, 2-part, MAD study followed by DDI study Part 1: Randomized, double-blind, placebo-controlled MAD study Part 2: Open-label, DDI study	Three cohorts of 12 participants (9 active: 3 placebo) were dosed as follows: •15 mg zuranolone oral solution each morning for 7 days •35 mg zuranolone oral solution each morning for 7 days •30 mg zuranolone oral solution each morning for 7 days and then 7 days of evening dosing after washout of at least 7 days A fourth cohort of 12 participants was dosed as follows: •Day 1: Bupropion 100 mg •Day 2: Simvastatin 20 mg •Days 3 to 9: Open-label zuranolone 30 mg once daily •Day 10: Simvastatin 20 mg •Day 11: Bupropion 100 mg	48	Healthy male and female participants, aged 18 to 55 years (inclusive)	Cohort 1 through Cohort 3: 7 days; DDI Cohort: 11 days	Complete; Full

ADME	217-CLP-105	To investigate the route(s) of elimination and the mass balance of zuranolone based on total radioactivity concentrations in urine and fecal samples; To quantitate total radioactivity concentration equivalents and PK in plasma and whole blood after a single dose of 30-mg (~100 µCi) of [^{14}C]zuranolone; To characterize the PK of zuranolone and its metabolites in plasma; To examine the metabolism of zuranolone in humans and identify major metabolites in plasma, urine, and fecal specimens; To determine the percentage of ^{14}C radioactivity associated with cellular components in whole blood over time (e.g., whole blood:plasma partitioning ratio)	Phase 1, open-label, single-dose, single-period study	Single dose of 30-mg (~100 µCi) [^{14}C]zuranolone oral solution	8	Healthy male participants aged 19 to 55 years (inclusive)	Single dose	Complete; Full
5.3.3.2 Patient PK and Initial Tolerability Reports								
PK and Safety	217-CLP-118	To investigate the PK of zuranolone in adolescents (ages 12 to 17 years) with MDD	Phase 1, open-label study	50 mg zuranolone (body weight 54 kg or greater) or 40 mg zuranolone (body weight less than 54 kg) administered to first 10 enrolled participants. Remaining participants to receive 40 mg zuranolone with down titration to 30 mg if 40 mg is not tolerated. Each participant will receive oral investigational product once daily for 14 consecutive days.	18 participants planned, with a minimum of 12 post-pubertal females aged 15 to 17 years of age planned.	Male and female participants with MDD, aged 12 to 17 years	14 days	Active
5.3.3.3 Intrinsic Factor PK Study Reports								
PK in Special Populations (Renal Impairment)	217-CLP-107	To evaluate the PK of a single dose of zuranolone in participants with renal impairment and in participants with normal renal function	Phase 1, open-label, single-dose study	Single dose of zuranolone ProFill capsule 30 mg	24 (n = 18 with renal impairment)	Male and female participants, including healthy participants and participants with mild, moderate, or severe renal impairment, aged 18 to 80 years (inclusive)	Single dose	Complete; Full
Ex-vivo plasma protein binding	8393166	Quantify human plasma protein binding in participants with normal, mild, moderate, or severe renal impairment (Study 217-CLP-107)	—	Single dose of zuranolone ProFill capsule 30 mg	24 (n = 18 with renal impairment)	Male and female participants, including healthy participants and participants with mild, moderate, or severe renal impairment, aged 18 to	Single dose	Completed; Full

						80 years (inclusive)		
PK in Special Populations (Hepatic Impairment)	217-CLP-108	To evaluate the PK of a single dose of zuranolone in participants with hepatic impairment and in participants with normal hepatic function	Phase 1, open-label, single-dose study	A single dose of zuranolone ProFill capsule 30 mg for healthy participants and mild and moderate hepatic impairment cohorts with food. A single dose of zuranolone ProFill capsule 20 mg for severe hepatic impairment cohort with food.	24 (18 with hepatic impairment)	Male and female participants, including healthy participants and participants with mild, moderate, or severe hepatic impairment, aged 18 to 75 years (inclusive)	Single dose	Complete; Full
Ex-vivo plasma protein binding	8393167	Quantify human plasma protein binding in participants with normal, mild, moderate, or severe hepatic function (Study 217-CLP-108)	—	A single dose of zuranolone ProFill capsule 30 mg for healthy participants and mild and moderate hepatic impairment cohorts with food. A single dose of zuranolone ProFill capsule 20 mg for severe hepatic impairment cohort with food.	24 (18 with hepatic impairment)	Male and female participants, including healthy participants and participants with mild, moderate, or severe hepatic impairment, aged 18 to 75 years (inclusive)	Single dose	Completed; Full
PK in Special Populations (Lactating Women)	217-CLP-114	To evaluate the extent of zuranolone transfer into breast milk in lactating women	Phase 1, open-label study	Zuranolone capsules 30 mg once daily in the evening for 5 consecutive days	15	Healthy female participants at least 12 weeks' postpartum, lactating and pumping breast milk or actively breastfeeding at least 3 times per day, aged 18 to 45 years (inclusive)	5 days	Complete; Full
Ex-vivo plasma protein binding	8415515	Quantify human plasma protein binding in healthy lactating women (Study 217-CLP-114)	—	Zuranolone capsules 30 mg once daily in the evening for 5 consecutive days	15	Healthy female participants at least 12 weeks' postpartum, lactating and pumping breast milk or actively breastfeeding at least 3 times per day, aged 18 to 45 years (inclusive)	5 days	Completed; Full
PK in Special Populations (Elderly)	217-CLP-115	To assess the impact of age and sex on the PK of zuranolone in healthy elderly and non-elderly adults	Phase 1, open-label, parallel-design, multiple-dose study	Zuranolone capsules 50 mg once daily with food for 5 consecutive days Non-elderly participants who tolerated the 50-mg dose received a single higher dose (up to 100 mg) of zuranolone on Day 6	36 (18 per age cohort)	Healthy male and female participants, including elderly (aged ≥ 65) and nonelderly (aged 18 to 45 years [inclusive])	Elderly participants: 5 days Non-elderly participants: 6 days	Complete; Full
Safety and PK	1805A3711 (conducted by Shionogi & Co., Ltd [a development partner for zuranolone])	To evaluate the safety and tolerability after single and multiple dose administration of S-812217 in Japanese healthy adults and Japanese healthy elderly	Phase 1 Part A: randomized, double-blind, placebo-controlled study Part B: randomized, open-label, 2-period crossover study Part C: randomized, double-blind, 3-period crossover study	Part A: Japanese healthy adults: S-812217 (zuranolone) capsule 10, 20, 30 mg. Single dose and daily for 7 days in the fed state. White healthy adults: S-812217 (zuranolone) capsule 20, 30 mg. Single dose and daily for 7 days in the fed state. Part B: 2 single doses of S-812217 (zuranolone) capsules 30 mg, under fasted and fed conditions. Part C: 10, Single dose S-812217 (zuranolone) capsules 30 mg in the fed state.	Part A: 72 Part B: 12 Part C: 8	Healthy male and female Japanese or white participants, aged 20 to 55 years (inclusive) Healthy Japanese elderly participants, aged 65 to 75 years (inclusive)	Part A: Single dose once (for 1 day) and multiple dose 7 times (for 7 days) Part B: 2 days Part C: 3 days	Complete; Full
5.3.3.4 Extrinsic Factor PK Study Reports								
PK and DDI	217-CLP-106	To evaluate the effect of rifampin (strong CYP3A inducer) and itraconazole (strong CYP3A inhibitor) on the PK of zuranolone	Phase 1, open-label, 2-part, 2-period, fixed-sequence study	Part A: 2 doses of zuranolone ProFill capsules 30 mg (on Days 1 and 11) and a once-daily dose of rifampin 600 mg for 7 days (Days 4 to 10). Part B: 2 doses of zuranolone ProFill capsules 20 mg (on Days 1 and 9) and a daily dose of itraconazole 200 mg for 8 days (Days 5 to 12).	Part A: 16 Part B: 16	Healthy male and female participants, aged 18 to 55 years (inclusive), with a body mass index between 18 and 30 kg/m^2 and weight ≥ 50 kg	Part A: 11 days Part B: 12 days	Complete; Full

5.3.4 Reports of Human PD Studies								
5.3.4.1 Healthy Subject PD and PK/PD Study Reports								
Human Abuse Potential	217-CLP-110	To assess the abuse potential of single oral doses of zuranolone relative to placebo and alprazolam in nondependent, recreational CNS depressant users	Phase 1 Part A (Dose selection): Randomized, double-blind, placebo-controlled, dose escalation parallel groups Part B (Treatment Phase): Randomized, double-blind, active- and placebo-controlled, 6-way crossover	Part A: Single dose of zuranolone capsule (60 mg, 80 mg, or 90 mg) or placebo Part B: Qualification phase: single dose of alprazolam 2 mg and placebo separated by ~24 hours Treatment Phase: 3 doses of zuranolone capsules (30 mg, 60 mg and 90 mg), 2 doses of alprazolam (1.5 mg and 3 mg), and 1 dose of placebo, each separated by 7 days	Part A: 24 Part B: 75	Male and female CNS depressant users who used CNS depressants for recreational, nontherapeutic reasons and who were otherwise generally healthy, aged 18 to 55 years (inclusive)	Part A: Single dose Part B: 3 doses of alprazolam, 3 doses of zuranolone, and 2 doses of placebo each separated by 7 days	Complete; Full
PD, PK, and DDI	217-CLP-111	To evaluate the neurocognitive effects of multiple doses of zuranolone administered alone and in combination with ALP (Part A) or EtOH (Part B)	Phase 1, 2-part, randomized, double-blind, placebo-controlled, 2-period crossover study with and without a single dose of ALP (Part A) or EtOH (Part B)	Part A and Part B: zuranolone capsules 30 mg or placebo administered once daily for 6 days. Part A: ALP placebo and ALP 1 mg administered approximately 4 hours following administration of Zuranolone or placebo on Day 5 and Day 6, respectively, in Periods 1 and 2 Part B: EtOH placebo and EtOH 0.7 g/kg (men) and 0.6 g/kg (women) administered approximately 4.5 hours following administration of zuranolone or placebo on Day 5 and Day 6, respectively, in Periods 1 and 2	Part A: 25 Part B: 24	Healthy male or female participants with a habitual bedtime between 9 pm and 12 am (midnight), aged 18 (Part A) or 21 (Part B) to 55 years (inclusive)	6 days of zuranolone and 6 days of placebo separated by a minimum 7-day washout; Part A: Single dose of placebo for ALP (Day 5) and a single dose of ALP (Day 6) in each of the 2 periods; Part B: and a single dose of placebo for EtOH (Day 5) and a single dose of EtOH (Day 6) in each of the 2 periods	Complete; Full
PD, PK	217-CLP-112	To evaluate the effect of zuranolone on the Fridericia-corrected QT interval	Phase 1, double-blind, double-dummy, placebo- and active-controlled, parallel group (with nested cross over for moxifloxacin), multiple-dose TQT study	Group 1: zuranolone capsules 50 mg and 100 mg and/or placebo once daily for 9 days (placebo on Day 1 and Day 9; zuranolone on Day 2 to Day 8) Group 2A/2B: zuranolone placebo for 9 days, active reference therapy, (moxifloxacin), or reference therapy placebo single dose crossover only on Day 2 and Day 9	Group 1: 32 Group 2A: 16 Group 2B: 16	Healthy male and female participants, aged 18 to 55 years (inclusive)	Group 1: zuranolone 50 mg capsule once daily Days 2-7; zuranolone 100 mg Day 8 Placebo for moxifloxacin Group 2: Placebo for zuranolone Day 1 to Day 9 Single dose of moxifloxacin 400 mg or placebo on Day 2 and Day 9 (per nested crossover)	Complete; Full
Safety and PD	217-CLP-113	To assess the next-day residual effects of zuranolone relative to placebo on simulated driving performance using the Country Vigilance Divided Attention driving scenario on the Cognitive Research Corporation Driving Simulator - MiniSim	Phase 1, randomized, double-blind, active- and placebo-controlled, 4-arm, 4-period crossover study	Treatment A: zuranolone capsules 30 mg on Days 1 through 5 Treatment B: zuranolone capsules 30 mg on Days 1 through 4, and zuranolone 60-mg on Day 5 Treatment C: zopiclone 7.5 mg on Day 1 and Day 5 Treatment D: placebo on Days 1 through 5	Total: 60: 4 groups of 15 participants per sequence	Healthy male and female participants, aged 21 to 65 years (inclusive)	5 days of inpatient treatment separated by 7 to 14 days washout, 4-way crossover sequences including zuranolone regimens or placebo or zopiclone; for 4 different regimens and a total of 20 days of treatment	Complete; Full

PK, PD, and DDI	217-CLP-116	To evaluate the neurocognitive effects of multiple doses of zuranolone 50 mg administered alone and in combination with a single dose of ALP (Part A) or EtOH (Part B)	Phase 1, 2-part, randomized, double-blind, placebo-controlled, 2-period crossover study	Parts A and B: zuranolone capsules 50 mg once daily for 9 days and placebo once daily for 9 days, separated by washout Part A: 2 doses of alprazolam and 2 doses of placebo for ALP on Day 1 and Day 5, and either of the two on Day 9 Part B: 2 doses of EtOH and 2 doses of placebo for EtOH on Day 1 and Day 5, and either of the two on Day 9	Part A: 24 Part B: 25	Healthy male and female participants Part A: aged 18 years and older Part B: aged 21 years and older	All participants: 9 days for zuranolone and 9 days for placebo separated by a minimum 7-day washout Part A participants also received 2 to 4 single doses of ALP and 2 to 4 single doses of placebo for ALP Part B participants also received 2 to 4 single doses of EtOH and 2 to 4 single doses of placebo for EtOH	Complete; Full
Safety and PD	217-CLP-117	To assess the next-day effects of zuranolone 50 mg relative to placebo on simulated driving performance using the Country Vigilance Divided Attention driving scenario on the Cognitive Research Corporation Driving Simulator -MiniSim	Phase 1, randomized, double-blind, active- and placebo-controlled, 4-arm, 4-period crossover study	Treatment A: zuranolone capsules 50 mg once daily for 7 days Treatment B: zuranolone capsules 50 mg once daily for 6 days and zuranolone 100 mg for 1 day Treatment C: zopiclone 7.5 mg Days 1 and 7 Treatment D: placebo once daily for 7 days Each treatment is separated by washout	67	Healthy male and female participants, 21 years and older	7 days for each of the 4 periods: •zuranolone for 7 consecutive days during 2 periods •2 single doses of zopiclone during 1 period •Placebo in all periods	Complete; Full
PD	217-EXM-101	To determine the overall effect of evening administration of zuranolone on sleep	Phase 1, randomized, double-blind, multiple-dose, 3-way crossover, phase followed by open-label administration of zuranolone	Periods 1, 2, 3: 30 (± 15) minutes prior to lights out, zuranolone capsules 30 mg or 45 mg or placebo administered orally with food Period 4 (PK assessment): zuranolone capsules 30 mg administered orally with food	45	Healthy male and female participants, aged 18 to 64 years (inclusive)	Periods 1, 2, 3: Single dose each of zuranolone and placebo in a crossover fashion Period 4: Single dose of zuranolone	Complete; Full
5.3.5 Reports of Efficacy and Safety Studies								
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
Efficacy and Safety	217-PPD-201	To determine if treatment with zuranolone reduces depressive symptoms in participants with severe PPD compared with placebo, as assessed by the change from baseline in the 17 item HAM-D total score at Day 15	Phase 3, randomized, double-blind, parallel-group, placebo-controlled study	Part A: Zuranolone oral solution 15 mg or placebo BID for 2 days, and then zuranolone oral solution 20 mg or placebo BID for 12 days Part B: Zuranolone capsules 30 mg or placebo in the evening with food for 14 days	Part A: 1 Part B: 151	Female participants with severe PPD, aged 18 to 45 years (inclusive)	Part A: 14 days Part B: 14 days	Complete; Full

Efficacy and Safety	217-PPD-301	To determine if treatment with zuranolone reduces depressive symptoms in adults with severe PPD compared to placebo	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, study	Zuranolone capsules 50 mg or placebo once daily for 14 days	Zuranolone 50 mg: 98 Placebo: 98	Female participants with severe PPD, aged 18 to 45 years (inclusive)	14 days	Complete; Full
5.3.5.2 Study Reports of Uncontrolled Clinical Studies								
Safety	217-MDD-201A	To evaluate the safety and tolerability of zuranolone oral solution 30 mg	2-part study Part A: Phase 2a, open-label study	Zuranolone oral solution 30 mg dose administered in the evening with food for 14 days	13	Male and female participants with moderate to severe MDD, aged 18 to 65 years (inclusive)	14 days	Complete; Full
Safety	217-MDD-303A	To determine the safety and tolerability of initial treatment and/or repeated re-treatment(s) with zuranolone in adults with MDD experiencing a major depressive episode at study entry for de novo participants over a 1-year period	Phase 3, open-label, long-term, longitudinal study	For participants enrolled prior to Protocol Amendment 3: zuranolone capsules 30 mg for 14 days; potential for re-treatment(s) with zuranolone for 14 days (with at least 8 weeks between treatments) For participants enrolled after Protocol Amendment 3: zuranolone capsules 50 mg for 14 days; potential for re-treatment(s) with zuranolone for 14 days (with at least 8 weeks between treatments)	1238 30 mg only: 645 50 mg only 513 30 mg in Treatment cycle 1 and 50 mg in at least one repeat treatment cycle: 80 (924 dosed as of the data cut-off date for the interim CSR.)[b]	Male and female participants with MDD, aged 18 to 75 years (inclusive)	14 days, with potential for repeated 14-day treatment courses through the 48-week Observational Period (starting at Day 70 or later)	Clinically complete as of submission cutoff date; Full Interim (217-MDD-303A Interim)[b], and Full
Safety	217-MDD-303B[c]	To determine the safety and tolerability of initial treatment and/or repeated re-treatment(s) with zuranolone in adults with MDD experiencing a major depressive episode at entry in the parent study for rollover participants over a 1-year period	Phase 3, open-label, long-term, longitudinal study	Zuranolone capsules 50 mg for 14 days; potential for re-treatment(s) with zuranolone for 14 days (with at least 8 weeks between treatments)	118	Male and female participants with MDD who have completed treatment in a double-blind study of zuranolone (Study 217-MDD-305 [parent study]) and completed the final end-of-study visit in the parent study, aged 18 to 75 years (inclusive)	14 days, with potential for repeated 14-day treatment courses through the 48-week Observational Period (starting at Day 70 or later), up to a maximum of 4 treatment cycles in Study 217-MDD-303B (plus the initial double-blinded cycle in the parent study)	Clinically complete as of the submission cutoff date; Full
5.3.5.4 Other Study Reports								
Efficacy	217-MDD-201B	To determine if treatment with zuranolone capsules (30 mg) reduces depressive symptoms in participants with moderate to severe MDD compared to matching placebo	2-part study Part B: Phase 2, randomized, double-blind, placebo-controlled study	Zuranolone capsules 30-mg or matching placebo once daily for 14 days	89	Male and female participants with moderate to severe MDD, aged 18 to 65 years (inclusive)	14 days	Complete; Full
Efficacy and Safety	217-MDD-301A	To evaluate the efficacy of zuranolone in the treatment of MDD compared to placebo	Phase 3, double-blind, randomized, placebo-controlled study	Zuranolone capsules 30 mg, 20 mg or placebo for 14 days	Placebo: 190 Zuranolone 20 mg: 188 Zuranolone 30 mg: 192	Male and female participants with MDD, aged 18 to 65 years (inclusive)	14 days	Complete; Full

Efficacy and Safety	217-MDD-301B	To evaluate the efficacy of zuranolone in the treatment of MDD compared to placebo	Phase 3, double-blind, randomized, placebo-controlled study	Zuranolone capsules 50 mg or placebo for 14 days	Zuranolone: 268 Placebo: 269	Male and female participants with MDD, aged 18 to 64 years (inclusive)	14 days	Complete; Full
Efficacy and Safety	217-MDD-302	To evaluate the efficacy of zuranolone with a fixed, repeated treatment regimen in the prevention of relapse in participants with MDD who have responded to open-label treatment with zuranolone	Phase 3 study with an open-label phase followed by a randomized, double-blind, placebo-controlled phase *Note: the study closed early due to business decisions. No safety concerns were noted.	Open-label Phase: zuranolone capsules 30 mg in the evening for 14 days. Double-blind Phase; zuranolone capsules 30 mg or placebo in the evening for (5) 14-day treatment periods	Open-label Phase: 53 Double-blind Phase: 2	Generally healthy male and female participants with MDD, aged 18 to 65 years (inclusive)	Open-label Phase: once daily for 14 days Double-blind Phase: five 14-day treatment periods of blinded IP, each separated by a 6-week follow-up period	Complete (closed early); Synoptic
Efficacy and Safety	217-MDD-304	To determine the effect of zuranolone on overall insomnia symptoms in participants with comorbid MDD and insomnia	Phase 3, randomized, double-blind, placebo-controlled study *Note: the study closed early due to business decisions. No safety concerns were noted.	Placebo for 2 days followed by zuranolone 30-mg capsules or placebo for 14 days followed by placebo for 7 days	Single-blind Run-in Placebo: 169 Double-blind Period: Total: 86 zuranolone: 43 Placebo: 43	Male and female participants with comorbid MDD and insomnia, aged 18 to 64 years (inclusive)	2 days placebo; 14 days zuranolone, followed by 7 days placebo	Complete; Full
Efficacy and Safety	217-MDD-305	To evaluate the efficacy of zuranolone plus an antidepressant in the treatment of MDD compared to placebo plus an antidepressant	Phase 3, randomized, double-blind, parallel-group, placebo-controlled study	Zuranolone capsules 50 mg or placebo once daily for 14 days, plus 1 of 2 classes of open-label antidepressant therapies from Day 1 through the end of the study	zuranolone + ADT: 212 Placebo + ADT: 218	Male and female participants with MDD, aged 18 to 64 years (inclusive)	14 days	Complete; Full
Efficacy and Safety	1818A3731 (conducted by Shionogi & Co Ltd [a development partner for zuranolone])	To evaluate the superiority of S-812217 (zuranolone) at 20 mg and 30 mg to placebo in participants with moderate or severe MDD	Phase 2, double-blind, randomized, placebo-controlled study	S-812217 (zuranolone) capsules 30 mg, S-812217 (zuranolone) capsules 20-mg, or placebo once daily for 14 days	S-812217 (zuranolone) 30 mg: 82 S-812217 (zuranolone) 20 mg: 85 Placebo group: 82	Male and female participants with moderate to severe MDD, aged 18 to 75 years (inclusive)	14 days	Complete; Full
Efficacy and Safety	2122A3734 (conducted by Shionogi & Co Ltd [a development partner for zuranolone])	To evaluate the superiority of S-812217 (zuranolone) to placebo in participants with depression, as measured by the change from baseline in HAM-D17 total score at Visit 4 (Day 15 ± 1) of Part A.	Phase 3, 2-part study. Part A: randomized, double-blind, placebo-controlled Part B: open-label extension, repeat treatment	Part A: S-812217 (zuranolone) capsule 30 mg or placebo once daily for 14 days Part B: S-812217 (zuranolone) capsule 30 mg once daily for 14 days	Part A: 400 planned (200 each in zuranolone and placebo groups) Part B: at least 100 planned Part A: zuranolone: 205 Placebo: 199 Part B: Total entered: 304 (144 from zuranolone and 160 from placebo groups), of which 271 (128 and 143, respectively) were dosed in Cycle 1	Japanese male and female participants with moderate to severe MDD, aged 18 to 75 years (inclusive)	Part A: 14 days Part B: 14 days, with potential for repeated 14-day treatment courses with a maximum of 6 treatment courses in a 1-year duration	Active, blinded for efficacy

Efficacy and Safety	2207A3736 (conducted by Shionogi & Co Ltd [a development partner for zuranolone)]	To evaluate the efficacy of an add-on treatment with S-812217 in comparison with placebo in Japanese participants with depression taking an antidepressant, as measured by the response rate in HAM-D17 at Visit 4 (Day 15 ± 1) of Part A.	Phase 3, 2-part study. Part A: randomized, double-blind, placebo-controlled Part B: open-label extension, retreatment	Part A: S-812217 (zuranolone) capsule 30 mg or placebo once daily for 14 days Part B: S-812217 (zuranolone) capsule 30 mg once daily for 14 days	Part A: 100 planned (50 each in zuranolone and placebo groups) Part B: no target sample size Part A: zuranolone: 55 Placebo: 52 Part B: Total entered: 82 (47 from zuranolone and 35 from placebo groups), of which 76 (44 and 32, respectively) were dosed in Cycle 1	Male and female participants with MDD, aged 18 to 75 years (inclusive)	Part A: 14 days Part B: 14 days, with potential for repeated 14-day treatment courses with a maximum of 6 treatment courses in a 1-year duration	Active, blinded for efficacy
Efficacy and Safety	217-ETD-201AB 217-ETD-201C	Parts A and B: To compare the effect of 7 days administration of zuranolone capsules to placebo on the change in tremor severity, as measured by the change from randomization (Day 8) in the accelerometer-based Kinesia™ kinetic tremor combined score (i.e., the sum of kinesia kinetic tremor scores from both sides of the body) at Day 14 Part C: To assess the effect of 14 days administration of zuranolone capsules on tremor severity, as measured by the change from baseline (Day 1) in the accelerometer-based Kinesia upper limb tremor combined score (i.e., the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) at Day 15	Phase 2a, Part A: open-label Part B: double-blind, placebo-controlled, randomized withdrawal study Part C: open-label	Part A: 1 Open-label 10 mg oral solution or capsule on Day 1, 20 mg on Day 2, and 30 mg in the morning with food on Days 3 to 7 Part B: Double-blind 30 mg zuranolone (SAGE 217) capsule in the evening or placebo for 7 days Part C: 10 mg on Day 1, 20 mg on Day 2, 30 mg on Day 3. Doses on Days 1 through 3 were taken in the evening with food. On Days 4 through 14, 10 mg in the morning with food and 30 mg in the evening with food for a total daily dose of 40 mg	Part A: 14 (2 zuranolone oral solution and 12 zuranolone capsules) Part B: 8 (4 placebo and 4 zuranolone capsules) Part C: 18	Male and female participants with ET, aged 18 to 80 years (inclusive)	Part A: 7 days Part B: 7 days Part C: 14 days	Complete; Full[d]

Safety	217-BPD-201A	To evaluate the safety and tolerability of zuranolone in subjects with bipolar I/II disorder with a current major depressive episode	Phase 2, 2-part study Part A: open-label study Part B: double-blind, randomized, placebo-controlled, parallel-group study *Note Part B was not conducted	Zuranolone capsules 30 mg in the evening with food daily for 14 days	Part A: 35 Part B: 0	Male and female participants with bipolar I/II disorder with a current major depressive episode, aged 18 to 65 years (inclusive)	14 days	Complete; Abbreviated
Part A: Safety; Part B: Efficacy and Safety	217-PRK-201A; 217-PRK-201B	Part A: To evaluate the safety and tolerability of zuranolone oral solution Part B: To evaluate the effect of zuranolone capsules as an adjunct to antiparkinsonian agent(s) on the severity of Parkinson's disease tremor symptoms	Parts A and B: Phase 2a, 2-part, open-label study	Part A: Zuranolone oral solution 30 mg administered in the morning with food for 4 days Part B: Zuranolone capsules 20 mg in the evening for 2 days followed by zuranolone capsules 30 mg in the evening for 5 days. Participants on a stable dose of antiparkinsonian agent(s) continue taking them for the duration of the study	Part A: 15 Part B: 14	Part A: Male and female participants with idiopathic Parkinson's disease, aged 40 to 75 years (inclusive) Part B: Male and female participants with idiopathic Parkinson's disease of moderate severity, aged 40 to 75 years (inclusive)	Part A: 7 days (3 days of levodopa, followed by 4 days of zuranolone) Part B: 7 days	Complete; Full

ADME = absorption, distribution, metabolism, and excretion; ADT = antidepressant therapy; ALP = alprazolam; BA = bioavailability; BID = twice daily; CNS = central nervous system; CSR = clinical study report; CYP = cytochrome P450; DDI = drug-drug interaction; EEG = electroencephalography; ET = essential tremor; EtOH = ethanol; HAM-D = Hamilton Depression Rating Scale; MAD = multiple ascending dose; MDD = major depressive disorder; MTD = maximum tolerated dose; PK = pharmacokinetic; PD = pharmacodynamic; PPD = postpartum depression; SAD = single ascending dose; TQT = thorough QT.
Note: "Capsule" when used alone refers to the Autofill capsule.
Note: Study 217-CLP-104 evaluated the taste profile of zuranolone oral solution in which all doses were expectorated; therefore, this study is not included in this application.
[a] Clinical studies referenced in this module are described in relation to their status as of the 03 February 2024 data cutoff date for this submission.
[b] Full Interim CSR 217-MDD-303A Interim reports on the study through the US NDA data cutoff date of 15 June 2022.
[c] Of the 118 participants dosed in Study 217-MDD-303B, 57 received placebo and 61 received zuranolone in the parent study (Study 217-MDD-305).
[d] There are 2 CSRs provided. CSR 217-MDD-ETD-201C comprises a report for Parts A, B, and C. CSR 217-ETD-201AB is a 1-page document with a link to CSR 217-ETD-201C.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

Zuranolone was rapidly absorbed following a single dose of the zuranolone oral solution under fasted conditions, with C_{max} generally achieved approximately 1 to 2 hours postdose. When administered as a capsule formulation under fasted or fed condition, C_{max} was achieved between 5 and 6 hours postdose.

Zuranolone drug substance has low aqueous solubility and exhibits high permeability (Papp: 5.60×10^{-6} cm/s), characteristics consistent with a Biopharmaceutic Classification System Class 2 compound. Zuranolone appears to be passively permeable with no efflux mediated by Caco-2 cells. Zuranolone absolute bioavailability has not been formally evaluated. Food increases the bioavailability of zuranolone when administered as a capsule formulation.

Distribution

The volume of distribution ranged from 804 to 888 L, indicating that zuranolone is distributed to peripheral tissues. The V1/F estimated using popPK methods was 588 L.

Zuranolone is highly bound to plasma proteins, with mean binding >99.5% in healthy participants, participants with various degrees of renal and hepatic impairment, and lactating women.

Following multiple-dose administration of zuranolone 30 mg once daily, the amount of zuranolone in breast milk is very low compared to the maternal dose. Concentrations were approximately 50% of those in plasma, and zuranolone is expected to be cleared from breast milk as rapidly as plasma.

Elimination

Zuranolone and its metabolites are eliminated in both urine and faeces. In the human ADME study, comparable amounts of the administered radioactive dose were recovered in urine (45.1%) and faeces (40.6%). Based on comparisons of plasma zuranolone concentration relative to plasma total radioactivity, metabolites of zuranolone contributed upwards of 94% of circulating plasma total radioactivity. Low recoveries of unchanged zuranolone in faeces and urine indicate the clearance of zuranolone is primarily via metabolism. The estimated terminal t½ was 16.7 to 23.1 hours following a single dose of zuranolone. The estimated terminal elimination t½ of zuranolone was 19.71 or 24.63 hours following a single dose of Autofill capsule 30 mg after a high-fat meal or a low-fat meal in healthy participants. The effective t½ determined from the accumulation of AUC following repeated dosing to steady state was estimated to be 14.08 hours.

Dose proportionality and time dependencies

Zuranolone exposures increased approximately dose proportionally over the dose range of 0.25 to 66 mg with the oral solution and 10 to 90 mg with the Autofill capsule. The PK parameters of zuranolone did not change after multiple dosing, indicating that zuranolone follows time-independent PK.

Special populations

Study 217-CLP-107: Renal impairment

Study 217-CLP-107 was designed to evaluate the PK, safety, and tolerability of a single oral dose of zuranolone in 18 participants with renal impairment and in 6 participants with normal renal function. Each participant received a single oral dose of zuranolone 30 mg with food.

Six participants with severe renal impairment, defined as eGFR < 30 mL/min/1.73 m^2 and not on dialysis, were assigned to Cohort 1. After Cohort 1 was completely enrolled, 6 participants with normal renal function, defined as eGFR ≥ 90 mL/min/1.73 m^2 or eGFR < 90 mL/min/1.73 m^2 with stable serum creatinine values at screening and admission, were matched with respect to sex (1:1), mean age (± 10 years), and mean BMI (± 20%) to participants in the severe renal impairment cohort and assigned to Cohort 2. After review of safety, tolerability, and PK data from Cohorts 1 and 2, the Data Review Committee recommended continuing the study with enrolment of 6 participants with mild renal impairment (60 to 89 mL/min/1.73 m^2) and 6 with moderate renal impairment (30 to 59 mL/min/1.73 m^2). Blood samples were collected up to 96 hours for PK analysis.

Statistical comparisons presented were performed using cohorts defined based on eGFR at baseline (primary analysis). Baseline eGFR was selected for the primary analysis because it represented renal function nearest to the time of dose administration.

The median age of participants ranged from 66.5 to 71.0 years, and the mean weight ranged from 76.93 to 91.47 kg across groups. Overall, C_{max} and AUC values were generally increased in participants with renal impairment compared to participants with normal renal function. There was lack of a strong relationship between plasma exposure (C_{max} and AUC) of zuranolone and eGFR across the range of eGFR evaluated.

Zuranolone was highly protein bound in plasma, with > 99.5% bound to plasma proteins in all participants. The fraction unbound in plasma was similar at 5 and 24 hours postdose. No meaningful differences in zuranolone C_{max} were observed between participants with mild, moderate or severe renal impairment and those with normal renal function, while zuranolone AUC_{∞} increased by 33%, 42%, and 38% in participants with mild, moderate, and severe renal impairment, respectively, compared to participants with normal renal function. There was no evidence of a strong relationship between plasma exposure (C_{max} and AUC) of zuranolone and eGFR across the range of eGFR evaluated.

A single dose of zuranolone 30 mg was generally well tolerated in adult participants with renal impairment or normal renal function; no new safety signals were identified.

Study 217-CLP-108: Hepatic impairment

Study 217-CLP-108 was designed to evaluate the PK, safety, and tolerability of a single dose of zuranolone in participants with hepatic impairment and normal hepatic function. Each participant received a single oral dose of zuranolone 30 minutes with food. Participants in the mild, moderate, and normal cohorts received zuranolone 30 mg, and participants in the severe cohort received a zuranolone 20 mg. Blood samples were collected up to 96 hours for PK analysis.

Six participants with moderate hepatic impairment, determined by the Child-Pugh classification, and 6 participants with normal hepatic function were assigned to Cohorts 1 and 2, respectively. After Cohort 1 was completely enrolled, 6 participants in the normal cohort (Cohort 2) were matched to Cohort 1 participants with respect to sex (1:1), mean age (± 10 years), and mean BMI (± 20%). After review of the data from Cohorts 1 and 2, the Data Review Committee recommended to continue the study with enrolment of participants with severe (Cohort 3) and mild (Cohort 4) impairment.

The median age of participants ranged from 58.0 to 63.5 years, and the mean weight ranged from 82.65 to 99.32 kg across groups.

Plasma zuranolone C_{max} was approximately 24% lower, while $AUC_{0\text{-last}}$ and AUC_{∞} were approximately 39% and 56% higher, respectively, in the severe cohort than the normal cohort. Plasma exposure of zuranolone (C_{max} and AUC) was similar between participants with mild or moderate impairment and those with normal hepatic function, with mean values for C_{max} and AUC in the hepatic cohorts within approximately 85% of the values observed in the normal cohort.

There was no indication of a strong relationship between zuranolone plasma exposure and hepatic function as indicated by Child-Pugh scores; however, exposure tended to increase in the presence of reduced albumin or increased prothrombin time.

Zuranolone was > 99.5% bound to plasma proteins and was independent of drug concentration over the range of concentrations observed in this study. Mean protein binding was relatively consistent across all cohorts, with no observed correlation between zuranolone fraction unbound at 5 hours postdose and Child-Pugh Score.

No difference in the TEAE profile between participants with hepatic impairment and participants with normal hepatic function was observed. No significant safety findings were observed in participants with hepatic impairment.

Study 217-CLP-115: Age and sex effects

Study 217-CLP-115 was an open-label, parallel-design, multiple-dose study, conducted in 2 separate age cohorts (healthy elderly [≥ 65 years] and nonelderly [≥ 18 and ≤ 45 years] males and females) to evaluate the effect of age and sex on the PK, safety, and tolerability of zuranolone.

All elderly participants received zuranolone 50 mg once daily in the morning with food for 5 consecutive days. The dose may have reduced to 40 mg once daily for intolerable AEs at any time during the 5-day dosing period. An approximately equal number of male and female participants were to be dosed, with no more than 10 of either sex dosed in the cohort. Sixteen of the 18 elderly participants received zuranolone 50 mg for 5 days; 2 participants had dose reductions due to TEAEs.

The nonelderly cohort was dosed in 3 staggered groups (Groups A through C). The dosing groups were balanced by sex (up to 4 males or 4 females may have been dosed in a group; however, no more than

10 of either sex may have been dosed in the cohort overall). All participants received zuranolone once daily in the morning with food for 6 consecutive days (50 mg on Day 1 through Day 5 and 70, 90, or 100 mg on Day 6).

Serial blood samples were collected up to 96 hours for PK analysis.

The median age was 71.5 years (range: 66 to 81 years) in the elderly cohort and 37.0 years (range: 22 to 44 years) in the nonelderly cohort. The mean weight was similar between the elderly and nonelderly cohorts (73.54 and 76.28 kg, respectively). The median age was higher in male participants compared to female participants (66.0 years [range: 30 to 75 years] and 43.0 years [range: 22 to 81 years], respectively). Additionally, mean weight was higher in male participants (79.41 kg [range: 60.9 to 111.8 kg]) compared to female participants (69.89 kg [range: 50.5 to 91.7 kg]).

Mean predose plasma zuranolone concentrations suggested that steady state was achieved by Day 5 of dosing in elderly and nonelderly participants. Steady-state plasma exposure of zuranolone was higher in both male and female elderly participants compared to nonelderly participants. Overall, C_{max} increased approximately 27% and $AUC_{0-\tau}$ increased approximately 32% (excluding one participant with significantly lower exposure than others) in elderly participants compared to nonelderly participants

Steady-state plasma exposure of zuranolone was slightly lower in both elderly and nonelderly female participants compared to male participants. In another study, the PK of zuranolone was similar between healthy nonelderly and elderly Japanese participants. Overall, the age effect on the PK of zuranolone is not considered to be clinically meaningful.

Table 4. **Age effect on the PK of zuranolone**

	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	56	-	-

Overall, C_{max} decreased 12% and AUC0-τ decreased 8% (excluding one participant) in female participants compared to male participants.

Race (47.8% White, 32.6% Black or African American, 17.2% Asian, and 2.3% other) was retained as a covariate in the popPK model, with Black or African American participants having a 13.7% higher CL/F compared to participants of other races.

In the popPK analysis, body weight had a small effect on the PK of zuranolone.

Study 217-CLP-114: Lactating women

Distribution of zuranolone into breast milk was modelled by partitioning of plasma and breast milk concentrations using partition coefficient. The partition ratio of breast milk to plasma was approximately 0.51.

Study 217-CLP-114 was an open-label study to evaluate the extent of zuranolone transfer into breast milk; the effect of zuranolone on breast milk production; and the PK, plasma protein binding, and safety and tolerability of zuranolone in healthy lactating female participants. Each participant received an oral dose of zuranolone 30 mg, 30 minutes after the start of the evening meal for 5 days. Breast milk samples from Day 1 to Day 12 and blood samples up to 168 hours postdose on Day 5 were collected for PK analysis.

A total of 15 participants were enrolled and received zuranolone. The median age of participants was 30 years, and the mean weight was 85.41 kg.

The amount of zuranolone in breast milk was very low, with an estimated mean relative infant dose of 0.357% and a daily infant dose of 0.0012493 mg/kg/day on Day 5.

During the 5-day treatment period, there was a small mean decrease of 41.2 mL (8.3%) per day in the milk volume collected at steady state compared to baseline. Milk production continued to trend down after completion of the treatment period; by the end of the follow-up period on Day 11, breast milk collection decreased by a mean (SD) of 162.8 mL (183.73), with 13 of 14 participants showing a decrease from baseline in expressed milk. The decrease in the volume of breast milk collected over the course of the study, particularly during the follow-up phase, was accompanied by an overall trend toward a lower daily frequency of collection, which may have contributed to the decrease in milk volume collected. Interpretation of the effect of zuranolone on milk production is limited due to the variability in interparticipant milk production at baseline, the lack of a placebo arm, and the sample size.

Zuranolone was highly protein bound in plasma, with a free fraction ≤ 0.52% in all participants. The fraction unbound in plasma was similar at time near t_{max} and 24 hours postdose, with an overall GM fraction unbound of 0.327%. The results suggested that plasma protein binding is independent of zuranolone concentrations observed in this study. Lactation did not alter the PK profile of zuranolone relative to other populations.

Milk concentration was further evaluated using PK modelling techniques, which showed that the partition ratio of breast milk and plasma concentration was approximately 0.507.

Table 5. ***Daily infant dose and relative infant dose of zuranolone (Study 217-CLP-114)***

Visit	**Zuranolone 30 mg QD (N = 14)** **Mean (SD)**	
	Daily Infant Dose (mg/kg/day)	**Relative Infant Dose (%)**
Day 1	0.0007774 (0.00066607)	0.2174451 (0.18978696)
Day 5	0.0012493 (0.00082741)	0.3566163 (0.23723799)
Days 1 to 11	-	0.3140414 (0.23321970)

Pharmacokinetic interaction studies

Due to the potential for decreased exposure, zuranolone should not be used with CYP3A4 inducers. The dose of zuranolone should be adjusted to 30 mg when used with a strong CYP3A4 inhibitor. Co-administration of repeated 50 mg doses of zuranolone with alcohol or alprazolam led to greater impairment in psychomotor performance compared with zuranolone alone. Therefore, a dose reduction of zuranolone should be considered if use with a CNS depressant medicinal product is unavoidable.

In a clinical DDI study, repeated administration of zuranolone did not alter the exposure of simvastatin (CYP3A4 substrate) or bupropion (CYP2B6 substrate); therefore, zuranolone is not expected to cause a drug interaction with substrates of CYP3A4 or CYP2B6. Zuranolone did not change significantly the PK of alprazolam.

Pharmacokinetics using human biomaterials

In vitro, zuranolone did not inhibit CYP1A2 or CYP2C19 and had very low inhibitory potency to CYP2B6, CYP2C9, CYP2D6, or CYP3A4. Zuranolone was a direct inhibitor of CYP2C8 with an IC_{50} of 14 µM. A risk-based analysis that considered factors such as C_{max} and unbound fraction indicated zuranolone is unlikely to cause a clinically significant drug interaction due to inhibition of CYPs.

The interaction of zuranolone with the human BSEP, BCRP, and MDR1 efflux transporters and with human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 uptake transporters was evaluated *in vitro*. Although zuranolone exhibited mild inhibition of some transporters, further evaluation using methods outlined in the EMA guidance supports that at clinically relevant concentrations, zuranolone is not expected to inhibit any of the transporters evaluated.

2.6.2.2. Pharmacodynamics

Mechanism of action

The *in vitro* and *in vivo* nonclinical studies in different species have described the targeted pharmacology of zuranolone. *In vitro*, zuranolone potentiated the activity at representative synaptic and extrasynaptic $GABA_A$ receptors. *In vivo* PD assays, zuranolone exhibited dose-related anticonvulsant, electroencephalographic, anxiolytic-like, and sedative effects consistent with the $GABA_A$ receptor positive allosteric modulator (PAM) mechanism. The clinical pharmacology of zuranolone has been characterised in a series of clinical studies in healthy participants and participants with postpartum depression (PPD) or major depressive disorder (MDD) to support the proposed indication for zuranolone, which is related with the mechanism of action (MoA).

Due to its MoA, zuranolone may exert antidepressant effects by enhancing GABAergic inhibition, in particular tonic inhibition due to GABA extrasynaptic receptors and may provide a mechanism to normalise function in brain networks dysregulated during PPD.

Primary and Secondary pharmacology

Primary pharmacology

As there are no disease-related PD markers of use for dose selection in patient studies, the applicant provided no clinical primary pharmacology studies.

Secondary pharmacology

Secondary pharmacology of zuranolone have been characterized in studies evaluating the effect of zuranolone on abuse potential, next day driving, effect on sleep and on cardiac safety.

Analysis of abuse-related data from human studies of zuranolone indicates that the abuse potential of zuranolone is similar to that of drugs whose MoA involves the allosteric modulation of GABAa receptors.

Zuranolone impaired next day driving but the effect diminished with repeat administration.

Study 217-EXM-101 was a double-blind, placebo-controlled, 3-way crossover study to assess the effects of zuranolone (30 or 45 mg) on sleep in a 5-hour phase-advance model of insomnia in healthy participants. In healthy participants, administration of single doses of zuranolone (30 and 45 mg) improved polysomnography (PSG)-assessed sleep efficiency (SE), duration, maintenance, and subjective sleep quality compared with placebo in a phase-advance model of insomnia.

Zuranolone did not have a clinically relevant effect on the QTc (TQT study: 217-CLP-112) or any other ECG parameters at concentrations up to 2-fold the mean Cmax,ss following administration of the recommended dose of 50 mg.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Methods

The bioanalytical methods used to measure concentrations of zuranolone in human plasma, urine, and breast milk were developed according to principles outlined in EMA and other relevant regulatory guidelines available at the time. The bioanalytical methods for the quantitation of zuranolone were assessed for accuracy, precision, selectivity, and reproducibility and are considered suitable for the determination of zuranolone concentrations in human plasma, urine, and breast milk. The long term stability in plasma is of 367 days at -80°C, and the ISR (Incurred Sample Reanalysis) analysis performed in several studies confirmed the adequate ability of the method.

The analytical methods for the other analytes (for the DDI studies) are also considered acceptable.

The PK data analysis is standard and acceptable.

The popPK study was developed in two parts: an initial model was developed with data from healthy subjects and patients with MDD and a final model was updated with data from PPD patients.

In the first part, nonlinear mixed effects modelling was used to develop the popPK model using data following single or multiple dose oral administration of zuranolone. Model building started with a simple one compartment, first-order absorption model and increased stepwise in complexity until further improvement in fit was not supported by the data. Upon establishing the structural model, the impact of individual patient characteristics (e.g., body weight, age, race, sex, liver function etc.) were assessed using also a stepwise covariate modelling. The final model was qualified by numerical and graphical goodness of fit (GOF) checks, including visual predictive checks (VPCs). The disposition and elimination of zuranolone in plasma was best described by a two-compartment model, with a double transit compartment absorption model (TCAM) model to characterize the drug absorption after oral administration. Excretion of zuranolone into breast milk was modelled by partitioning of plasma and breast milk concentrations using partition coefficient (kp). Apparent clearance (CL/F) was 34 L/h and comparable across healthy volunteers and MDD patients. Apparent central volume of distribution (V1/F) was large with an estimate of 580 L. Following oral administration of zuranolone under fed conditions using the Autofill formulation, approximately 73.3% of total bioavailable drug was absorbed through the first TCAM chain. Estimates for mean transit time - first chain (MTT1) and number transit compartments – first chain (NTR1) were 2.67 h and 3, indicating an apparently faster absorption relative to the second TCAM chain, with mean transit time - second chain (MTT2) and number transit compartments - second chain (NTR2) estimates of 4.31 h and 24.8, respectively. The partition ratio of breast milk and plasma concentrations was approximately 0.499. Formulation, food status, dose, age, body weight and gender were each found to have a statistically significant influence on the zuranolone PK, although the nature and magnitude of the effects varied. The apparent central volume of distribution (V1/F) and apparent peripheral volume of distribution (V2/F) were found to proportionally increase with weight and different between males and females. The apparent plasma clearance (CL/F) was affected by age and body weight. Administration of zuranolone with food increased relative bioavailability (Frel) 1.7-fold, shortened MTT2 3.7-fold, and increased NTR1 3.5-fold compared with fasted administration. Relative bioavailability was dose-dependent and decreased slightly at higher dose levels. The Profill formulation was estimated to result in a 1.13-fold increase in Frel compared to the Autofill formulation. Overall, the model parameters were logical and their relevance confirmed by bootstrapping. Several parameters presented high shrinkage, but since covariate selection was based on automated stepwise covariate search, this is of limited relevance. Overall, the final model demonstrated appropriate agreement between predicted and observed data values. The corresponding GOF plots stratified by zuranolone dose and study did not reveal any structural bias between doses or

studies. The prediction-corrected VPC of the final popPK model stratified by study did not also reveal any relevant bias.

In the second part, the previous model was initially used to evaluate predictive performance in PPD patients with good initial agreement. In any case, the popPK model was then refined and potential differences in zuranolone PK between healthy participants and subjects with MDD and PPD were assessed. Since the previously developed model in healthy participants and MDD patients adequately described the zuranolone PK data no adaptations to the structural model were necessary. However, the predictive value of individual subject characteristics was reassessed in a covariate analysis with Forward Inclusion and Backward Elimination following by further simplification by testing the removal of small covariate effects from the model. The final popPK model was identical to the previous model developed except for one extra included covariate effect, namely race on CL/F. Again, the same good diagnostic characteristics, as seen in the previous model, were also observed in the final one.

Absorption

No studies were performed with an IV administration; thus, the absolute bioavailability is not known. The applicant did perform, however, a mass balance study and several *in vitro* determinations that may shed some understanding on the absorption potential of the drug. Based on its low aqueous solubility and high Caco-2 permeability, zuranolone is probably a BCS class 2 drug. No effect of efflux transporters was observed in this cellular system. Based on the mass balance study and the radioactivity recovered in urine, at least 45% of the oral dose was absorbed. Furthermore, the low fraction of dose excreted in the faeces as parent drug (1.61% of dose) also may indicate that zuranolone is highly absorbed. This study was performed with the oral solution in fasting.

Food increases the oral bioavailability for the capsule formulations that are similar to the bioavailability of the oral solution in fasting. This may indicate that drug solubilization is, indeed, the limiting step of the oral absorption.

Three formulations were used in the zuranolone clinical development program: 1) oral solution, 2) ProFill capsule, and 3) Autofill capsule. Initial Phase 1 and early Phase 2 clinical studies used a cyclodextrin-based oral solution formulation of zuranolone (available as a 1 and 6 mg/mL aqueous stock solution of zuranolone drug substance containing 40% w/v hydroxypropyl-β-cyclodextrin), which was diluted with a 0.025 mg/mL solution of sucralose in sterile water for injection to achieve the selected dosages. Subsequent clinical studies used an immediate-release oral capsule formulation (ProFill or Autofill). The ProFill formulation was developed to progress multiple-dose clinical studies of zuranolone. It was a variable drug load, direct-blend formulation manually filled into Size 1, white, opaque, hard gelatin capsules manufactured at 5-, 10-, 20-, 25-, and 30-mg strengths. Subsequent to the ProFill capsule, common blend Autofill capsules were developed to prepare for large-scale production and commercialisation. Using the 30-mg ProFill capsule composition (12.0% w/w zuranolone) as a starting point, the relative proportion of the same excipients was adjusted, and roller compaction and dry granulation were introduced to the process to improve the flow properties of the blend and enable large-scale production, which included automated encapsulation. The blend composition in the proposed Autofill commercial image is identical to the Autofill clinical trial material, the only differences between the clinical trial material and the proposed commercial image being the capsule colour and imprinting ink on the capsules. Clinical studies were conducted to assess the relative bioavailability of the oral solution to the ProFill capsule (Study 217-CLP-103) and from the ProFill capsule to the Autofill capsule (Study 217-CLP-109). Both ProFill and Autofill formulations were used in studies that support the efficacy and safety of zuranolone.

Regarding study 217-CLP-103, the ProFill formulation showed lower bioavailability versus de oral solution when dosed in fasted conditions. However, it showed bioequivalence in AUC when dosed with

a standard meal or high fat meal *versus* the oral solution in fasting. Maximum observed concentration (C_{max}) was always under-bioavailable, showing a slower rate of absorption. Regarding Study 217-CLP-109, following administration with a high-fat meal, C_{max} and $AUC_{0\text{-last}}$ with the Autofill capsule were 18% and 14% lower, respectively, than with the ProFill capsule. The effect of the formulation was also explored in the population PK analysis. The ProFill formulation was estimated to result in a 1.11-fold increase in relative bioavailability compared to the Autofill formulation. These small differences should not be relevant.

The highest dose evaluated in clinical efficacy studies in PPD was 50 mg, which was administered each evening for 14 days using a single 20-mg and a single 30-mg Autofill capsule. To simplify administration and minimise potential medication errors, an additional capsule strength of 25 mg was developed for commercialisation such that the recommended 50-mg dose will be provided as two 25-mg capsules. The 25 mg capsule is dose proportional with the 30 mg and 20 mg formulations and shows similar in vitro dissolution.

Zuranolone is a highly lipophilic molecule with a LogP of 4.3 and with a very low aqueous solubility. Its solubility at pH 1.2, 4.5 and 6.8 is around 0.5 ug/mL. In this regard, there is a high potential for increase in bioavailability due to food interaction. A food-effect study using low-fat (12 g fat; 24% kcal) and high-fat (57 g fat; 58% kcal) meals was conducted with the Autofill capsule at a dose of 30 mg. Maximum observed concentration (C_{max}) increased 3- to 4-fold and $AUC_{0\text{-last}}$ increased by 55% to 90% when the Autofill capsule was administered with either a low- or high-fat meal compared with the fasted condition. Zuranolone PK has been characterised at doses up to 90 mg following consumption of a meal with moderate-fat content (approximately 25 g fat; 30% kcal). Single-dose administration of the zuranolone Autofill capsule with a moderate-fat meal facilitated absorption at the recommended dose of 50 mg, as well as at higher doses of 60 and 90 mg. After multiple-dose administrations of 50 mg with a moderate-fat meal, zuranolone absorption was maintained with variability comparable to that observed after single-dose administration. In consideration of the increased bioavailability under fed conditions and to facilitate absorption and maximise bioavailability, zuranolone capsules (ProFill and Autofill) were dosed under fed conditions in clinical pharmacology and efficacy and safety studies. It is recommended that zuranolone be dosed with fat-containing food.

Distribution

Based on the single ascending dose (SAD) and multiple ascending dose (MAD) studies and the correspondent non-compartmental analysis, the apparent volume of distribution (V/F) seems to be around 800-1000 L. This value is confirmed by the popPK analysis were V1/F and V2/F presented values of 588 L and 636 L, respectively. This is compatible with a very lipophilic drug behaviour.

The *in vitro* plasma protein binding of zuranolone at a concentration of 10 µM was determined in human plasma using rapid equilibrium dialysis. Zuranolone was highly bound to plasma proteins with a mean percent-bound of 98.8%. An additional study was conducted to determine the concentration dependence of protein binding to human plasma proteins and to examine the relative affinities to human serum albumin (HSA) or α1-acid glycoprotein (AAG). There was no concentration-dependent effect on the binding of zuranolone to human plasma proteins. Zuranolone showed a higher affinity for HSA (≥ 99.2% bound) than AAG (≥ 89.7% bound). This, again, is compatible to a very lipophilic drug behaviour.

Following multiple-dose administration, the amount of zuranolone in breast milk was very low when compared to the maternal dose, at around 0.3-0.4% of the mother dose. This results in a daily infant dose of around 0.0012 mg/kg/day if the mother is taking 30 mg once daily (QD). Zuranolone concentrations in breast milk over time tracked closely to those in plasma (with a milk to plasma ratio of around 0.5) with no apparent nonlinearity over the concentration range; thus, assuming passive

transport, it is expected that zuranolone exposure in breast milk would increase proportionally to plasma zuranolone exposure. Assuming a dose-proportional increase of daily infant dose and maternal zuranolone dose, the daily infant dose following multiple doses of zuranolone 50 mg once daily (1 mg/day for a 50 kg mother) is projected to be 0.002082 mg/kg/day or 0.0073 mg/day for a 3.5 kg newborn Overall, these values do not seem relevant and the SmPC is sufficiently cautious in section 4.6.

Elimination

The mass balance study was made in single dose after the administration of an oral solution in fasting conditions. The PK of the oral solution was linear in the range of 0.25 to 66 mg in single dose and also on the range of 15 to 35 mg in multiple doses. The total of the identified dose in the excreta was close to 90% and is, thus, acceptable. Most of the identified dose, 45.1%, was in the urine in the form of metabolites. In the faeces, around 41% was collected with less than 2% as zuranolone. Collection of samples up to 336 h post-dose seems appropriate.

In total, identified/characterized and unidentified components in plasma accounted for approximately 34% and 6% of total plasma radioactivity exposure, respectively. The low overall percentage of quantified metabolites (approximately 40%) suggests the presence of numerous low-level metabolites that were below the limit of quantitation. Identified/characterized metabolites in urine cumulatively accounted for 26% of dose, whereas unidentified components accounted for 9.21% of dose. In total, characterized/identified metabolites of zuranolone in faeces from human subjects accounted for 19.5% of the dose, whereas unidentified metabolites accounted for 4.9% of dose. Taking in consideration the number of observed metabolites and the fact that many presented trace levels, this is acceptable.

Overall, this indicate that metabolism is the main route of elimination and that renal excretion, either due to the high protein binding and due to the high lipophilicity, should be of negligible relevance.

Regarding the estimated terminal t½ of zuranolone in the different studies, it varied from 16 to 25 hours after single dose administrations. The effective t½ determined from the accumulation of AUC following repeated dosing to steady state was estimated to be around 14 hours.

From the samples obtained in the mass-balance study, radiochemical and LC-MS analyses of plasma identified/characterized zuranolone and 20 trace to minor metabolites in human subjects after a single oral dose of ^{14}C-zuranolone. No metabolites with an AUC greater than 10% of the total drug related radioactivity AUC were observed. *N*-des(pyrazole-carbonitrile)-dihydroxy-zuranolone carboxylic acid metabolite M125 was the most abundant radiolabelled component in plasma from human subjects, with a mean plasma exposure (AUC_{0-t}) of 2140 ng equivalents ^{14}C-zuranolone hour/g (ng eq h/g) or 7.45% of total plasma radioactivity. Zuranolone was a minor plasma component that had a mean plasma exposure of 1400 which accounted for 4.87% of total plasma radioactivity exposure. Unidentified metabolite M63 was the second most abundant component in plasma, with a mean plasma exposure of 1850 ng eq h/g or 6.44% of total plasma radioactivity. Radiochemical and LC-MS analyses of urine identified/characterized 23 trace (<1% of dose) to minor (<10% of dose) metabolites after a single oral dose of ^{14}C-zuranolone to human subjects. Zuranolone was not detected in urine from human subjects. In addition, 22 trace unidentified radioactive components were detected by radiochemical analysis, but no definitive LC-MS characterization could be assigned. Radiochemical analysis of faeces samples collected from human subjects quantitated 54 radioactive components. LC-MS analyses identified/characterized zuranolone and 29 trace (<1%) to minor (10% of total radioactivity) metabolites. An additional 24 trace radioactive components could not be characterized by LC-MS.

The CYP enzymes involved in the oxidative metabolism of zuranolone were evaluated using human liver microsomes. Based on these data, CYP3A enzymes play a role in the oxidative metabolism of zuranolone in human liver microsomes. The enzymes CYP2C8, CYP2C9, and CYP2B6 are also involved in the metabolism of zuranolone, but to a lesser degree.

Zuranolone is a chiral compound with 8 chiral centres. The C3 epimer of zuranolone, M117, is present in human plasma. Zuranolone and its corresponding C3 epimer M117 were minor plasma components that had mean plasma exposures of 1400 and 737 ng eq h/g, respectively, which accounted for 4.87% and 2.56% of total plasma radioactivity exposure, respectively. It is proposed that chiral inversion of the C-3-alpha hydroxy group is responsible for the production of zuranolone epimer M117, which is 20 times less potent than zuranolone and not expected to contribute to the activity of zuranolone.

As referred before, two metabolites, M125 and M63, circulate at plasma exposures greater than zuranolone (M125 with 7.45% of total plasma radioactivity and M63 with 6.44% of radioactivity) although none can be considered a major metabolite (≥10% of total radioactivity) according to the new M12 ICH guideline. The metabolite M63, which was associated with an estimated half-life of 63.5 hours, has been identified as a mixture of four different glucuronide or sulphate conjugates. Several other metabolites seem to have exposures (AUC_{0-t}) >25% of the zuranolone. These are M61, M13/87, M99, M171, M21, M117 and M135. Their elimination half-life was not always possible to be determined. Some of these were not considered for the DDI evaluations.

The CYP enzymes involved in the oxidative metabolism of zuranolone were evaluated using human liver microsomes. In order to identify the specific CYP enzymes responsible for oxidative metabolism, zuranolone (2 µM) was incubated in the presence or absence of specific inhibitors for CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Based on these data, CYP3A enzymes play a major role in the oxidative metabolism of zuranolone in human liver microsomes with >90% inhibition of hydroxylated metabolites formation. The CYP enzymes 2C8, 2C9, and 2B6 also involved in the metabolism of zuranolone but to a lesser degree with an average of 40%, 30% and 25% inhibition of hydroxylated metabolites formation, respectively. Of these, only CYP2C9 is of concern, regarding genetic polymorphism. However, due to the multiple oxidation routes and the low relevance of the CYP2C9, this should not be problematic.

Dose proportionality and time dependency

The C_{max} and AUC of single and multiple doses for the oral solution were dose proportional in the study dose range (0.25 to 66 mg SD and 15 to 35 mg MD). Regarding the Autofill capsule, dose linearity was demonstrated from 10 to 30 mg in single dose and can also be considered in AUC in the dose range of 30 to 60 mg. A departure from linearity was observed in higher doses. This was confirmed in the popPK analysis, where relative bioavailability was dose dependent and decreased slightly at higher dose levels. Relative to a 30-mg dose, bioavailability was 19% lower at a 100-mg dose level and only 5% lower at the recommended dose of 50 mg. This is probably due to solubility issues, more visible with the solid formulations. Overall, linearity at the proposed doses can be assumed.

Based on visual inspection, plasma zuranolone concentrations reached steady state in 3 to 5 days, which is consistent with the observed terminal elimination half-life of around 15-25 h. The accumulation in a once-daily dosing is minimal, at around 140% in both C_{max} and AUC. More relevant, PK parameters of zuranolone did not change after multiple dosing, indicating that zuranolone follows time-independent PK.

Pharmacokinetics in the target population

In the final population PK analysis, interindividual variation (IIV) was included on Frel, MTT1, CL/F,

V1/F, V2/F, NTR1, Frac and kp and estimates were 20.8% CV, 38.1% CV, 29.6% CV, 47.7% CV, 9.41% CV, 53.9% CV, 143% CV and 22.6% CV, respectively. Post-hoc PK parameter estimates for patients showed an IIV of around 40% and 45% for C_{max} and AUC after administration of 20-50 mg doses. In the BE study, the IIV, based on the residual variability of the ANOVA, was 31% and 32% for C_{max} and AUC, respectively. This medium to high variability is expected in a BCS class 2 drug.

In the popPK analysis, the PK of zuranolone was similar between healthy participants and participants with PPD or MDD. Apparent CL/F of zuranolone was 32.7 L/h and comparable across healthy participants and participants with PPD or MDD. The presence of PPD or MDD (or any additional health conditions in these populations) did not translate into a different zuranolone PK profile. In addition, the PK of zuranolone in participants with MDD receiving concomitant ADT therapy with one of several selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitor (SNRIs) obtained in study 217-MDD-305 was comparable to the PK in healthy participants and participants with MDD not receiving concomitant ADT therapy. The initially developed model for zuranolone in healthy participants and MDD patients adequately described the PPD data, and no major revision of the model was needed.

The therapeutic windows ws proposed to be defined between 30 mg and 50 mg doses of Zuranolone. This is based on the study 217-MDD-301 that suggests that the 20 mg dose is not effective in MDD and the fact that, generally, the 50 mg dose shows a good safety profile. Based on this, an AUC between 900 to 1500 ng.h/ml is expected to define the therapeutic margin.

Special populations

The applicant evaluated the possible differences in PK for subjects with impaired renal function, impaired hepatic function, differences in gender, ethnic factors, weight, age, and lactating women.

A renal impairment study (CLP-107) was performed where a total of 24 subjects were enrolled and received the study drug (18 subjects with renal impairment and 6 subjects with normal renal function). Renal impaired subjects included six subjects with severe renal impairment, (eGFR <30 mL/min/1.73 m^2) and not on dialysis, six subjects with moderate renal impairment, (eGFR 30<59 mL/min/1.73 m^2) and six subjects with mild renal impairment, (eGFR 60<89 mL/min/1.73 m^2). All 24 subjects completed the study. The variability in C_{max} and AUC was moderate to high in most cohorts, with the geometric percent coefficient of variation (CV%) for C_{max} and AUCs ranging from 19.1% to 61.0% and 20.1% to 37.9%, respectively. Overall, C_{max} and AUC values were generally increased in subjects with renal impairment compared to subjects with normal renal function (T/R ratios of around 135% in all classes of renal impaired subjects) but the increase in plasma exposure of zuranolone did not appear to be correlated with decreasing eGFR. Zuranolone was highly protein bound in plasma, with a free fraction <0.5% in all subjects.

The observed results are unexpected and may be due to the inclusion of a small number of subjects in each group and a higher clearance value observed in the normal subjects group. The popPK analysis, regarding covariates retained in the PK model, included age, body weight and Black or African American race on CL/F, body weight and sex on volumes of distribution and dose, food and formulation on bioavailability. Simulations made with this model showed that CL/F in subjects with normal renal function enrolled in CLP-107 was relatively high in comparison to the zuranolone CL/F in subjects with normal renal function enrolled in other clinical studies. The CL/F subjects with renal impairment enrolled in CLP-107 was comparable to CL/F in subjects with normal renal function enrolled in other clinical studies. Also, simulations showed that the zuranolone exposure is comparable among subjects with mild, moderate, or severe renal impairment and subjects with normal renal function after QD administration of 50 mg zuranolone. However, despite this, the applicant is proposing in the SmPC to recommend a dose in patients with moderate or severe renal impairment of 30 mg taken orally once

daily with fat-containing food in the evening during the 14-day treatment period. From the dedicated study, there is a significative increase in the T/R ratio for the severe (AUCinf T/R = 2.01) and for the moderate renal impairment (AUCinf T/R = 1.52). For the mild group, although an increase is also seen, it was not considered significant (AUCinf T/R = 1.43). The popPK model, however, did not identified the renal function as a relevant co-variate. In this regard, the number of subjects with mild renal impairment in the popPK study was significant (n = 521) and considered large enough for the outweigh the contradictory results. In opposition, the moderate and severe renal impairment data sets in the popPK data sets were comparatively smaller (n = 24 and n = 9, respectively) and probably without the ability to influence the final model conclusions. Also, in support of the proposed dose reduction, the 30 mg dose, that would compensate the possible exposure increase in the severe and moderate groups, is also considered efficacious.

A hepatic impairment study was performed in six participants per cohort (mild, moderate and severe hepatic impairment as well as normal). Hepatic impairment classification was based on the Child-Pugh criteria. Each participant received a single 30-mg (mild, moderate, and normal cohorts) or 20-mg (severe cohort) dose of zuranolone. All 24 participants completed the study. Dose-normalized C_{max} and AUCs of zuranolone were unchanged in mild and moderate hepatic impairment compared to normal hepatic function. After dose normalization, there was a 24% reduction in C_{max} and 56% increase in AUC_{∞} in severe hepatic impairment compared to normal hepatic function. Zuranolone was highly bound to plasma proteins, with mean binding >99.5% in all participants. There was no correlation between zuranolone fraction unbound and Child-Pugh score. In the popPK analysis, zuranolone CL/F was not affected by hepatic function (normal, mild, moderate, or severe) using the National Cancer Institute Organ Dysfunction Working group classification based on AST or bilirubin. It is described that this criterium tend to classify subjects as less impaired *versus* Child-Pugh and, thus, the number of severe subjects considered in the model is expectably low.

Following a single dose of zuranolone 20 mg of ProFill capsule, AUC_{∞} was 1074 ng·h/mL (53.7 ng·h/mL/mg) in participants with severe hepatic impairment, which is equivalent to 44.6 ng·h/mL/mg after adjusting for the relative bioavailability between Autofill and ProFill capsules. Thus, multiple-dose administration of zuranolone 30 mg in patients with severe hepatic impairment is projected to provide an $AUC_{0-\tau}$ of 1337 ng·h/mL, which is comparable to the $AUC_{0-\tau}$ of 1306 ng·h/mL following multiple doses of zuranolone 50 mg in healthy participants. In this context, the proposal in SmPC for recommending a 30 mg dose once daily in patients with severe hepatic impairment (Child-Pugh class C) is supported.

It can be observed a small difference in the exposure of zuranolone in females when compared to males. Typically, the exposure was slightly lower in females but in a non-clinically significant way. This may be justified by a slightly higher volume of distribution in females, probably due to the high lipophilicity of the drug.

No relevant differences in exposure of zuranolone between Japanese and White healthy participants were observed after single and multiple dose administration of zuranolone, where C_{max} and AUC in Japanese participants were 90% and 104% of those of White participants. Race (47.8% White, 32.6% Black or African American, 17.2% Asian, and 2.3% other) was retained as a covariate in the popPK model, with Black or African American participants having a 13.7% higher CL/F compared to participants of other races. Black and African American are described to have a higher percentage of normal metabolizers for CYP2C9 that can possibly justify this slightly higher CL/F. In any case, the difference in CL/F is not considered to be clinically meaningful and no dose adjustment based on race is recommended.

In the popPK analysis, body weight had a small effect on the PK of zuranolone. The apparent plasma clearance (CL/F) was affected by body weight with an estimated exponent of 0.27. The typical values

of CL/F across the 5th to 95th weight percentiles ranged from 29 to 41 L/h, resulting in expected AUC of 1200 to 1700 ug.h/L. These values are around the mean values observed in the several clinical studies (1500 ug.h/L). Regarding the apparent central and peripheral volumes of distribution these were found to proportionally increase with weight. Overall, the body weight effects on the PK of zuranolone are not considered to be clinically meaningful, and no dose adjustment is recommended based on weight.

In study 217-CLP-115, steady-state plasma exposure of zuranolone was moderately higher in both male and female elderly participants compared to non-elderly participants. Overall, C_{max} and AUC_{tau} of zuranolone increased approximately 27% and 32%, respectively, in elderly participants as compared to non-elderly participants. In another study in Japanese healthy subjects no difference in plasma exposure levels of zuranolone was seen between Japanese healthy adults and elderly. No large difference in plasma exposure levels of zuranolone were also seen between Japanese and white healthy adults.

In the popPK model, age was a relevant covariate in CL/F with a power coefficient of -0.164. Based on this, the typical values of CL/F across the 5th to 95th age percentiles of all the population (ages from 18 to 81) ranged from 30.2 to 40.6 L/h, resulting in expected AUC of 1230 to 1760 ug.h/L. These values are, again, around the mean values observed in the several clinical studies (1500 ug.h/L). As such, the age effects on the PK of zuranolone are not considered to be clinically meaningful, and no dose adjustment is recommended to the elder patients.

In study 217-CLP-114, plasma PK of zuranolone in lactating female participants was evaluated on Day 5 following daily administration of zuranolone 30 mg. Given the sparse PK sampling in the overnight period (i.e., no collections between 4 and 12 hours following evening dosing), the observed plasma PK profile of zuranolone in lactating women was, in general, similar to other populations. The median plasma t_{max} was 12.0 hours, the mean C_{max} was 58.21 ng/mL, and the median t½ was 32.0 hours. Because plasma PK sampling in the overnight period was sparse, C_{max} will be an underestimate of the true value and t_{max} will not be estimated accurately.

Regarding paediatric population, a waiver was provided for males from birth to less than 18 years of age and prepubertal females. Regarding post pubertal females less than 18 years of age with postpartum depression the PIP has not yet been completed and all measures are deferred.

Drug-drug interaction (DDI)

In vitro

The potential for zuranolone to inhibit human CYP enzymes was investigated in four *in vitro* studies utilizing human liver microsomes incubated in the presence of clinically relevant marker substrates.

In Study SSN-626 and Study SSN-627, zuranolone at concentrations up to 100 µM was incubated in pooled human liver microsomes (1 mg/mL) in the presence of a NADPH regenerating system to assess inhibition of CYP enzymes 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4/5 (testosterone and midazolam).

In both studies, no inhibition (i.e., IC_{50} > 100 µM) was noted for CYP1A2, CYP2C19, or CYP3A4/5 (testosterone). The IC_{50} values were determined for CYP2B6 (40 and 26 µM), CYP2C9 (60 and 57 µM), CYP2D6 (63 and 44 µM), and CYP3A4/5 (midazolam, 67 and 40 µM).

In Study SSN-02183, zuranolone was incubated in pooled mixed-gender human liver microsomes (0.05 and 0.1 mg/mL) in 50 mM potassium phosphate buffer to assess direct, time and metabolism-dependent inhibition of CYP enzymes 1A2, 2C9, 2C19, 2D6, and 3A4/5 (testosterone and midazolam). The final target concentrations of zuranolone ranged from 0.03 to 30 µM for CYP3A4/5 and 0.003 to 3 µM for all other CYPs. Later studies used a top concentration of 3 µM which was sufficient to characterize drug interaction risk given clinical concentrations and is free of solubility issues. Inhibition

assays were performed with and without a 30-minute preincubation in the presence and absence of NADPH to assess direct, time-dependent and metabolism-dependent inhibition. Zuranolone was not a direct inhibitor of CYP1A2, CYP2C19, or CYP2D6 activities. Zuranolone directly inhibited CYP3A4/5-mediated midazolam 1-hydroxylation and testosterone 6β-hydroxylation activities with IC_{50} values of 16 and 29 µM, respectively. For CYP2C9, a maximum of 22% direct inhibition at the highest zuranolone concentration of 3 µM; therefore, the associated IC_{50} for CYP2C9 value was reported as > 3 µM. There was no evidence of time or metabolism-dependent inhibition of any of the CYP enzymes evaluated by zuranolone.

In Study SSN-01539, zuranolone was similarly incubated in pooled mixed-gender human liver microsomes (n = 200) in 50 mM potassium phosphate buffer to assess direct, time- and metabolism-dependent inhibition of select CYP enzymes, namely CYP2B6 and CYP2C8. Zuranolone (at concentrations ranging from 0.02 to 20 µM) was incubated with and without a 30-minute preincubation in the presence and absence of NADPH, followed by a 5-minute incubation at 37°C with marker substrates to assess direct, time-dependent, and metabolism-dependent inhibition. Under these experimental conditions, zuranolone did not cause direct, time-, or metabolism-dependent inhibition of CYP2B6. Zuranolone was a direct inhibitor of CYP2C8 with an IC_{50} of 14 µM, however there was little to no evidence that zuranolone caused time- or metabolism-dependent inhibition of CYP2C8.

A risk assessment was conducted for CYP inhibition according to current EMA guidance with stricter cut-off values than the ones required in the ICH M12 guidance on drug interaction studies. Using the basic model of reversible inhibition [I]/Ki to assess systemic DDI risk, [I]/Ki value did not exceed 0.02 for any of the CYP enzymes, indicating that zuranolone is not likely to cause a clinically significant drug interaction with concomitantly administered substrates of the CYPs evaluated. The clinically relevant concentration of 121 ng/mL was used to estimate DDI risk. This value was the mean C_{max} at steady state from the elderly cohort in Study 217-CLP-115 and is generally the most conservative estimate of exposure for the 50 mg capsule. To evaluate the potential for inhibition of gut CYP3A, a similar approach was employed. The [I] was calculated as total dose divided by 250 mL of fluid contents. While using a total dose of 50 mg suggests that zuranolone could precipitate a drug interaction with gut CYP3A, a 50 mg dose of zuranolone is not fully soluble in 250 mL of intestinal fluid. The maximum solubility of zuranolone (Form C) in fed state simulated intestinal fluid (FeSSIF) is 16.01 µg/mL, indicating that the maximum amount of dissolved drug in the intestine following a 50 mg dose should not exceed 4.002 mg. Using this correction, the [I]/Ki value for CYP3A is 2.70 and 4.89 using testosterone and midazolam, respectively, as probe substrates. These [I]/Ki values are below 10 indicate that zuranolone is unlikely to inhibit intestinal CYP3A.

The potential for zuranolone metabolites to inhibit CYP enzymes was investigated in two *in vitro* studies using human liver microsomes incubated in the presence of clinically relevant substrates. Metabolites M125 and M117 were evaluated for their potential to inhibit CYP enzymes due to their presence in human plasma at estimated exposures greater than zuranolone. CYP inhibition studies were conducted with metabolites M135 and M136 as they were determined to be less polar than zuranolone based on their chromatographic elution following zuranolone, and abundance at greater 25% of the AUC of circulating zuranolone. However, several other metabolites presented AUC_{0-t} >25 of the zuranolone AUC_{0-t}, namelly M63, M61, M13/87, M99, M171 and M21 (M106). As mentioned before, none of the zuranolone metabolites was considered major. As such, and according to the general requirements under the M12 ICH guideline and under a pragmatic rule, none is proposed to be studied in vitro for its DDI potential. It should be mentioned, however, that several metabolites do show an AUC in the same or higher order of magnitude of the parent compound, namely, M63, M125, M99 and M135/M136. Of these, M63 was not tested in vitro due its mixed structure and M99 due to its very low C_{max} value. M117 was indeed tested due to its high relative abundance (approximately 50% of zuranolone's AUC). M21, with a slighter higher relative abundance than M117 was not tested.

However, its is a close structural analogue of M125, that showed little to none CYP inhibition potential. None of the principal metabolites showed significant activity when compared to zuranolone. Overall, the approach taken by the applicant follows the new M12 requirements and seems appropriate. The metabolites M125 and M117 at concentrations up to 10 µM and M135 and M136 at concentrations up to 15 µM were incubated in human liver microsomes in a buffer mixture to assess direct, time- and metabolism-dependent inhibition of CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 (testosterone and midazolam). Inhibition assays were performed with and without a 30-minute preincubation in the presence and absence of a NADPH regenerating system.

M125 was not a direct, or metabolism-dependent inhibitor of any CYPs examined.

M117 was a direct inhibitor CYP2C8 with an IC_{50} value of 6.3 µM. For CYP2B6, CYP2C9, CYP2C19, CYP3A4/5 (midazolam-mediated), and CYP3A4/5 (testosterone-meditated) the associated IC_{50} value for these CYPs was reported at > 10 µM. It was not a metabolism-dependent inhibitor of any CYPs examined.

The metabolite M135 directly inhibited CYP2B6, CYP2C8, CYP2C19, and CYP2D6 with IC_{50} values of 14, 3.9, 13, and 0.43 µM, respectively. For CYP2C9, CYP3A4/5 (midazolam-mediated) and CYP3A4/5 (testosterone-meditated), the associated IC_{50} for these CYPs was reported to be > 15 µM. It was a metabolism-dependent inhibitor of midazolam- and testosterone-mediated CYP3A4/5 at the highest concentration of 15 µM.

The metabolite M136 directly inhibited CYP2C8 with an IC_{50} value of 8.9 µM. For CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 (testosterone-mediated) an associated IC_{50} value of > 15 µM was reported. It was a metabolism-dependent inhibitor of testosterone-mediated CYP3A4/5 at the highest concentration of 15 µM and also a potential metabolism-dependent inhibitor of midazolam-mediated CYP3A4/5.

There was no evidence of time-dependent inhibition in any of the CYP enzymes evaluated by any of the metabolites. There was some evidence of metabolism dependent inhibition for M135 and M136 against CYP3A4/5 but was of low potency and not deemed to be clinically relevant. Using the basic model of reversible inhibition [I]/Ki to assess systemic DDI risk, none of the metabolites showed the potential to precipitate a clinical drug interaction with any CYP enzymes tested.

The potential for zuranolone to induce human CYP enzymes was investigated *in vitro* using cultured human hepatocytes. Induction was measured by mRNA expression and catalytic activity assays selective for CYP1A2, CYP2B6, and CYP3A4. Zuranolone was incubated in preparations of cryopreserved human hepatocytes from three separate donors at concentrations of 0.1, 0.3, 1, 3, 10, and 30 µM. Vehicle control and appropriate positive controls (omeprazole [50 µM] for CYP1A2, phenobarbital [1000 µM] CYP2B6, and rifampicin [25 µM] for CYP3A4) were tested in parallel. In a concurrent MTT (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2H-tetrazolium bromide) assay, zuranolone up to 30 µM caused no reduction of cell viability.

In all three lots of human hepatocytes, zuranolone was not an inducer of CYP1A2. In CYP2B6 mRNA assays, slight induction response was noted in all three lots of human hepatocytes occurring at zuranolone concentrations of 10 or 30 µM. An increase in CYP2B6 catalytic activity was noted occurring at zuranolone concentration of 30 µM. The lowest concentration where no mRNA induction or increase in catalytic activity was observed was >1000 times higher than observed unbound C_{max} (0.003 µM). In CYP3A4 mRNA assays, induction response was noted in all three lots of human hepatocytes occurring at zuranolone concentrations of 3 or 30 µM. No induction of CYP3A4 activity was observed in any of the three hepatocyte lots tested. The lowest concentration where no mRNA induction or increase in catalytic activity was observed was >300 times higher than observed unbound C_{max} (0.003 µM). In conclusion, zuranolone was not an inducer of CYP1A2 mRNA or catalytic activity but showed induction

of CYP2B6 and CYP3A4 mRNA and CYP2B6 catalytic activity. No studies on the CYP induction potential of the metabolites were presented. However, since the induction studies of zuranolone itself were made on cryopreserved hapatocytes that were determined to be viable in the presence of zuranolone and metabolically competent at the end of the incubation, the induction potential of the metabolites is considered to be also indirectly assessed.

The effect of zuranolone on transporters was evaluated in two *in vitro* studies. The permeability of zuranolone and its potential to inhibit BCRP, P-gp, and MRP-2 transporters were assessed *in vitro* using Caco-2 cells. Caco-2 cells were co-dosed with either 10 µM rosuvastatin (BCRP substrate) or 10 µM talinolol (P-pg and MRP-2 substrate) alone or with zuranolone at concentrations of 0.25, 2.5, 7.5, 15, and 25 µM for 2 hours. The Papp (apical-to-basal) of zuranolone at 10 µM after a 2-hour incubation was 5.60 x 10^{-6} cm/s, suggesting that zuranolone is highly permeable. Zuranolone appears to be passively permeable. Zuranolone does not appear to be an inhibitor of BCRP, P-gp, or MRP-2.

The interaction of zuranolone with human BSEP, BCRP, and MDR1 efflux transporters and human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 uptake transporters was determined in HEK293 or MDCKII cells. Zuranolone was tested in vesicular transport inhibition assay, at concentrations of 0.3, 0.63, or 6.3 µM with HEK293 cells stably expressing BCRP, BSEP, and MDR1 transporters and their respective probe substrates, in uptake transporter inhibition assay at concentrations of 0.25, 0.3, 2.5, or 3 µM with MDCKII or HEK293 cells stably expressing human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2 and their respective probe substrates, in uptake transporter substrate assay at concentrations of 0.3 and 3 µM in HEK293 cells expressing OATP1B1 and OATP1B3 in the presence and absence of a known inhibitors and in bidirectional transport determined in control, BCRP or MDR1 transfected MDCKII monolayers with zuranolone at 1, 10, 50, and 100 µM. Positive control experiments confirmed the function of all the transporters in the applied cells and the value of permeability and functional controls in the MDCKII monolayer assay met the acceptance criteria.

Zuranolone inhibited MDR1-, and BCRP-mediated probe substrate transport by 23% and 33%, respectively. Furthermore, zuranolone inhibited MATE1-, MATE2-K-, OATP1B1-, OATP1B3-, and OCT1-mediated probe substrate transport by 23%, 42%, 33%, 27%, and 39% respectively, at the highest tested concentration. Zuranolone did not interact with BSEP-, OAT1, OAT3, or OCT2-mediated transport.

To evaluate the potential for clinically relevant transporter inhibition of MDR1 (P-gp) and BCRP by zuranolone, a risk assessment outlined in the current EMA DDI guidance document was employed, where a (0.1*dose/250 mL)/Ki value of less than 1 indicates low risk of a transporter DDI. A 50 mg dose of zuranolone is not fully soluble in 250 mL of intestinal fluid. The maximum amount of dissolved drug in the intestine following at 50 mg dose should not exceed 4.002 mg. Furthermore, determination of an IC_{50} for these transporters was not possible as 50% inhibition of the transporters was not attained at the maximum solubility in the assay system. At the maximal solubility-limited intestinal concentration of 39.09 µM, a (0.1*dose/250 mL)/Ki value of less than 1 would require a Ki of 3.9 µM or more. At the maximum feasible testing concentration for the transporter assays (3 or 6.3 µM), 50% inhibition was not reached. This indicates that zuranolone is at low risk for precipitating a transporter-based drug interaction with MDR1 or BCRP.

Evaluation of drug interaction risk based on inhibition of hepatic transporters OATP1B1 and OATP1B3 was conducted by calculating 25*Imaxu,inlet/Ki and a value > 1 indicates the potential to inhibit OATP transporters. The results indicate that there is low potential for clinical inhibition of OATP1B1 or OATP1B3 transporters at clinically relevant concentrations.

Accumulation of zuranolone was similar in cells which expressed OATP1B1 or OATP1B3 compared to control cells (transporter-specific fold accumulations were < 2), indicating no active accumulation of

zuranolone under the tested conditions. The Papp of zuranolone was similar in the basal-to-apical and in the apical-to-basal direction, indicating no active transport of zuranolone in the MDCKII-MDR1 or MDCKII-BCRP cells. The net efflux ratios were > 1 in both cases at all applied conditions. Therefore, zuranolone is not a substrate of OATP1B1, OATP1B3 uptake or MDR1 and BCRP efflux transporters.

Overall, the presented studies suggest a low potential for zuranolone and the selected metabolites as perpetrators of DDI.

In vivo

Incubation with ketoconazole (a strong cytochrome P450 [CYP]3A inhibitor) *in vitro* inhibited metabolite formation, suggesting that CYP3A may be primarily responsible for the metabolism of zuranolone. As such, a clinical study was designed to evaluate the potential impact of CYP3A induction and inhibition on *in vivo* systemic exposure to zuranolone following a single dose of zuranolone in healthy adult subjects. The magnitude of the effect was evaluated without and with the concomitant administration of the perpetrator drug, that was administered during 7 (rifampin 600 mg/day - inducer) to 8 (itraconazole 200 mg/day - inhibitor) days prior to the test. A total of 16 subjects for each perpetrator drug. In the presence of rifampin, zuranolone C_{max} and AUC_{inf} were reduced to 31% and 15%, respectively, of the control values observed during administration of zuranolone alone. The results demonstrate a clear effect of rifampin on zuranolone exposure. Based on this, the applicant included the following text in the SmPC: "Systemic exposure (area under the curve to infinity [AUC_{inf}]) to zuranolone is reduced by 85% in the presence of rifampin (strong CYP3A inducer) (see section 5.2). Concomitant use of zuranolone with a CYP3A inducer decreases the exposure of zuranolone which may reduce the efficacy of zuranolone. Concomitant use of zuranolone with CYP3A inducers should be avoided." This is acceptable. Also, in the same study, coadministration of itraconazole increased zuranolone AUC 63% compared to zuranolone alone. Maximum observed concentration (C_{max}) was increased 25%. Based on this, the applicant proposed that the dose of zuranolone should be reduced to 30 mg when using with a strong CYP3A inhibitor, as multiple-dose administration of zuranolone 30 mg given concomitantly with a strong CYP3A4 inhibitor is projected to provide an AUC_{0-T} of 1214 ng·h/mL, which is comparable to the AUC_{0-T} of 1306 ng·h/mL following multiple doses of zuranolone 50 mg given alone. Simulations based on a PBPK model for zuranolone predict a weak interaction (AUC GMR ≥1.25 and <2) for moderate CYP3A Inhibitors supporting the lack of need for dose adjustment in these concomitant use situations.

Also, it is expected that fraction metabolized by CYP2C8, CYP2C9, and CYP2B6 is lower than the fraction metabolized by CYP3A4 based on in vitro data. Given the fact that inhibition of CYP3A4 by a strong inhibitor intraconazole resulted in an AUC increase of 1.62-fold, inhibition with either a strong inhibitor of CYP2C8, CYP2C9, or CYP2B6 is not expected to result in a relevant exposure increase. Dose adjustments or additional DDI studies for zuranolone when used concomitantly with inhibitors of CYP2C8, CYP2C9, or CYP2B6 are therefore not required.The PK of zuranolone was also evaluated when given concomitantly with alprazolam and ethanol, at zuranolone doses of 30 mg and 50 mg. Zuranolone is a synthetic positive allosteric modulator of γ-aminobutyric acid-gated chloride channel ($GABA_A$) receptors, the major class of inhibitory neurotransmitters in the brain. *In vivo* and pharmacological data provide evidence that zuranolone is a potent modulator of multiple subtypes of $GABA_A$ receptors. So, two studies were performed in order to investigate the neurocognitive effects of steady-state zuranolone co-administered with central nervous system depressants, alprazolam (ALP) or ethanol (EtOH). In these, the PK of zuranolone was also evaluated when given concomitantly with alprazolam and ethanol as a secondary objective. The PK of zuranolone at doses of 30 and 50 mg was unchanged in the presence of alprazolam or ethanol. In addition, multiple doses of 50 mg zuranolone had no effect on the single dose PK of alprazolam. Ethanol C_{max} and AUC_{0-last} decreased following

coadministration of multiple doses of zuranolone 50 mg by 14% and 19%, respectively. This is not clinically relevant.

Regarding the possibility of DDI with zuranolone as perpetrator, the *in vitro* studies only identified the possibility of zuranolone to act as an inducer of CYP2B6 and CYP3A4. As such, a clinical drug interaction cohort was conducted as part of clinical Study 217-CLP-102, where relevant probe substrates (100 mg bupropion for CYP2B6 and 20 mg simvastatin for CYP3A as single dose) were administered before and after 7 days of dosing with zuranolone, 30 mg as oral solution. No effect on the PK were observed for these probe substrates following repeat administration of zuranolone, indicating that the *in vitro* findings were not followed by significant *in vivo* results.

Pharmacodynamics

Zuranolone is an orally bioavailable synthetic neuroactive steroid (NAS). The applicant developed a set of non-clinical *in vitro* and *in vivo* studies that demonstrated that zuranolone exhibits positive allosteric modulation of the GABAA receptor. Zuranolone enhances GABA activity at synaptic and extrasynaptic receptors and increase cell surface expression of $GABA_A$ receptors in *in vitro* studies. *In vivo* PD assays, zuranolone exhibited dose-related anticonvulsant, electroencephalographic, anxiolytic-like, and sedative effects consistent with the $GABA_A$ receptor positive allosteric modulator (PAM) mechanism.

The clinical pharmacology of zuranolone has been characterised in a series of clinical studies in healthy participants and participants with postpartum depression (PPD) or major depressive disorder (MDD) to support the proposed indication for zuranolone, which is related with the mechanism of action (MoA).

Due to the MoA, zuranolone may exert antidepressant effects by enhancing GABAergic inhibition, in particular tonic inhibition due to GABA extrasynaptic receptors and may provide a mechanism to normalise function in brain networks dysregulated during postpartum depression (PPD).

As there are no disease-related PD markers of use for dose selection in patient studies, the applicant provided no clinical primary pharmacology studies, which is understood. The recommended dose is based on clinical studies and exposure-response models. No formal dose-response studies were performed prior to the pivotal trial.

The applicant developed also clinical studies where he evaluated the pharmacodynamic (PD) effects on ECG parameters, cognitive endpoints, driving ability, sleep architecture, and the potential for abuse. Exposure-response (ER) analyses were conducted with combined data from several studies, including studies in participants with PPD or major depressive disorder (MDD).

Thorough QT study

The Study 217-CLP-112 was a Phase 1, single-centre, double-blind, double-dummy, placebo- and active-controlled, parallel-group, multiple-dose thorough QT (TQT) study of zuranolone in healthy male and female participants. In this study the applicant used two doses of zuranolone: 50 mg (therapeutic dose) and 100 mg (supra therapeutic dose). The assay sensitivity was evaluated using Moxifloxacin 400 mg. Zuranolone did not have a clinically relevant effect on the QTc, as per the upper bound of the 90% CI of ΔΔQTcF in the by-time-point analysis, or any other ECG parameter at concentrations up to approximately 205 ng/mL (2-fold the mean C_{max} following administration of the therapeutic recommended dose of zuranolone: 50 mg). There were also no participants with QTcF >480 ms or ΔQTcF >60 ms. Two participants had a ΔQTcF >30 ms ≤60 ms in the zuranolone 50 mg group, two in the zuranolone 100 mg group and one in the placebo group.

The results from the study 217-CLP-112 (Thorough QT study) are adequately reflected in the section 5.1 of the SmPC.

"Pharmacodynamic effects:

Cardiac electrophysiology

At a dose up to 2 times the MRHD, zuranolone does not cause clinically significant QTc interval prolongation nor any other clinically significant effect on other electrocardiography (ECG) parameters."

Driving ability

The study 217-CLP-113 was a randomised, double-blind, active- and placebo-controlled, 4-arm, 4-period crossover study to assess the effects of zuranolone (30 mg) on next-day driving and cognition in healthy adult participants. The study 217-CLP-117 was a randomised, double-blind, active- and placebo-controlled, 4-treatment, 4-period crossover study to assess the effects of zuranolone (50 mg) on next-day simulated driving performance and cognition in healthy adult participants. In both studies, zuranolone impaired next day driving but the effect diminished with repeat administration. For the 30 mg strength, the effects seem to diminish after 5 days of dosing, however with the 50 mg strength the difference to placebo remained statistically significant also after 7 days of dosing. Majority of subjects felt safe to drive before the driving simulation i.e., they could not correctly estimate their driving abilities. The studies showed a dose-response relationship, which was also confirmed in PK-PD analysis. The applicant advises not to drive or operate machines within 12 hours of taking zuranolone. The results of the popPK-SDLP modelling of 217-CLP-113 and 217-CLP-117 driving results support this time selection.

Study 217-EXM-101 was a double-blind, placebo-controlled, 3-way crossover study to assess the effects of zuranolone (30 or 45 mg) on sleep in a 5-hour phase-advance model of insomnia in healthy participants. In healthy participants, administration of single doses of zuranolone (30 and 45 mg) improved polysomnography (PSG)-assessed sleep efficiency (SE), duration, maintenance, and subjective sleep quality compared with placebo in a phase-advance model of insomnia. No adverse effects on sleep were reported in this double-blind, placebo-controlled, 3-way crossover study.

Abuse potential

Study 217-CLP-110 was a 2-part phase I study to evaluate the abuse potential of orally administered zuranolone compared to orally administered alprazolam and placebo in 60 healthy, nondependent, male and female, recreational CNS depressant users. Participants had used CNS depressants (e.g., benzodiazepines, barbiturates, and zolpidem) for recreational, nontherapeutic reasons at least 10 times in their lifetime and at least once in the 12 weeks prior to screening. The study investigated single oral doses of 30 mg, 60 mg and 90 mg of zuranolone, alprazolam 1.5 mg and 3 mg, and placebo, which were administered in a cross-over setting. The study demonstrated lower abuse potential of zuranolone 30 mg and 60 mg vs. both doses of alprazolam, but higher than that of placebo. There was no difference between zuranolone 90 mg and both doses of alprazolam in abuse potential. Analysis of abuse-related data from human studies of zuranolone indicates that the abuse potential of zuranolone is similar to that of drugs whose MoA involves the allosteric modulation of $GABA_A$ receptors.

Study 217-CLP-111 and Study 217-CLP-116 evaluated the neurocognitive effects and safety of zuranolone Autofill capsules administered at doses of 30 mg (Study 217-CLP-111) and 50 mg (Study 217-CLP-116) alone or in combination with single doses of alprazolam (1 mg) or ethanol (0.7 g/kg [males]; 0.6 g/kg [females]) in healthy participants. Cognitive effects in both studies were assessed based on performance on a battery of computerised tasks covering a range of cognitive domains. These studies show that alprazolam and ethanol can promote an increase in the effects of zuranolone. In case of concomitant administration with CNS antidepressants, a dose reduction is proposed. In fact, based on the results obtained in the studies: 217-CLP-111 and 217 CLP 116, a dose reduction of zuranolone to 30 mg or 40 mg is recommended when administered concomitantly with ethanol or alprazolam, according to medical assessment/decision. The applicant has included in the SmPC

(section 4.5) a list of potential CNS depressant medicinal products that should be avoided in combination with zuranolone including opioids, benzodiazepines, non-benzodiazepine hypnotics, gabapentinoids, and sedating antidepressants.

Genetic factors

The applicant has not carried out dedicated studies to verify whether there are pharmacodynamic responses to zuranolone dependent on genetic factors. Studies were only carried out on the influence of intrinsic factors. The impact of participant population weight, race, age and sex was evaluated using data from dedicated clinical studies. The PK/PD of zuranolone was similar between healthy adult participants and participants with PPD or MDD. No dose adjustments are necessary based on weight, race, age, or sex.

Exposure-response

An exposure-response analysis for efficacy was performed with combined data from 6 clinical studies (2 PPD and 4 MDD) to evaluate the relationship between plasma concentration and HAMD-17 total score. There was a significant inverse relationship between zuranolone exposure and HAMD-17 total score, characterised by a linear increase in response over the range of plasma concentrations achieved following doses of 20 mg to 50 mg, once daily. Zuranolone provided a median reduction over that of placebo in HAMD-17 total score on day 15 of 0.5, 0.7, 0.9, and 1.1 points at the median exposure from doses of 20, 30, 40, and 50 mg, respectively. In conclusion, Exposure-response analyses were performed with combined data from PPD and MDD studies. Indeed, results are generally comparable between the two models and consistent with the data. The Sub-division of MDD and PPD patients in the models is therefore not needed.

The clinical data in conjunction with ER modelling support the use of 50 mg as the recommended dose.

2.6.4. Conclusions on clinical pharmacology

Pharmacokinetics

An extensive clinical pharmacology plan was undertaken by the applicant. Zuranolone's clinical PK behaviour can be considered well described.

Pharmacodynamics

The clinical pharmacodynamic characterization of zuranolone can generally be considered adequate to support the proposed indication. No dedicated PD efficacy studies were performed. Exposure-response analyses were performed with combined data from PPD and MDD studies. Indeed, results are generally comparable between the two models and consistent with the data. The sub-division of MDD and PPD patients in the models is therefore not needed.

The performed thorough QT study was negative. Abuse potential of zuranolone was confirmed in a dedicated Phase I study, which suggests that zuranolone has lower abuse potential than alprazolam in the recommended doses. Alprazolam and ethanol have been shown to promote an increase in the effects of Zuranolone. In case of concomitant administration of zuranolone with CNS antidepressants, a dose reduction is proposed. In fact, based on the results obtained in the studies: 217-CLP-111 and 217 CLP 116, a dose reduction of zuranolone to 30 mg or 40 mg is recommended when administered concomitantly with ethanol or alprazolam, according to medical assessment/decision.

Significant adverse effects on driving ability were confirmed in two simulated driving studies, which demonstrated persistent effects after multiple dosing of 50 mg zuranolone.

Pharmacodynamic interaction with alprazolam was demonstrated for the 50 mg zuranolone strength in psychomotor function. This is reflected in the SmPC.

2.6.5. Clinical efficacy

Table 6. **Overview of PPD Efficacy Study Designs**

Characteristic	**Study 217-PPD-301 (MAIN study)**	**Study 217-PPD-201B**[a] (Supportive study)
Design	Randomised, double-blind, parallel-group, placebo-controlled, multicentre study of zuranolone in adult participants with PPD	
Population	• Female participants aged 18 to 45 years of age, inclusive, who met DSM-5 criteria for a major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery. • HAMD-17 total score of ≥ 26 at Screening and Day 1 • ≤ 6 months postpartum at Screening and Day 1 (Protocol Version 1); ≤ 12 months postpartum at Screening and Day 1 (Protocol Version 2) • Concomitant antidepressants permitted at baseline if taken at the same dose for at least 30 days prior to Day 1 adjustments to antidepressant or anxiety medications or any new pharmacotherapy regimens prohibited throughout the study.	• Female participants aged 18 to 45 years of age, inclusive, who met DSM-5 criteria for a major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery. • HAMD-17 total score of ≥ 26 at Screening and Day 1 • ≤ 6 months postpartum at Screening and Day 1 • Concomitant antidepressants permitted at baseline if taken at the same dose for at least 30 days prior to Day 1; adjustments to antidepressant or anxiety medications or any new pharmacotherapy regimens prohibited until completion of Day 15 assessments.
Dose and dose regimen (capsule formulation in both studies)	50 mg (Autofill) Once daily at 8:00 PM with fat-containing food for 14 days	30 mg (ProFill) Once daily at 8:00 PM with food for 14 days
Number of participants planned/randomised (randomisation ratio)	192/200 (1:1) 99 randomised to zuranolone 101 randomised to placebo	140/153 (1:1) 77 randomised to zuranolone 76 randomised to placebo

Characteristic	Study 217-PPD-301 (MAIN study)	Study 217-PPD-201B[a] (Supportive study)
Number of participants treated/completed study	196: 98/84 zuranolone 98/86 placebo	151: 78[b]/73[b] zuranolone 73/69 placebo
Primary efficacy analysis population (n)	Full Analysis Set: all randomised participants who were administered IP with a valid baseline total score and at least 1 postbaseline total score in at least 1 of HAMD-17, HAM-A, MADRS, CGI-S, EPDS, or PHQ-9 or ≥ 1 postbaseline value of CGI-I, with participants analysed according to their randomised treatment group (98 zuranolone 50 mg [Autofill]; 97 placebo)	Efficacy Set: all participants in Part B who were administered IP and had a valid baseline and ≥ 1 postbaseline efficacy assessment, with participants analysed according to their randomised treatment group (76 zuranolone 30 mg [ProFill]; 74 placebo[b])
Primary efficacy endpoint	Change from baseline in HAMD-17 total score at Day 15	
Key secondary efficacy endpoints	• Change from baseline in HAMD-17 total score at Day 3, 28, and 45 • Change from baseline in CGI-S score at Day 15	• None specified

[a] Only 1 participant was dosed in Study 217-PPD-201 Part A; data not included in Summary of Clinical Efficacy.
[b] Participants are summarised by treatment received. Two participants in Study 217-PPD-201B were randomised to placebo but received at least 1 dose of zuranolone in error and are included in the zuranolone group.

2.6.5.1. Dose response study(ies)

There were no specific dose-response studies.

The efficacy of zuranolone in participants with PPD has been studied in two placebo-controlled, double-blind, randomised studies. Zuranolone was administered once daily in the evening with food for 14 days. Based on the totality of the data, the Applicant recommended dose of zuranolone is 50 mg taken orally once-daily in the evening with fat-containing food for 14 days; dose reduction may be considered for patients who do not tolerate 50 mg. In the clinical study performed at the 50 mg dose level, Study 217-PPD-301, a dose reduction for tolerability to 40 mg once daily was allowed. In the supportive study 217-PPD-201B, a 30 mg daily dose was used.

2.6.5.2. Main study(ies)

Study 217-PPD-301 and Study 217-PPD-201B were conducted according to GCP. Both studies had prospective protocols and were conducted at multiple centres. The studies were appropriately powered, well-controlled and support the finding of efficacy for zuranolone in PPD. The analysis methods were prospectively developed. However, only Study 217-PPD-301 can be considered the main study. Study 217-PPD-201B was conducted with a lower than the proposed dose, and the study population was also not similar to the population in the main study.

Study 217-PPD-301

Study 217-PPD-301 was a multicentre, randomised, double-blind, placebo-controlled, parallel group trial to assess the efficacy and safety of zuranolone 50 mg (Autofill) in adult participants diagnosed with PPD. It was an appropriately powered, well-controlled study and supports the finding of efficacy for zuranolone in PPD.

Methods

- **Study participants**

Females between 18 and 45 years of age, inclusive, who met criteria for an MDE with peripartum onset beginning no earlier than the third trimester and no later than the first 4 weeks following delivery per the DSM-5 (diagnosed by Structured Clinical Interview for DSM-5 Axis I Disorders) and had a HAMD-17 total score of ≥ 26 at Screening and Day 1 (prior to randomisation). Eligible participants who were on stable doses of antidepressant treatment (≥ 30 days) were included in the study. Participants must have been ≤ 6 months postpartum at Screening and Day 1 (in Protocol Version 1), or ≤ 12 months postpartum at Screening and Day 1 (as of Protocol Version 2, amendment 1 [29 January 2021]).

- **Treatments**

During the Treatment Period (14 days including baseline visit), blinded investigational product (IP) was self-administered with fat-containing food each evening at approximately 8:00 PM. As local regulations permitted, IP administration was monitored via a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion. Participants who could not tolerate the 50 mg Autofill formulation (as determined by the Investigator) could receive a reduced dose of 40 mg for the remainder of the Treatment Period. At the discretion of the Investigator, participants who could not tolerate the 40 mg dose were discontinued from IP.

There was no planned rescue treatment. Concomitant use of antidepressant medications was permitted, provided participants were on a stable dose for at least 30 days prior to Day 1, and agreed to continue on a stable dose through completion of the Day 45 assessments. Initiation of new psychotropic medications that may potentially have had an impact on efficacy and/or safety endpoints were not allowed within 30 days (or >5 half-lives of the psychotropic medication) prior to Day 1 through completion of the Day 45 assessments. On Day 1, eligible participants were stratified based on use of antidepressant treatment (current/stable or not treated/withdrawn ≥30 days or >5 half-lives) and randomized within each stratum to 1 of 2 treatment groups (SAGE-217 50 mg or matching placebo) in a 1:1 ratio.

- **Objectives**

The primary objective was to determine if treatment with zuranolone reduces depressive symptoms in adults with severe postpartum depression (PPD) compared to placebo.

- **Outcomes/endpoints**

The primary efficacy endpoint was: Change from baseline in the HAMD-17 total score at Day 15.

The key secondary endpoints were: a) Change from baseline in HAMD-17 total score at Day 3; b) Change from baseline in HAMD-17 total score at Day 28; c) Change from baseline in HAMD-17 total score at Day 45; d) Change from baseline in CGI-S score at Day 15.

Other secondary endpoints related to the primary objective were: i) HAMD-17 response at Day 15 and Day 45; ii) HAMD-17 remission at Day 15 and Day 45; iii) CGI-I response at Day 15; iv) Change from baseline in the MADRS total score at Day 15; v) Change from baseline in HAMD-17 subscale at Day 15

Table 7. **Estimands for primary objective**

Population	Adult participants with a diagnosis of severe PPD (baseline HAMD-17 total score ≥26)
Treatment condition<s>	Assignment to zuranolone, regardless of discontinuation, compared to assignment to placebo regardless of discontinuation.
Endpoint (variable)	Primary: Change from baseline in HAMD-17 total score at Day 15 Key secondary: • Change from baseline in HAMD-17 total score at Days 3, 28 and 45 • Change from baseline in CGI-S score at Day 15
Population-level summary	Model-based estimate of the difference between zuranolone and placebo treatments in mean change from baseline
Intercurrent events and strategy to handle them	
Premature discontinuation of treatment for any reason	Treatment policy
Initiation of prohibited medications such as new antidepressants or benzodiazepines	Treatment policy

- **Sample size**

Using a two-sided test at an alpha level of 0.05, a sample size of approximately 86 evaluable participants per treatment group would provide 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAMD-17 total score at Day 15, assuming an SD of 8 points. Assuming a 10% dropout and a 1:1 randomisation ratio within each stratum (antidepressant use at baseline, yes or no), approximately 192 randomised participants (96 per treatment group) would be required to obtain 86 evaluable participants per treatment group. Evaluable participants were defined as those randomised participants who received IP and had a valid baseline and at least 1 postbaseline HAMD-17 assessment. Additional participants may have been randomised if the dropout rate was higher than 10%.

- **Randomisation and blinding (masking)**

Participants who met the entrance criteria were randomized in a stratified manner based on the use of antidepressant treatment (current/stable not treated/withdrawn ≥30 days or >5 half-lives) at baseline. Randomization within each stratum was in a 1:1 ratio (SAGE-217 50 mg: matched placebo). Randomization was performed centrally via an IRT system, based on a randomization schedule generated by an independent statistician. Participants, clinicians, and the study team were blinded to treatment allocation until the time of unblinding after the database was locked.

Participants, clinicians, and the study team were blinded to treatment allocation until database lock. During the study, the blind was to be broken by the investigator via the IRT system only when the safety of a participant was at risk and the treatment plan was dependent on the investigational product (IP) received. No unblinding occurred during the study.

- **Statistical methods**

The Full Analysis Set (FAS) was defined as all randomized participants who were administered IP with valid baseline total score and at least 1 post-baseline total score in at least one of HAMD-17, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I. Efficacy analyses were

conducted using the FAS, the primary efficacy analysis was performed using the Per Protocol Set, defined as all participants in the FAS without any major protocol deviations that could affect efficacy. In addition, the Per Protocol Set excluded FAS participants who consumed <22 capsules (i.e., <80% of assigned number of capsules), participants who consumed incorrect IP (i.e., IP other than that to which they were randomized to receive) at any time during the study, and participants or study personnel who were unblinded to participant's treatment assignment before database lock.

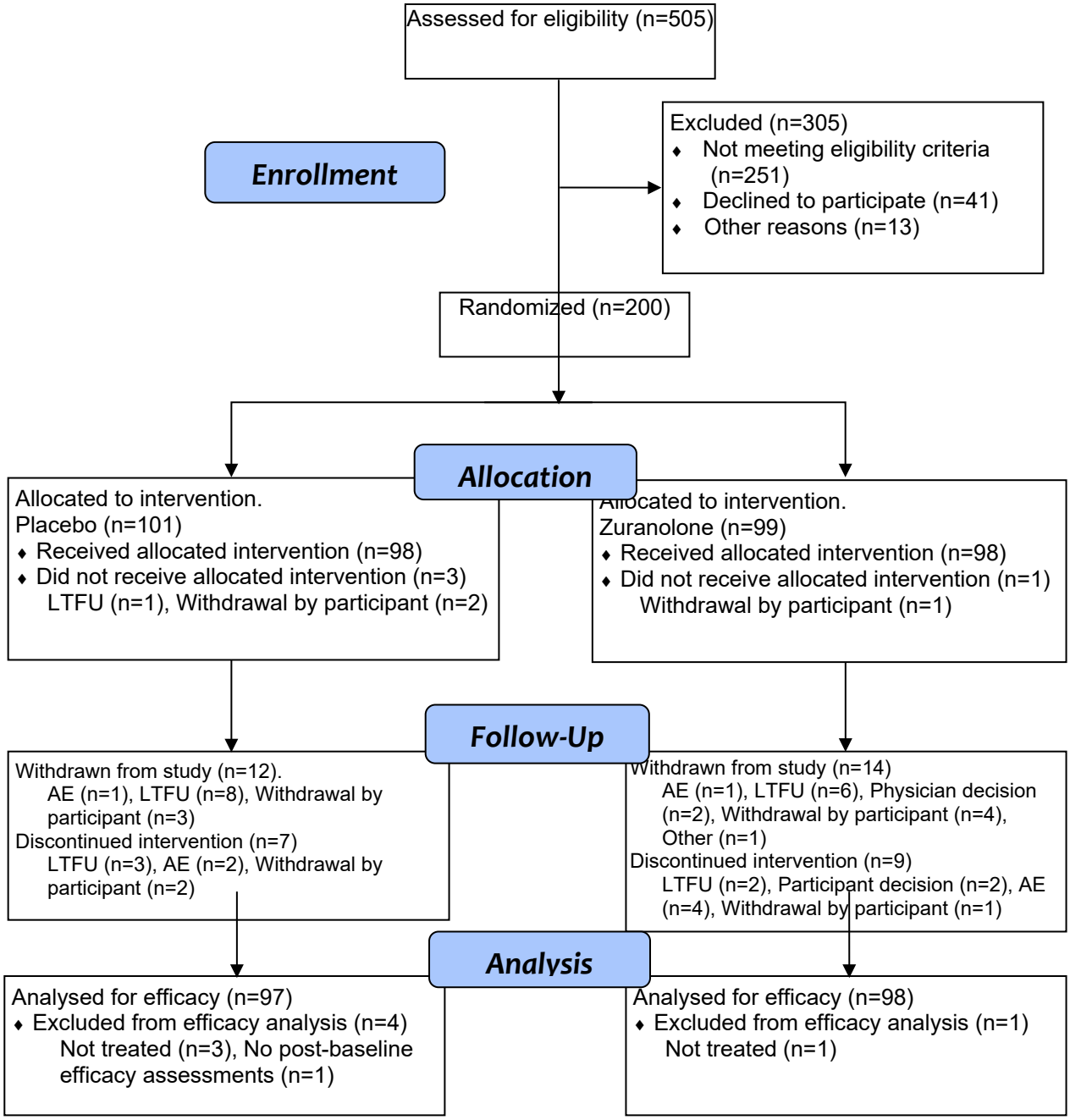
Safety analyses were conducted using the Safety Set, defined as all participants who self-administered blinded IP. Safety data were analysed by the actual IP received.

Change from baseline HAMD-17 total score was analysed using a mixed effects model for repeated measures (MMRM) that included treatment (SAGE-217 or placebo), baseline HAMD-17 total score, antidepressant use at baseline (yes or no), assessment time point, and time point-by-treatment interaction as explanatory variables. All explanatory variables were treated as fixed effects. All postbaseline time points were included in the model. The main comparison was between SAGE-217 and placebo at Day 15. Model-based point estimates (i.e., treatment difference in LS mean, 95% confidence intervals [CIs], and p-values) were reported. The p-value was interpreted at two-sided 5% level of significance. If the comparison of SAGE-217 *versus* placebo was significant at the 0.05 level, the hypothesis testing for the key secondary endpoints followed with a multiplicity adjustment.

Results

A total of 196 participants (98 placebo, 98 SAGE-217) received at least 1 dose of IP. Four participants were randomized but not treated with IP due to withdrawal by participant (2 placebo, 1 SAGE-217) and lost to follow-up (1 placebo). One hundred and eighty participants (91 placebo, 89 SAGE-217) completed IP. One hundred and seventy participants (86 placebo, 84 SAGE-217) completed the study. Lost to follow-up (8 placebo,6 SAGE-217) and withdrawal by subject (3 placebo, 4 SAGE-217) were the most frequently reported reasons for discontinuation of the study.

*Table 8**. Participant flow***



- **Recruitment**

Date of first participant's consent: 08 June 2020. Date of last participant's last visit: 12 April 2022.

- **Conduct of the study**

The original protocol, dated 01 April 2020, had 1 country-specific amendment and was globally amended once.

The primary purpose of Protocol Amendment 1 (version 1, UK) for the United Kingdom (UK), dated 18 September 2020, was to address comments provided by the UK MHRA regarding the emergency unblinding procedure and early termination procedures; this amendment applied to trials conducted in the UK only. Clarifications to the protocol are outlined below: Clarified that participants stopping

participation during the Treatment Period were to undergo all End of Treatment Visit procedures, while those stopping participation after the end of treatment were to undergo all Early Termination Visit procedures. Revised emergency unblinding procedures to specify that investigators could break the blind via the IRT system without consulting with medical monitor or Sage personnel.

The primary purpose of global Protocol Amendment 1 (version 2), dated 29 January 2021, was to modify how participants who discontinued IP would be followed in the study as well as to integrate the 2 protocol versions (US [01 April 2020] and UK [18 September 2020] versions) into 1 global protocol. Other changes were implemented, as outlined below: a) Added COVID-19 questions to be asked to document information regarding diagnosis, isolation, and/or hospitalisation due to COVID-19 as part of medical history, AE collection, and prior/concomitant medication/procedure collection throughout the study; b) Broadened the eligibility criteria to include women who were up to 12 months postpartum (modification to inclusion criterion #9). The criterion for the diagnosis of PPD, including the onset of symptoms, remained the same (inclusion criterion #7) per DSM-5. The extension to 12 months was instituted so that a broader population of participants could be reached, consistent with DSM-5. c) Clarified that a participant with an index pregnancy that resulted in neonatal/infant death would be excluded (modification to exclusion criterion #6). d) Added details on the estimand specified in the protocol per FDA request. e) Removed the definition of overdose from Section 12.4 to align with current Sage practice and other protocols. Cases of overdose were to be collected as reported by the investigator and recorded as an AE. f) Increased the number of sites where the study was to be conducted. g) Aligned the prohibited medication section with medications listed as exclusion criteria.

All studies were GCP compliant.

- **Baseline data**

Table 9. **Participant disposition (all randomised participants) [CSR 217-PPD-301]**

Category	Placebo n (%)	Zuranolone n (%)	Overall n (%)
Number of participants randomised	101	99	200
Number of participants received IP	98	98	196
Completed study[a]	86 (87.8)	84 (85.7)	170 (86.7)
Prematurely withdrawn from study	12 (12.2)	14 (14.3)	26 (13.3)
Lost to follow-up	8 (8.2)	6 (6.1)	14 (7.1)
Withdrawal by subject	3 (3.1)	4 (4.1)	7 (3.6)
Adverse event	1 (1.0)	1 (1.0)	2 (1.0)
Physician decision	0	2 (2.0)	2 (1.0)
Other[b]	0	1 (1.0)	1 (0.5)
Completed IP	91 (92.9)	89 (90.8)	180 (91.8)
Prematurely discontinued IP	7 (7.1)	9 (9.2)	16 (8.2)
Adverse event	2 (2.0)	4 (4.1)	6 (3.1)
Lost to follow-up	3 (3.1)	2 (2.0)	5 (2.6)
Withdrawal by subject	2 (2.0)	1 (1.0)	3 (1.5)

Category	Placebo n (%)	Zuranolone n (%)	Overall n (%)
Subject decision	0	2 (2.0)	2 (1.0)

Note: Denominators for percentages are the number of participants who were randomised and received IP.

[a] A participant was a completer if they completed the last Follow-up Visit.

[b] Other reason for premature withdrawal from the study was due to a conflict in the participants new work schedule.

Table 10. **Demographic and baseline characteristics (safety set) [CSR 217-PPD-301]**

Variable	Placebo (N = 98)	Zuranolone (N = 98)	Overall (N = 196)
Age at informed consent date (years)			
Mean (SD)	31.0 (5.95)	30.0 (5.90)	30.5 (5.93)
Median	31.0	30.0	31.0
Min, max	19, 43	19, 44	19, 44
18 to 24 years	12 (12.2)	19 (19.4)	31 (15.8)
25 to 45 years	86 (87.8)	79 (80.6)	165 (84.2)
Ethnicity, n (%)			
Not Hispanic or Latino	56 (57.1)	64 (65.3)	120 (61.2)
Hispanic or Latino	42 (42.9)	33 (33.7)	75 (38.3)
Race, n (%)			
White	69 (70.4)	68 (69.4)	137 (69.9)
Black or African-American	18 (18.4)	25 (25.5)	43 (21.9)
More than One Race	2 (2.0)	3 (3.1)	5 (2.6)
Other	4 (4.1)	0	4 (2.0)
American Indian or Alaska Native	3 (3.1)	0	3 (1.5)
Asian	1 (1.0)	1 (1.0)	2 (1.0)
Not Reported	1 (1.0)	1 (1.0)	2 (1.0)
Education level, n (%)			
Less than or equal to 12th grade, no diploma	3 (3.1)	4 (4.2)	7 (3.7)
12th grade diploma or GED	32 (33.3)	30 (31.6)	62 (32.5)
Some college but no degree	25 (26.0)	22 (23.2)	47 (24.6)
Occupational associate degree	3 (3.1)	2 (2.1)	5 (2.6)
Academic associate degree	6 (6.3)	6 (6.3)	12 (6.3)
Bachelor’s degree	17 (17.7)	24 (25.3)	41 (21.5)

Variable	Placebo (N = 98)	Zuranolone (N = 98)	Overall (N = 196)
Master's degree	9 (9.4)	5 (5.3)	14 (7.3)
Professional degree	1 (1.0)	2 (2.1)	3 (1.6)
Civil/Marital status, n (%)			
Married	50 (52.1)	37 (38.9)	87 (45.8)
Never married	37 (38.5)	39 (41.1)	76 (39.8)
Divorced	3 (3.1)	7 (7.4)	10 (5.2)
Domestic partner	6 (6.3)	11 (11.6)	17 (8.9)
Single	0	1 (1.1)	1 (0.5)
Employment status			
Full-time (≥35 hours per week)	24 (25.0)	32 (33.7)	56 (29.3)
Part-time (<35 hours per week)	10 (10.4)	7 (7.4)	17 (8.9)
Retired	0	1 (1.1)	1 (0.5)
Unemployed	54 (56.3)	44 (46.3)	98 (51.3)
Other	8 (8.3)	11 (11.6)	19 (9.9)
BMI (kg/m^2)			
≤18.4	0	0	0
18.5 to 24.9	22 (22.4)	20 (20.6)	42 (21.5)
25 to 29.9	34 (34.7)	24 (24.7)	58 (29.7)
≥30	42 (42.9)	53 (54.6)	95 (48.7)
Country			
US	96 (98.0)	95 (96.9)	191 (97.4)
Rest of world	2 (2.0)	3 (3.1)	5 (2.6)
Baseline antidepressant use[a]			
Yes	15 (15.3)	15 (15.3)	30 (15.3)
No	83 (84.7)	83 (84.7)	166 (84.7)
Onset of PPD			
3rd trimester	31 (31.6)	34 (34.7)	65 (33.2)
Postpartum	67 (68.4)	64 (65.3)	131 (66.8)
History of PPD			
1st episode	87 (88.8)	81 (82.7)	168 (85.7)
Recurrent	11 (11.2)	17 (17.3)	28 (14.3)

Variable	Placebo (N = 98)	Zuranolone (N = 98)	Overall (N = 196)
COVID-19 history			
COVID-19	0	1 (1.0)	1 (0.5)
SARS-CoV-2 test positive	6 (6.1)	3 (3.1)	9 (4.6)
Not impacted	92 (93.9)	94 (95.9)	186 (94.9)

- **Numbers analysed**

Of the 505 screened participants, 305 were screen failures. Two-hundred participants were consented and randomised into the study, of whom 196 participants received blinded IP (98 placebo, 98 zuranolone). Four participants were randomised but not treated with IP due to withdrawal by participant (2 placebo, 1 zuranolone) and lost to follow-up (1 placebo).

The majority of participants in each group completed IP (92.9% placebo, 90.8% zuranolone). The percentage of participants who prematurely discontinued IP was similar between groups (7.1% placebo, 9.2% zuranolone). The most frequently reported reasons for discontinuation of IP were, AE (2.0% placebo, 4.1% zuranolone) and lost to follow-up (3.1% placebo, 2.0% zuranolone).

Most participants in each group completed the study (87.8% placebo, 85.7% zuranolone). The most frequently reported reasons for discontinuing the study were, lost to follow-up (8.2% placebo,6.1% zuranolone) and withdrawal by subject (3.1% placebo, 4.1% zuranolone). Only one participant (1%) in either of the treatment groups discontinued from the study due to an AE.

- **Outcomes and estimation**

Outcomes and estimation

A summary of efficacy results is provided in Table below.

Table 11. **Summary of efficacy results in Study 217-PPD-301 (FAS)**

Efficacy Endpoint	Placebo (N = 97)	Zuranolone 50 mg (Autofill) (N = 98)	p-value[a]
Primary: LS mean change (SE) from baseline in HAMD-17 total score at Day 15	(n = 90) -11.6 (0.823)	(n = 93) -15.6 (0.817)	0.0007
LS mean treatment difference (95% CI)	-4.0 (-6.3, -1.7)		
Key Secondary:			
LS mean change (SE) from baseline in HAMD-17 total score at Day 3	(n = 96) -6.1 (0.710)	(n = 98) -9.5 (0.704)	0.0008
LS mean treatment difference (95% CI)	-3.4 (-5.4, -1.4)		

Efficacy Endpoint	Placebo (N = 97)	Zuranolone 50 mg (Autofill) (N = 98)	p-value[a]
LS mean change (SE) from baseline in HAMD-17 total score at Day 28	(n = 85) -13.4 (0.875)	(n = 77) -16.3 (0.884)	0.0203
LS mean treatment difference (95% CI)	-2.9 (-5.4, -0.5)		
LS mean change (SE) from baseline in HAMD-17 total score at Day 45	(n = 85) -14.4 (0.902)	(n = 84) -17.9 (0.903)	0.0067
LS mean treatment difference (95% CI)	-3.5 (-6.0, -1.0)		
LS mean change (SE) from baseline in CGI-S total score at Day 15	(n = 90) -1.6 (0.139)	(n = 93) -2.2 (0.138)	0.0052
LS mean treatment difference (95% CI)	-0.6 (-0.9, -0.2)		
Other Secondary:			
Percentage of participants with HAMD-17 response[b] at Day 15 n (%)	(n = 90) 35 (38.9)	(n = 93) 53 (57.0)	0.0209
Odds ratio (95% CI)	2.020 (1.112, 3.670)		
Percentage of participants with HAMD-17 remission[c] at Day 15 n (%)	(n = 90) 15 (16.7)	(n = 93) 25 (26.9)	0.1110
Odds ratio (95% CI)	1.781 (0.876, 3.621)		
LS mean change (SE) from baseline in HAM-A total score at Day 15	(n = 90) -10.6 (0.697)	(n = 92) -12.8 (0.693)	0.0235
LS mean treatment difference (95% CI)	-2.2 (-4.2, -0.3)		
LS mean change (SE) from baseline in MADRS total score at Day 15	(n = 90) -14.6 (1.209)	(n = 92) -19.7 (1.202)	0.0034
LS mean treatment difference (95% CI)	-5.1 (-8.4, -1.7)		
Percentage of participants with CGI-I response[d] at Day 15 n (%)	(n = 90) 42 (46.7)	(n = 93) 62 (66.7)	0.0089
Odds ratio (95% CI)	2.232 (1.223, 4.072)		

[a] All p-values and LS means are from MMRM analysis, with the exception of HAMD-17 response, HAMD-17 remission, and CGI-I response, which are from model-based GEE analysis.

[b] HAMD-17 response is defined as ≥ 50% reduction from baseline in HAMD-17 total score.

[c] HAMD-17 remission is defined as a HAMD-17 total score ≤ 7.

[d] CGI-I response is defined as a CGI-I score of very much improved or much improved.

Note: n numbers refer to the number of participants with data at the time point.

HAMD 17 responder rate by study visit

Summary of Hamilton Rating Scale for Depression (HAM-D) Response by Study Visit
Full Analysis Set

	Placebo(N=97)		SAGE-217(N=98)	
Study Visit	n[1]	Response[2]	n[1]	Response[2]
Day 3	96	12(12.5%)	98	26(26.5%)
Day 8	95	24(25.3%)	93	47(50.5%)
Day 15	90	35(38.9%)	93	53(57.0%)
Day 21	83	35(42.2%)	84	50(59.5%)
Day 28	85	35(41.2%)	77	48(62.3%)
Day 45	85	46(54.1%)	84	52(61.9%)

MADRS responder rate by study visit

Summary of Montgomery-Åsberg Depression Rating Scale (MADRS) Response by Study Visit
Full Analysis Set

	Placebo (N=97)		SAGE-217 (N=98)	
Study Visit	n[1]	Response[2]	n[1]	Response[2]
Day 8	94	25 (26.6%)	93	44 (47.3%)
Day 15	89	33 (37.1%)	92	52 (56.5%)
Day 28	81	35 (43.2%)	76	45 (59.2%)
Day 45	84	43 (51.2%)	84	55 (65.5%)

CGI-I responder rate by study visit

Summary of Clinical Global Impression - Improvement (CGI-I) Response by Study Visit
Full Analysis Set

	Placebo (N=97)		SAGE-217 (N=98)	
Study Visit	n[1]	Response[2]	n[1]	Response[2]
Day 3	95	13 (13.7%)	98	29 (29.6%)
Day 8	95	30 (31.6%)	93	55 (59.1%)
Day 15	90	42 (46.7%)	93	62 (66.7%)
Day 21	83	45 (54.2%)	84	60 (71.4%)
Day 28	85	48 (56.5%)	77	56 (72.7%)
Day 45	85	56 (65.9%)	84	62 (73.8%)

EPDS

Model-based Results on Change from Baseline in Edinburgh Postpartum Depression Scale (EPDS) by Study Visit
Full Analysis Set

Study Visit Statistics	Placebo (N=97)	SAGE-217 (N=98)
Day 3		
LS Mean (SE)	-2.3 (0.491)	-3.8 (0.486)
(95% CI for LS Mean)	(-3.3, -1.3)	(-4.8, -2.8)
SAGE-217 - Placebo		
LS Mean (SE)		-1.5 (0.694)
(95% CI for LS Mean)		(-2.9, -0.1)
p-value		0.0324
Day 8		
LS Mean (SE)	-6.2 (0.590)	-8.4 (0.595)
(95% CI for LS Mean)	(-7.4, -5.0)	(-9.6, -7.2)
SAGE-217 - Placebo		
LS Mean (SE)		-2.2 (0.840)
(95% CI for LS Mean)		(-3.8, -0.5)
p-value		0.0098
Day 15		
LS Mean (SE)	-8.4 (0.662)	-10.3 (0.660)
(95% CI for LS Mean)	(-9.7, -7.1)	(-11.6, -9.0)
SAGE-217 - Placebo		
LS Mean (SE)		-2.0 (0.937)
(95% CI for LS Mean)		(-3.8, -0.1)
p-value		0.0377

Model-based Results on Change from Baseline in Edinburgh Postpartum Depression Scale (EPDS) by Study Visit
Full Analysis Set

Study Visit Statistics	Placebo (N=97)	SAGE-217 (N=98)
Day 21		
LS Mean (SE)	-9.3 (0.688)	-11.0 (0.685)
(95% CI for LS Mean)	(-10.7, -8.0)	(-12.3, -9.6)
SAGE-217 - Placebo		
LS Mean (SE)		-1.7 (0.973)
(95% CI for LS Mean)		(-3.6, 0.3)
p-value		0.0911
Day 28		
LS Mean (SE)	-9.5 (0.731)	-11.3 (0.745)
(95% CI for LS Mean)	(-11.0, -8.1)	(-12.8, -9.9)
SAGE-217 - Placebo		
LS Mean (SE)		-1.8 (1.046)
(95% CI for LS Mean)		(-3.9, 0.3)
p-value		0.0875
Day 45		
LS Mean (SE)	-9.8 (0.758)	-12.2 (0.761)
(95% CI for LS Mean)	(-11.3, -8.3)	(-13.7, -10.7)
SAGE-217 - Placebo		
LS Mean (SE)		-2.4 (1.076)
(95% CI for LS Mean)		(-4.5, -0.3)
p-value		0.0278

PHQ9

Model-based Results on Change from Baseline in Patient Health Questionnaire (PHQ-9) Total Score by Study Visit
Full Analysis Set

Study Visit Statistics	Placebo (N=97)	SAGE-217 (N=98)
Day 3		
LS Mean (SE)	-2.3 (0.462)	-2.0 (0.456)
(95% CI for LS Mean)	(-3.2, -1.4)	(-2.9, -1.1)
SAGE-217 - Placebo		
LS Mean (SE)		0.3 (0.649)
(95% CI for LS Mean)		(-1.0, 1.5)
p-value		0.6912
Day 8		
LS Mean (SE)	-5.9 (0.617)	-7.7 (0.620)
(95% CI for LS Mean)	(-7.1, -4.6)	(-8.9, -6.4)
SAGE-217 - Placebo		
LS Mean (SE)		-1.8 (0.874)
(95% CI for LS Mean)		(-3.5, -0.1)
p-value		0.0410
Day 15		
LS Mean (SE)	-8.6 (0.652)	-10.5 (0.651)
(95% CI for LS Mean)	(-9.9, -7.3)	(-11.8, -9.2)
SAGE-217 - Placebo		
LS Mean (SE)		-1.9 (0.922)
(95% CI for LS Mean)		(-3.7, 0.0)
p-value		0.0444

Abbreviations: CI = Confidence interval; LS = Least-squares; SE = Standard error.
Note: The PHQ-9 total score was calculated as the sum of the 9 individual item scores. A negative change indicates improvement. Model used is the Mixed Model for Repeated Measures (MMRM) with treatment(SAGE-217 or placebo), baseline PHQ-9 total score, anti-depressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with a unstructured covariance structure.

Model-based Results on Change from Baseline in Patient Health Questionnaire (PHQ-9) Total Score by Study Visit
Full Analysis Set

Study Visit Statistics	Placebo (N=97)	SAGE-217 (N=98)
Day 21		
LS Mean (SE)	-9.0 (0.655)	-10.6 (0.651)
(95% CI for LS Mean)	(-10.3, -7.7)	(-11.9, -9.4)
SAGE-217 - Placebo		
LS Mean (SE)		-1.6 (0.924)
(95% CI for LS Mean)		(-3.4, 0.2)
p-value		0.0811
Day 28		
LS Mean (SE)	-9.2 (0.692)	-10.5 (0.703)
(95% CI for LS Mean)	(-10.6, -7.9)	(-11.9, -9.2)
SAGE-217 - Placebo		
LS Mean (SE)		-1.3 (0.987)
(95% CI for LS Mean)		(-3.3, 0.6)
p-value		0.1846
Day 45		
LS Mean (SE)	-9.8 (0.728)	-11.7 (0.731)
(95% CI for LS Mean)	(-11.2, -8.4)	(-13.2, -10.3)
SAGE-217 - Placebo		
LS Mean (SE)		-1.9 (1.031)
(95% CI for LS Mean)		(-4.0, 0.1)
p-value		0.0625

The effect of zuranolone on HAMD 17 as compared to placebo started to diverge from day 3 and peaked by day 15 (4.0 point difference) decreasing afterwards, but maintaining a 3.5 point difference by day 45. This difference of 4 points is considered to be in the range of the minimally important difference (MID) for HAMD 17 (3 to 5 points). However, this must be put into the context of a condition where most patients improve within the studied period. In fact, the 4 point improvement occurred in both study arms within the initial 3 days. When considering a 50% improvement in score from baseline as responder definition, by day 15 57% had responded to zuranolone as compared to 38.9% in placebo. However, by day 28 the difference was no longer statistically significant and by day 45 this

response was reduced to 61.9% in zuranolone as compared to 54.1% in the placebo. This means that the primary endpoint was simply reached earlier with zuranolone than with placebo.

The other clinician rated endpoints were in line with the primary endpoint, with deviations from placebo early in the study, and a responder rate by day 15 for Montgomery-Åsberg Depression Rating Scale (MADRS) of 56.5% for zuranolone and 37.1% for placebo. This effect waned afterwards, and by day 45 there were 65.5% responders with zuranolone as compared to 51.2% for placebo. With Clinical Global Impression - Improvement (CGI-I), by day 15 there were 66.7% responders with zuranolone vs. 46.7% with placebo. Again, this difference decreased largely by day 45: 73.8% for zuranolone and 65.9% for placebo.

As for the patient reported outcomes, the magnitude of effect of zuranolone as compared to placebo were less clear:

EPDS: by day 15 there was a 49.6% reduction with zuranolone while placebo had a 40% reduction. By day 45 the reduction was 57.8% for zuranolone and 48.2% for placebo.

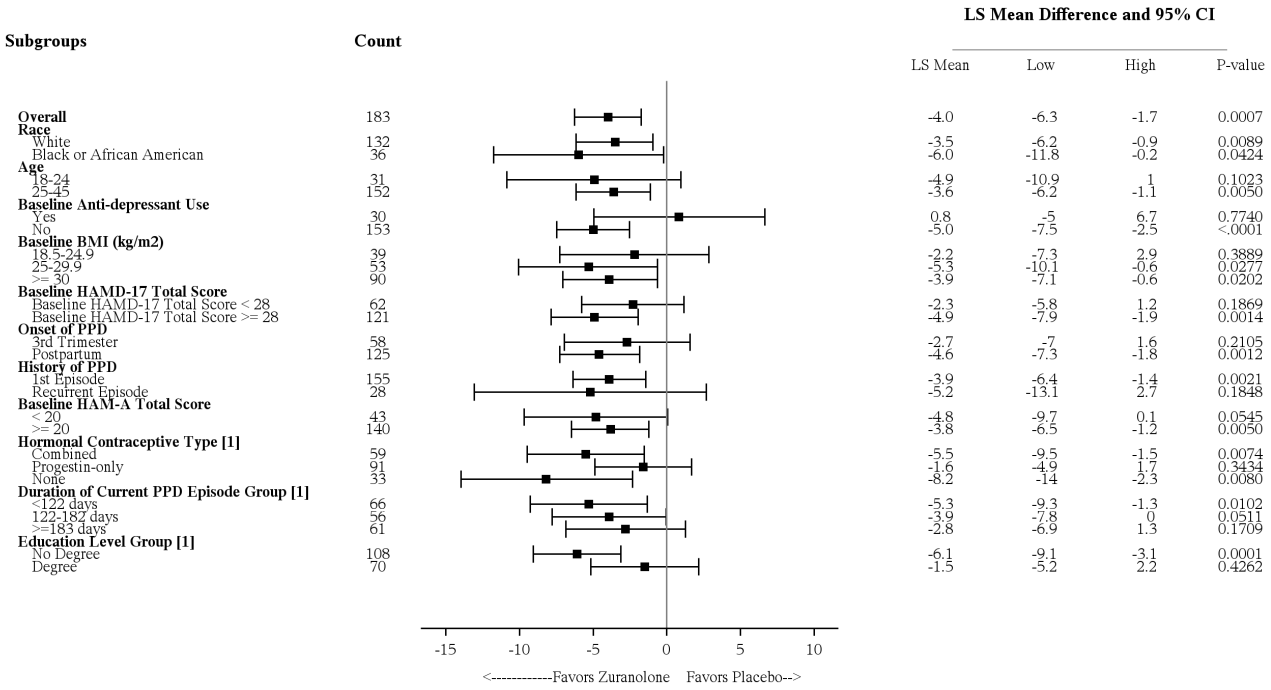
PHQ9: by day 15 there was an 85.7% improvement with zuranolone but placebo also had a 76.7% improvement as compared to baseline. By day 45 the improvement was similarly maintained 84.5% for zuranolone and 77.6% for placebo.

In conclusion, the results show that in the US population, zuranolone showed a relevant response as measured by HAMD 17, but the placebo also exhibited a relevant response, and both were sustained until the end of the study. Moreover, the maximal difference between arms peaked around day 15 and decreased afterwards. The net magnitude of effect was 4.0 points, which falls within the 3-5 points considered the minimal important difference for HAMD 17. This difference decreased to 3.5 points by day 45.

- **Ancillary analyses**

The LS mean difference in HAMD-17 total score at Day 15 favoured zuranolone in 24 of the 25 subgroups analysed, with the only exception being the ADT use at baseline = “Yes” subgroup

Figure 2. Forest plot of LS mean (95% CI) change from baseline in HAMD-17 total score by treatment group and demographic subgroups at Day 15 in Study 217-PPD-301 (FAS)



[1] Post hoc subgroup analysis.

Note 1: Results are from an MMRM with treatment, baseline HAMD-17 total score, antidepressant use at baseline, assessment timepoint, and timepoint-by-treatment interaction as fixed effects.

Note 2: The BMI ≤ 18 kg/m^2 subgroup was not included due to small number of participants.

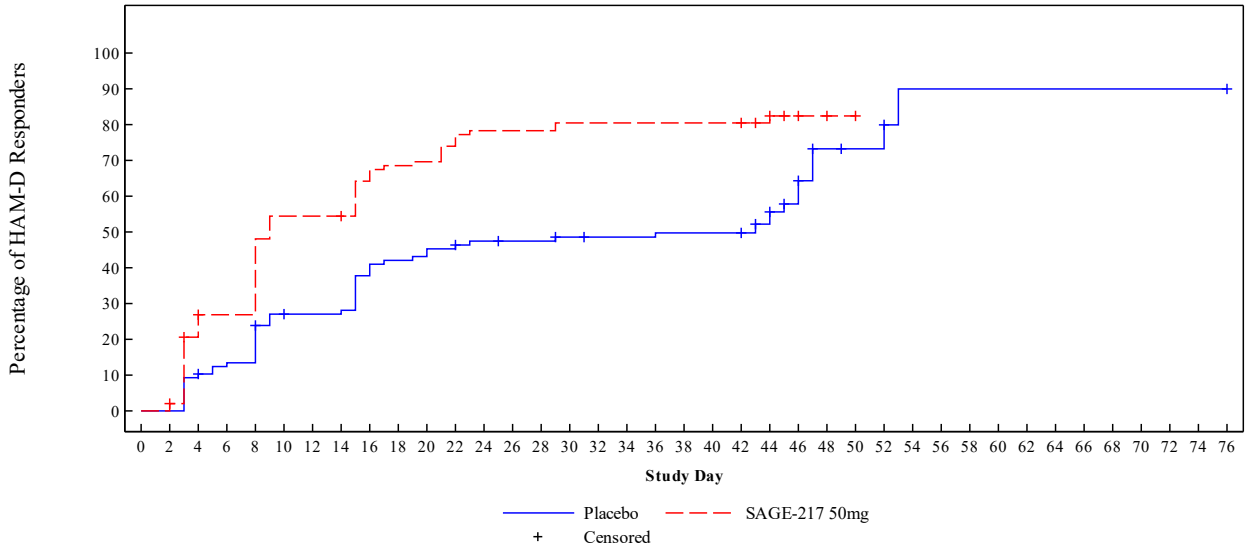
Source: CSR 217-PPD-301 post hoc Output.

In patients concomitantly treated with antidepressants, adding zuranolone may have a deleterious effect. Possible reasons, along with the possible risk of increase in suicidal thoughts early in the course of treatment were deliberated. However, mechanistically there is no reason to suspect altered efficacy compared to zuranolone monotherapy and no differences were identified in safety profile for zuranolone mono- or combination therapy. A general warning on lowering the dose if AEs occur is included in section 4.4, which is considered sufficient.

Time to HAMD-17 response and remission

Zuranolone showed a rapid response, with a median time to first HAMD-17 response of 9.0 days, compared with 43.0 days in the placebo group (Figure 1, and CSR 217-PPD-301). The median time to first HAMD-17 remission was 30.0 days in the zuranolone group compared with 50.0 days in the placebo group (Figure 3, and CSR 217-PPD-301).

Figure 3. Kaplan-Meier plot of time to first HAMD-17 response in Study 217-PPD-301 (FAS)



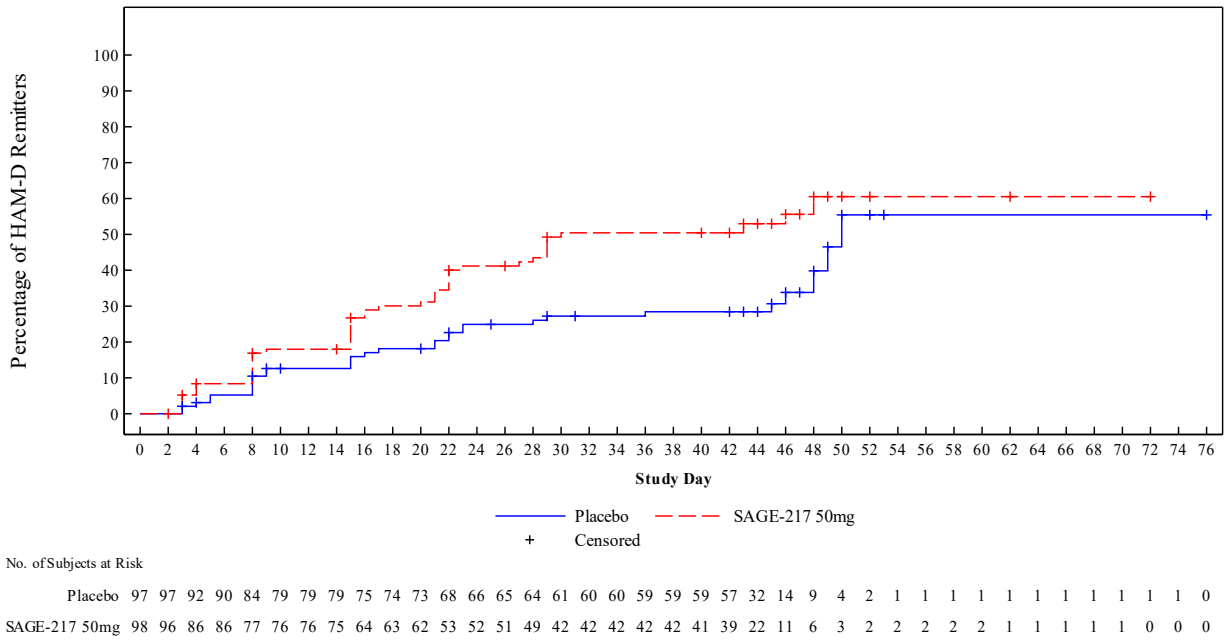
No. of Subjects at Risk

Placebo	97	97	86	83	72	68	68	67	55	54	51	49	48	47	47	45	44	44	43	43	43	41	20	8	5	4	2	1	1	1	1	1	1	1	1	1	0
SAGE-217 50mg	98	95	69	69	49	43	43	42	30	29	28	21	20	20	20	18	18	18	18	18	18	16	7	3	2	0	0	0	0	0	0	0	0	0	0	0	0

Note: HAMD-17 response is defined as a 50% or greater reduction from baseline in HAMD-17 total score. Days are calculated from the date of the first dose. Participants who are not responders are censored at the day of the last available HAMD-17 evaluation.

Source: CSR 217-PPD-301.

Figure 4. Kaplan-Meier plot of time to first HAMD-17 remission in Study 217-PPD-301 (FAS)



Note: HAMD-17 remission is defined as having a HAMD-17 total score of ≤7. Participants with no remission are censored at the day of the last available HAMD-17 evaluation.
Source: CSR 217-PPD-301.

Relapse and rebound in PPD

Relapse was defined as at least 2 consecutive HAMD-17 total scores ≥ 20 after Day 15 through Day 45 in participants who were HAMD-17 responders at Day 15. Rebound was defined as any HAMD-17 total score greater than or equal to baseline after Day 15 through Day 45 in participants who were HAMD-17 responders at Day 15.

In Study 217-PPD-301, relapse was low across treatment groups, experienced by 3 participants (5.7%) in the zuranolone (50 mg [Autofill]) group and 2 participants (5.7%) in the placebo group (CSR 217-PPD-301). Rebound was experienced by 1 participant (2.9%) in the placebo group and no participants in the zuranolone group.

As discussed earlier, the time to initial response is shorter with zuranolone than with placebo; however, this effect has only been observed with clinician based endpoints, and was not observed with PRO. It is how the patients feels that is most important to the mother-child interaction. Therefore, the benefit from zuranolone has not been demonstrated.

- **Summary of main efficacy results**

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

*Table 12**. Summary of efficacy for trial 217-PPD-301 (SKYLARK)***

Title: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF SAGE-217 IN THE TREATMENT OF ADULTS WITH SEVERE POSTPARTUM DEPRESSION			
Study identifier	Protocol number: 217-PPD-301 EudraCT number: 2020-001424-34 Clinical Trials.gov identifier (NCT number): NCT04442503		
Design	Study 217-PPD-301 was a randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of zuranolone in adults diagnosed with severe PPD. This study consisted of a Screening Period of up to 28 days, a 14-day double-blind Treatment Period, and a Follow-up Period through Day 45. Eligible participants were stratified based on use of baseline antidepressant treatment and randomised to zuranolone treatment or placebo on a 1:1 basis.		
	Duration of main phase: Duration of Run-in phase: Duration of extension phase:		45 days, including 14 days of treatment. No Run-in phase. The screening phase was up to 28 days. No extension phase. Patients were followed-up through to Day 45.
Hypothesis	Superiority		
Treatments groups	Zuranolone		Treatment: 50mg (Autofill) administered as 2 oral capsules (1 x 20-mg and 1 x 30-mg], once daily at 8:00 PM with fat-containing foods. Duration: Once daily for 14 days with last follow up at Day 45 Number randomised: 99
	Placebo		Treatment: Placebo capsules at 8:00 PM with fat-containing food Duration: Once daily for 14 days with last follow up at Day 45 Number randomised: 101
Endpoints and definitions	Primary	HAMD-17 total score	Change from baseline in HAMD-17 total score at Day 15.
	Key Secondary	HAMD-17 total score	Change from baseline in HAMD-17 total score at Days 3, 28, and 45
	Key Secondary	CGI-S score	Change from baseline in CGI-S score at Day 15
	Secondary	HAMD-17 response	HAMD-17 response, defined as a 50% or greater reduction from baseline in HAMD-17 total score, at Day 15
	Secondary	HAMD-17 remission	HAMD 17 remission, defined as a HAMD-17 total score of ≤ 7, at Day 15
Database lock	16 May 2022		
Results and Analysis			
Analysis description	**Primary Endpoint Analysis**		

Analysis population and time point description	The primary analysis population is the Full Analysis Set (FAS), defined as all randomised participants who were administered IP with valid baseline total score and at least 1 post-baseline total score in at least one of HAMD-17, HAM-A, MADRS, CGI-S, EPDS or PHQ-9, or at least 1 postbaseline value of CGI-I; participants were analysed according to their randomised treatment group. Of the 200 participants randomised, 196 participants were dosed with IP, 195 of whom were included in the FAS. The primary endpoint was the change from baseline in HAMD-17 total score assessed at Day 15.		
Endpoint: **Change from baseline in HAMD-17 total score at Day 15 (Primary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	97	98
	Number of participants n (at visit)	90	93
	LS Mean Change from Baseline	-11.6	-15.6
	Standard error	0.823	0.817
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	LS mean difference	-4.0	
	95% CI	(-6.3, -1.7)	
	P-value (MMRM)	0.0007	
Notes	The HAMD-17 total score was calculated as the sum of the 17 individual item scores. A negative change indicates improvement. Model used is the Mixed Model for Repeated Measures (MMRM) with treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure. Less than 10% of HAMD-17 total score data were considered missing at Day 15. The most frequently reported reasons for discontinuing the study were, lost to follow-up and withdrawal by participant. One participant in each treatment group discontinued from the study due to an AE. A sensitivity analysis to assess the impact of missing HAMD-17 total score was performed using multiple imputation, with missing values imputed using missing at random (if missing because participant withdrew due to pregnancy) or jump to reference (if missing for any other reason). The sensitivity analysis showed similar results to the primary analysis. A nominally significant p-value of 0.0006, indicated that the impact of missing data on the primary endpoint was negligible.		
Analysis description	**Secondary Endpoint Analysis**		

Analysis population and time point description	The analysis population for the secondary endpoints is the FAS. The secondary endpoints were assessed at Days 3, 15, 28 and 45 as follows: • Change from baseline in HAMD-17 total score at Days 3, 28 and 45 (key secondary endpoints) • Change from baseline in CGI-S score at Day 15 (key secondary endpoint) • HAMD-17 response at Day 15 • HAMD-17 remission at Day 15 To control the Type 1 error, if the comparison between zuranolone and placebo was significant at the 0.05 level for the primary endpoint, then the key secondary endpoints were tested sequentially according to the prespecified hierarchy below: • Change from baseline in HAMD-17 total score at Day 3 • Change from baseline in HAMD-17 total score at Day 28 • Change from baseline in HAMD-17 total score at Day 45 • Change from baseline in CGI-S score at Day 15		
Endpoint: **Change from baseline in HAMD-17 total score at Day 3 (Key secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	97	98
	Number of participants n (at visit)	96	98
	LS Mean Change from Baseline	-6.1	-9.5
	Standard error	0.710	0.704
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	LS mean difference	-3.4	
	95% CI	(-5.4, -1.4)	
	P-value (MMRM)	0.0008	
Notes	The HAMD-17 total score was calculated as the sum of the 17 individual item scores. A negative change indicates improvement. Model used is the Mixed Model for Repeated Measures (MMRM) with treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure.		
Endpoint: **Change from baseline in HAMD-17 total score at Day 28 (Key secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	97	98
	Number of participants n (at visit)	85	77
	LS Mean Change from baseline	-13.4	-16.3
	Standard error	0.875	0.884
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	LS mean difference	-2.9	
	95% CI	(-5.4, -0.5)	
	P-value (MMRM)	0.0203	

Notes	The HAMD-17 total score was calculated as the sum of the 17 individual item scores. A negative change indicates improvement. Model used is the Mixed Model for Repeated Measures (MMRM) with treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure.		
Endpoint: **Change from baseline in HAMD-17 total score at Day 45 (Key secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	97	98
	Number of participants n (at visit)	85	84
	LS Mean Change from baseline	-14.4	-17.9
	Standard error	0.902	0.903
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	LS mean difference	-3.5	
	95% CI	(-6.0, -1.0)	
	P-value (MMRM)	0.0067	
Notes	The HAMD-17 total score was calculated as the sum of the 17 individual item scores. A negative change indicates improvement. Model used is the Mixed Model for Repeated Measures (MMRM) with treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure.		
Endpoint: **Change from baseline in CGI-S score at Day 15 (Key secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	97	98
	Number of participants n (at visit)	90	93
	LS Mean Change from baseline	-1.6	-2.2
	Standard error	0.139	0.138
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	LS mean difference	-0.6	
	95% CI	(-0.9, -0.2)	
	P-value (MMRM)	0.0052	
Notes	CGI-S uses a 7-point scale. A negative change indicates improvement. Model used is the Mixed Model for Repeated Measures (MMRM) with treatment, baseline CGI-S score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure.		
Endpoint: **HAMD-17 response at Day 15 (Secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	97	98
	Number of participants n (at visit)	90	93

	Number of responders	35	53
	Percentage of responders	38.9	57.0
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	Odds ratio	2.020	
	95% CI	(1.112, 3.670)	
	P-value (GEE)	0.0209	
Notes	HAMD-17 response is defined as a 50% or greater reduction from baseline in HAMD-17 total score. Model used is a generalized estimating equation (GEE) for binary response model, with factors for treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction with unstructured covariance structure.		
Endpoint: **HAMD-17 remission at Day 15 (Secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	97	98
	Number of participants n (at visit)	90	93
	Number of remitters	15	25
	Percentage of remitters	16.7	26.9
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	Odds ratio	1.781	
	95% CI	(0.876, 3.621)	
	P-value (GEE)	0.1110	
Notes	HAMD 17 remission is defined as a HAMD-17 total score of ≤ 7. Model used is a generalized estimating equation (GEE) for binary response model, with factors for treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction with unstructured covariance structure.		

2.6.5.3. Clinical studies in special populations

See Clinical Pharmacology section.

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)

Pooled analyses of efficacy were not conducted for PPD studies, as no additional insight would be gained by pooling given that different dose levels of zuranolone were administered in each study (50 mg [Autofill] in Study 217-PPD-301 and 30 mg [ProFill] in Study 217-PPD-201B).

2.6.5.6. Supportive study(ies)

Table 13. **Summary of efficacy for trial 217-PPD-201 (ROBIN)**

Title: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of SAGE-217 in the Treatment of Adult Female Subjects with Severe Postpartum Depression			
Study identifier	Protocol number: 217-PPD-201 Clinical Trials.gov identifier (NCT number): NCT02978326		
Design	Study 217-PPD-201 was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of the efficacy, safety, and PK of SAGE-217 in adult participants diagnosed with severe PPD. This study was conducted in 2 parts: Part A and Part B. Part A, which used an oral solution of SAGE-217, was closed to enrolment when an oral capsule formulation became available, and Part B was introduced. The parts comprised distinct participants. Only 1 participant received study drug in Part A before it was closed to enrolment; thus, the results below are those for Part B only. Eligible participants were randomised to zuranolone treatment or placebo on a 1:1 basis in both parts of the study.		
	Duration of main phase:		45 days, including 14 days of treatment.
	Duration of Run-in phase:		No Run-in phase. The screening phase was up to 28 days.
	Duration of extension phase:		No extension phase. Patients were followed-up through to Day 45.
Hypothesis	Superiority		
Treatments groups	Zuranolone		Treatment: 30mg (ProFill) oral capsules at 8:00 PM with food Duration: Once daily for 14 days with last follow up at Day 45 Number randomised: 77
	Placebo		Treatment: Placebo oral capsules at 8:00 PM with food Duration: Once daily for 14 days with last follow up at Day 45 Number randomised: 76
Endpoints and definitions	Primary	HAMD-17 total score	Change from baseline in HAMD-17 total score at Day 15
	Secondary	HAMD-17 total score	Change from baseline in HAMD-17 total score at Days 3 and 45
	Secondary	HAMD-17 response	HAMD-17 response, defined as a 50% or greater reduction from baseline in HAMD-17 total score, at Day 15

	Secondary	HAMD-17 remission	HAMD 17 remission, defined as a HAMD-17 total score of ≤ 7, at Day 15
Database lock	13 February 2019		
Results and Analysis			
Analysis description	**Primary Endpoint Analysis**		
Analysis population and time point description	The primary analysis population is the Efficacy Set, defined as all participants in Part B who were administered IP and had a valid baseline and ≥ 1 postbaseline efficacy assessment; participants were analysed according to their randomised treatment group. Of the 153 participants randomised, 151 participants were dosed with IP, 150 of whom were included in the Efficacy Set. The primary endpoint was the change from baseline in HAMD-17 total score assessed at Day 15		
Endpoint: **Change from baseline in HAMD-17 total score at Day 15 (Primary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	74	76
	Number of participants n (at visit)	73	74
	LS Mean Change from Baseline	-13.6	-17.8
	Standard error	1.07	1.04
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	LS mean difference	-4.2	
	95% CI	(-6.9, -1.5)	
	P-value (MMRM)	0.0028	
Notes	The HAMD-17 total score was calculated as the sum of the 17 individual item scores. A negative change indicates improvement. Model used is the Mixed Model for Repeated Measures (MMRM) with treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure. Less than 5% of HAMD-17 total score data were considered missing at Day 15. The most frequently reported reasons for discontinuing the study were, withdrawal by participant and lost to follow-up. One participant in the zuranolone treatment group discontinued from the study due to an AE. A sensitivity analysis was planned but not conducted due to small amount of missing data (<5%)		
Analysis description	**Secondary Endpoint Analysis**		

Analysis population and time point description	The analysis population for the secondary endpoints is the Efficacy Set. No key secondary endpoints were specified and there was no adjustment for multiplicity. The secondary endpoints were assessed at Days 3, 15 and 45 as follows: • Change from baseline in HAMD-17 total score at Days 3 and 45 • HAMD-17 response at Day 15		
Endpoint: **Change from baseline in HAMD-17 total score at Day 3 (Secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	74	76
	Number of participants n (at visit)	74	74
	LS Mean Change from Baseline	-9.8	-12.5
	Standard error	0.95	0.93
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	LS mean difference	-2.7	
	95% CI	(-5.1, -0.3)	
	P-value (MMRM)	0.0252	
Notes	The HAMD-17 total score was calculated as the sum of the 17 individual item scores. A negative change indicates improvement. Model used is the Mixed Model for Repeated Measures (MMRM) with treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure.		
Endpoint: **Change from baseline in HAMD-17 total score at Day 45 (Secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	74	76
	Number of participants n (at visit)	69	73
	LS Mean Change from baseline	-15.1	-19.2
	Standard error	1.06	1.02
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	LS mean difference	-4.1	
	95% CI	(-6.7, -1.4)	
	P-value (MMRM)	0.0027	

Notes	The HAMD-17 total score was calculated as the sum of the 17 individual item scores. A negative change indicates improvement. Model used is the Mixed Model for Repeated Measures (MMRM) with treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as fixed effects with unstructured covariance structure.		
Endpoint: **HAMD-17 response at Day 15 (Secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	74	76
	Number of participants n (at visit)	73	74
	Number of responders	35	53
	Percentage of responders	47.9	71.6
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	Odds ratio	2.63	
	95% CI	(1.34, 5.16)	
	P-value (GEE)	0.0049	
Notes	HAMD-17 response is defined as a 50% or greater reduction from baseline in HAMD-17 total score. Model used is a generalized estimating equation (GEE) for binary response model, with factors for treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction with unstructured covariance structure.		
Endpoint: **HAMD-17 remission at Day 15 (Secondary endpoint)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Zuranolone
	Number of participants N (FAS)	74	76
	Number of participants n (at visit)	73	74
	Number of remitters	17	33
	Percentage of remitters	23.3	44.6
Effect estimate per comparison	Comparison groups	Zuranolone vs Placebo	
	Odds ratio	2.53	
	95% CI	(1.24, 5.17)	
	P-value (GEE)	0.0110	
Notes	HAMD 17 remission is defined as a HAMD-17 total score of ≤ 7. Model used is a generalized estimating equation (GEE) for binary response model, with factors for treatment, baseline HAMD-17 total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction with unstructured covariance structure.		

2.6.6. Healthcare professional engagement

Contributions received from Patients and Healthcare Professionals Organisations

From **Patients Organisation**, contribution was received from the *European Institute of Women's Health (EUWH)* who gave input on the PPD, causes and current treatments available, implications for the women, the child and family. The organisation welcomed new opportunities for treatment highlighting the fact that *any medical interventions should also be coupled with lifestyle and other contextual interventions*, that *the impact of any medication on the mother and child in the early stages after birth*, the need for a *rapid onset of relief due to the importance of resolving the PDD symptoms,* the *options for targeted treatment for different symptoms e.g. depression, anxiety*, the need for *regular monitoring for impact of the treatment, including adverse effects,* and the need to ensure *that side effects do not impact daily life, are reversible and well-articulated to patients and healthcare providers*.

From **Healthcare Professionals Organisations** contributions were received from the *European Union of General Practitioners* and the *European Psychiatric Association (Women's Mental Health Section)*. Both organisations focused on the added value of a new medicine that can be used for short duration opposing to SSRIs that need to be taken *for very long periods of time after the patient has recovered from depression*. Both organisations, like Patients' organisation, also highlighted the need to ensure the safety of the new drug for the women and for the child, with regards to breastfeeding. The new drug should not be associated *with significant sedation as seen for some antidepressants* (but not for SSRIs) *that may potentially impair maternal function* and ultimately *may place the child at risk.* In the opinion of the *European Psychiatric Association (Women's Mental Health Section)* the *relationship between zuranolone-induced sedation and ability to provide safe infant care has not been addressed* in the studies with zuranolone.

The *European Union of General Practitioners* also pointed out the potential of *weight gain* during the use of the medicine which will add to the natural difficulty of losing weight after pregnancy and the *restart of contraception shortly after giving birth* which may be linked to higher thromboembolic risk. The organisation calls the attention for the need of training GPs on how to prescribe the new drug as GPs often end up continue to prescribe a drug initiated by a psychiatrist that they are not familiar with.

The *European Psychiatric Association (Women's Mental Health Section)* provided information on the *current standards of care for PPD* which include *social*, *psychological and psychotherapeutic* interventions, *treatment of physical conditions that are causative or aggravating factors* and *somatic treatment that include range of antidepressant drugs and neurostimulation, including electro-convulsive therapy (ECT)*, which *is used for life-threatening cases where rapid improvement is required or where the illness is severe and all other treatments have failed.* The organisation considers that a new antidepressant medication associated with a *shortening of the treatment would be a major advantage* provided *the effectiveness in the long-term and in patients with recurrent depression is established.* The organisation calls the attention for the fact that *the majority of patients benefitting from current standards of care recover from major depressive episodes but a significant proportion fails to respond* and therefore *new treatments that are effective in non-responders are urgently needed*. In addition, *significant improvement in depressive symptoms is seen after 2-3 weeks of antidepressant therapy and a more rapid onset would be desirable*. Likewise, because a *gradual tapering down of antidepressant dosing over several weeks is required* to obviate *discontinuation symptoms*, *treatments not causing these symptoms would be desirable*. Specifically regarding zuranolone, the organisation refers to *preliminary data* (Deligiannidis et al, 2024) *that show that the relative infant dose of zuranolone during breastfeeding is low* despite the fact that MAA excludes breastfeeding. In this case, the patients *may choose to express and discard breast milk during the two*

weeks of treatment and resume breastfeeding after the end of treatment. Alternatively, if zuranolone is prescribed to breastfeeding women the advice of the Drugs and Lactation Database (2024) is to monitor the infant for excessive sedation. An important aspect, also of concern for the CHMP is the use of zuranolone during pregnancy and in women that may become pregnant again, considering *reports of foetal harm in animal studies*. The organisation addressed some aspects about PPD that are considered not well understood or not well considered namely the definition of PPD itself, the diagnostic criteria, and the timing of the onset of depressive episodes. *The diagnostic criteria for depression in the postnatal period vary in ICD 10/11 (ICD is widely used by health professionals in general in Europe) and DSM 5 (which are commonly used in research and by psychiatrists),* and from *where clinical trial data for zuranolone is largely based* on. *The time frame for the onset is from pregnancy to 4 weeks postpartum in DSM 5* while it only *includes the first 4 weeks after childbirth in ICD 10/11*. The organisation advises that in case zuranolone is approved, the diagnostic criteria used to set the indication should be specified for prescribers. Another important aspect raised is the fact no head-to-head double-blind RCTs have been conducted and therefore efficacy of zuranolone versus currently used antidepressants. They refer to a publication by Deligiannidis et al (2021) where a decrease *in the Hamilton Depression Rating Scale* of 4 points from an average baseline score of about 28 seems a relatively modest change. An additional aspect relates *with women with past episodes of depression that may not have been related to childbirth* and that *might be more vulnerable to relapse after the end of treatment with zuranolone*.

2.6.7. Discussion on clinical efficacy

Design and conduct of clinical studies

In this application two randomised, double-blind, placebo-controlled, multicentre studies were performed in patients with PPD. Although study designs were overall similar, only study 301 tested the SmPC-recommended 50 mg zuranolone dose, as such this study is considered pivotal. Due to variable treatment effects in depression studies, in principle two convincing pivotal studies are expected to assess the therapeutic efficacy. In this specific sub-population of PPD patients, one pivotal study, supported by results of additional study 201B are considered sufficient, since the results of the pivotal study are statistically compelling and clinically relevant. Post-partum depression is a very frequent condition: 4-20% of postpartum mothers in EU have PPD symptoms. Of these, about $1/5^{th}$ will have a formal diagnosis of PPD. The population who may benefit from drug treatment may reach 5% of all new mothers. In depression, the cultural and environmental aspects have a significant impact in the disease and the way the disease is perceived by the patients, supporting peers and colleagues. The study population was very skewed towards US, from both studies 201 (no European patient) and 301 (5 European patients). Of the 9 Spain and 5 UK study centres, only a couple have included patients in the trial, with only 3 patients from Spain and 2 from UK - 5 patients (2.6%) from Europe being admitted overall. The Applicant justified why most European study centres were opened and close without enrolment of patients, to confirm that there were no cultural or EU clinician treatment behaviour difference between Europe and US that might challenge the results. European centres were: a) opened late during the study; b) during COVID-19 pandemics in countries greatly affected at the time of study enrolment.

The confirmatory study was compared to placebo, which is an acceptable approach, since patients were allowed previous ADT if stable.

Regarding study conduct and how amendments might have had a significant impact, the applicant has listed all 16 cases of early dropouts presenting the justifications for its attrition. Only one participant was excluded due to mother – newborn bond loss and no other cases of amendment stringency have

caused loss to follow-up. It is unlikely that the dropouts would deviate the results from the presented trend.

Efficacy data and additional analyses

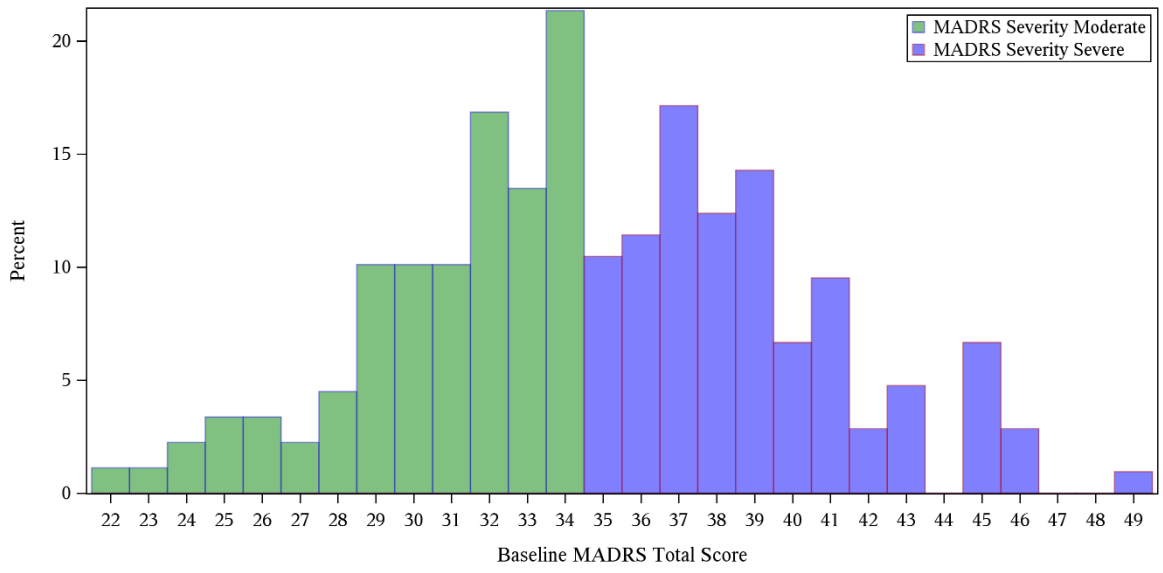
The claimed indication "postpartum depression in adults" was not fully in line with the study population, with regard to the severity of PPD and concomitant use of antidepressants. The applicant justified the extrapolation to other PPD severities (mild and especially moderate PPD), and the concomitant use of antidepressants.

Extrapolation to other PPD severities

The Applicant performed post-hoc subgroup analyses using literature-established severity thresholds for the MADRS [Müller 2000; Snaith 1986] to define subpopulations of both moderate (baseline MADRS total score 20-34) and severe (baseline MADRS total score ≥35) depression (N=89 and N=105, respectively). Although it is uncertain what definition for moderate and severe PPD most adequately reflects the clinical situation in patients, the provided analyses give additional information on efficacy, in groups of more (MADRS ≥35) and less (MADRS 20-34) severely affected patients. The moderate and severe population were generally similar, though a greater proportion of participants in the severe population had HAMD-17 total scores ≥28 at baseline and a greater proportion had Hamilton Anxiety Rating Scale (HAM-A) score ≥ 20 at baseline, as would be expected for a more severe group.

Post hoc histograms of the percentage of participants with each baseline MADRS total score show a distribution of baseline MADRS total scores (***Figure 5***). Additional evaluation of the baseline MADRS total scores in the moderate-severity subpopulation found that approximately 50% of participants in this category have a score ≤31, indicating good distribution of moderate-severity scores in this subpopulation, including participants with scores toward the lower bound of literature-established definitions for moderate severity [Müller 2000; Snaith 1986].

Figure 5. Histogram of Baseline MADRS Total Score by Baseline MADRS Severity: 217-PPD-301 – Full Analysis Set



Overall patients with a lower baseline PPD severity (MADRS up to 34) did not respond differently to zuranolone, in terms of change in HAMD-17 from baseline to day 15, compared to those with a higher baseline PPD severity (MADRS ≥35). Further, the safety profile was similar between the two subgroups. Therefore, the B/R for zuranolone is expected to be similar for patients with moderate and severe PPD. The general proposed indication for PPD after childbirth (of all severities - including mild

forms) is acceptable, in line with the Guideline for the treatment of depression (EMA/CHMP/185423/2010, Rev.3).

Although the mean MADRS total score is indicative of a population with severe PPD, the distribution of MADRS scores may be relevant for prescribers. Upon request, the applicant included the MADRS total score at baseline in the population characteristics table in SmPC section 5.1.

Concomitant use of antidepressants

Overall, 15% of participants in the pivotal study and 19% of participants in the supportive study were taking stable antidepressants at baseline. The majority of ADT use at baseline was sertraline (9.2% of all participants); all other agents used were at <3% and restricted to selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and bupropion. No tricyclic or tetracyclic antidepressants were used concomitantly. Based on the subgroup analyses (in both studies), the benefit of zuranolone was less apparent in patients who were using antidepressants concomitantly, compared to those who were not using antidepressants. Upon request, the concomitant use of antidepressants was further substantiated. It was agreed with the Applicant that the limitations of the subgroup analyses (limited sample size) pose uncertainties on the conclusions for the extent of the zuranolone effects within concomitant ADT. Further, no relevant differences in medical history, prior and concomitant medications, reasons for baseline ADTs, and duration of stable ADT use were found.

Use of zuranolone alone or with stable background ADTs can be accepted. Although the extent of treatment benefit of zuranolone in combination with ADTs remains uncertain, mechanistically there is no reason to suspect altered efficacy compared to zuranolone monotherapy. No differences in safety profile were identified for zuranolone mono- or combination therapy. In addition, discontinuation of stable ADTs prior to treatment with zuranolone may not be a desirable option for patients, due to the risk of side-effects, withdrawal and relapse.

The statement on the use of zuranolone alone or in combination with stable ADTs, in SmPC section 4.2, is acceptable. The proposed dose reduction for patients treated with CNS depressants (to 30 or 40 mg) in SmPC section 4.2 was, however, not agreed and was deleted. No data to inform on dose reductions with concomitant CNS depressants are available. A general warning on lowering the dose if AEs occur is included in section 4.4, which is considered sufficient.

Maintenance of effect

Maintenance of the initial anti-depressive effect of zuranolone, throughout the current depressive episode was discussed. Although occurrences of relapse were low during the study, the results were limited by the duration of the trial. In light of the natural course of a major depressive episode with peripartum onset, and the onset of effect of zuranolone, it is yet uncertain what an appropriate study duration would be, to claim sustained efficacy. Per the EMA guideline on clinical investigation of medicinal products in the treatment of depression (EMA/CHMP/185423/2010 Rev.3), it should be shown that a short-term effect can be maintained during the current episode.

It is not agreed that a follow up duration of 45 days is sufficient to identify loss of treatment effect. To support the durability of response for zuranolone, the applicant provided an overview of efficacy results in MDD patients treated with zuranolone for 14 days, and re-treated if needed (HAMD-17 total score ≥20). The time to first repeat treatment was 281 days for patients initially treated with 50 mg zuranolone. Overall, 54% of patients did not need additional treatment courses (up to 48 weeks). Although, extrapolation to the PPD situation is not justified and differences between MMD and PPD study populations are not taken into account, these MDD data do provide supportive information regarding the sustained response of zuranolone during an episode of depression.

Zuranolone has a rapid onset of action with a short course of active treatment, and PPD has significant consequences for the mother and baby. Therefore, it may be considered that rapid improvement in symptoms of depression, may be more important than sustained efficacy in this vulnerable population of patients. In addition, despite uncertainties in applicability for the PPD population, the results in the MDD population do support the ability of a durable response to zuranolone.

Further, the Applicant has performed post hoc analyses to address the CHMP's request to discuss the severity of PPD after a relapse (at least 2 consecutive HAMD-17 total scores of ≥20 after Day 15 HAM-D evaluation, including the last value) or loss of response/remission. The following HAMD-17 total score severity criteria were used to categorise participants: no depressive symptoms (total score ≤ 7), mild depressive symptoms (total score 8-16), moderate depressive symptoms (total score 17-23), and severe depressive symptoms (total score ≥24). Symptom severity in participants with relapse, loss of response, or loss of remission in 217-PPD-301 is shown below. Few participants in either study met criteria for relapse, with no discernible pattern in depressive symptoms at Day 45 noted. The majority of participants who had a loss of response or loss of remission had HAMD-17 total scores that were categorised as mild or moderate at Day 45, and few participants in either study had severe depressive symptoms.

It remains unclear how relapses should be handled in clinical practice. Therefore a statement to inform prescribers that no data are available - on follow-up treatment after a relapse or insufficient response with zuranolone - was included in SmPC section 4.2.

A clear rationale for the 14 day treatment period is lacking and it remains uncertain whether this is the most optimal treatment duration. Yet, the data indicate a beneficial effect of zuranolone without major safety issues.

Summary of Severity of PPD at Day 45 following Relapse or Loss of Day 15 HAMD-17 Response/Remission at Day 45: 217-PPD-301 - Full Analysis Set

	Placebo (N=97) n (%)	50 mg Zuranolone (N=98) n (%)
HAMD-17 response at Day 15 [1]	35 (36.1)	53 (54.1)
HAMD-17 relapse [2]	2 (5.7)	3 (5.7)
Day 45 HAMD-17 severity category [3]		
No depression (Total score: 0-7)	0	1 (33.3)
Moderate depression (Total score: 17-23)	0	2 (66.7)
Severe depression (Total score: >=24)	2 (100)	0
HAMD-17 response at Day 15 and non-missing HAMD-17 total score at Day 45	33	47
Loss of HAMD-17 response at Day 45 [4]	4 (12.1)	9 (19.1)
Day 45 HAMD-17 severity category [5]		
Mild depression (Total score: 8-16)	1 (25.0)	3 (33.3)
Moderate depression (Total score: 17-23)	1 (25.0)	5 (55.6)
Severe depression (Total score: >=24)	2 (50.0)	1 (11.1)
HAMD-17 remission at Day 15 [1]	15 (15.5)	25 (25.5)
HAMD-17 remission at Day 15 and non-missing HAMD-17 total score at Day 45	15	22
Loss of HAMD-17 remission at Day 45 [6]	4 (26.7)	3 (13.6)
Day 45 HAMD-17 severity category [7]		
Mild depression (Total score: 8-16)	3 (75.0)	2 (66.7)
Moderate depression (Total score: 17-23)	0	1 (33.3)
Severe depression (Total score: >=24)	1 (25.0)	0

NOTE 1: HAMD-17 response is defined as a >=50% reduction from baseline in HAMD-17 total score. HAMD-17 remission is defined as a HAMD-17 total score <=7. HAMD-17 relapse is defined as at least 2 consecutive HAMD-17 total score >=20 after Day 15 HAMD-17 evaluation including the last value.
NOTE 2: Percentage calculations based on: [1] full analysis set, [2] number with HAMD-17 response at Day 15, [3] number with HAMD-17 relapse, [4] number with HAMD-17 response at Day 15 and non-missing HAMD-17 total score at Day 45, [5] number with loss of HAMD-17 response at Day 45, [6] number with HAMD-17 remission at Day 15 and non-missing HAMD-17 total score at Day 45, [7] number with loss of HAMD-17 remission at Day 45.

The sample size used a 2-sided test at an alpha level of 0.05 and resulted that approximately 86 evaluable participants per treatment group would provide 90% power to detect a placebo-adjusted treatment difference of approximately 4 points in the primary endpoint, change from baseline in HAMD-17 total score at Day 15, assuming an SD of 8 points (CSR 217-PPD-301). They assumed a

10% dropout and a 1:1 randomization ratio within each stratum, resulting in approximately 192 randomized participants (96 per treatment group) per treatment group. This is considered to be appropriate.

A stratified randomization procedure was used based on baseline antidepressant use ("current/stable" versus "not treated/withdrawn ≥ 30 days or > 5 half-lives prior to Day 1"). Randomization schedules were generated by an independent statistician. The allocation to treatment group (SAGE-217 50 mg, or placebo) was based on a randomization schedule and performed centrally via an interactive response technology system, which is considered to be appropriate. The Sponsor, site personnel and participants were blinded until the database lock, which is considered sufficient.

Estimands were defined using the treatment policy strategy for the primary outcome, which is in accordance with the ICH guidelines. No estimands for key secondary endpoints are defined, however given that the key secondary endpoints are similar as the primary outcome, but at a later stage in time, the same treatment policy for the intercurrent events may be specified.

The primary analysis set for all efficacy analyses included all randomized participants who are administered the investigational product with valid baseline total score and at least 1 post-baseline total score. This is not a standard ITT analysis as indicated by the ICH-E9 guidelines for statistical analyses. The Applicant was requested to explain how this might impact results. In Study 217-PPD-301, only 5 randomised participants (4 randomised to placebo and 1 randomised to zuranolone) were excluded from the Full Analysis Set. The reasons were "Lack of any data post randomisation" (1 participant in the placebo arm), and both "Failure to take at least one dose of trial medication" and "Lack of any data post randomisation" (3 participants in the placebo and 1 participant in zuranolone arms). Since 217-PPD-301 was a double-blind randomised study, there was no knowledge of the treatment assignment that could have influenced either the decision whether to begin treatment or the decision whether to return for at least 1 post-baseline visit.

Primary efficacy was analysed using mixed effects model for repeated measures (MMRM) to determine the difference between treatment groups in change from baseline to Day 15. Missing data was imputed based on study withdrawal reason. A tipping point analysis was performed in the FAS using an added shift parameter to the imputed HAMD scores to evaluate the sensitivity of results to the missing at random (MAR) assumption.

No pre-planned interim analyses were conducted to re-estimate the sample size, or to stop the study for futility.

The original global protocol was amended once. Most changes were minor and unlikely to affect outcome, but there was an issue regarding the broadening of eligibility criteria. This pertained to the inclusion of women who were up to 12 months post-partum.

In total 10.3% of patients in the FAS had at least one major protocol deviation (8.2% zuranolone vs. 12.4% with placebo), mostly related to informed consent (5%) and eligibility criteria (3%). No patients were excluded from the analyses based on these deviations.

A PPD diagnosis based on DSM-5 criteria is considered adequate. However, it was not clear if a correct diagnosis of PPD was really ensured. Per DSM-5, the onset specifier of PPD is during pregnancy up to 4 weeks after delivery. In study 301 only patients in their third trimester of pregnancy up to 4 weeks after delivery were eligible. Upon request, the Applicant explained that allopregnanolone is expected to increase during pregnancy with a peak concentration during the 3rd trimester. Efficacy is therefore expected especially during this period. Zuranolone is indicated for the treatment of PPD after childbirth, the modified criteria for study eligibility do not impact the target population.

As the PPD diagnosis was made retrospectively with a latency of up to 12 months, it was questioned to what extent a diagnosis of a patient's condition one year earlier can be trusted as representative of the peripartum condition ('third trimester to 4 weeks post-delivery'). Therefore, the applicant provided a brief discussion concerning the accuracy of PPD diagnoses in the zuranolone studies. It was stated that a diagnosis at screening could be supported by clinical notes and referral documentation. It remains unknown for what portion of subjects the diagnosis could be confirmed/supported by historical documentation. Subgroup analyses by duration of PPD episode did not significantly impact the efficacy results. Therefore, it is considered that, although recall bias may be present, this most likely did not have a major impact on the outcome.

In total, 305 out of 505 participants were screen failures, of which the majority were not meeting the eligibility criteria. A relatively high number of screen failures could imply difficulties in adequate identification of the defined population. The applicant justified the screening failures: among patients not eligible for enrolment in study 301, most (21%) did not meet the inclusion criterium for severe depression (HAMD total score ≥26). Other reasons for not meeting eligibility criteria were variable and each applicable to less than 4% of the screened population. The target population are patients with PPD of all severities, and in line with clinical guidelines, patients with moderate or severe PPD are expected to be treated with zuranolone in clinical practice.

Pregnant women were not eligible to participate in the study, this can be understood, as exposure to a study drug may pose potential risks to a foetus, in particular considering the non-clinical studies indicating teratogenic risk. The applicant has included a contraindication for pregnancy to mitigate the risk that was identified in non-clinical studies (refer to safety section).

The population of patients with PPD pertains to women of child-bearing potential, an age restriction in the context of a clinical study would, per the definition of the disorder, is unnecessary. WHO currently (as per July 2024) considers the reproductive age for women to be up to 49 years. Potentially, not all relevant ages are represented in the study. The Applicant provided additional analyses of efficacy and safety data for zuranolone in the PPD (and for safety also MDD) population, upon request of a discussion on extrapolation of results to women >45 years of age. Based on provided information, there is currently no reason to suspect differences in safety and efficacy of zuranolone in patients with PPD >45 years of age.

In total 5 patients from EU were included in the study, the rest of patients were from the US. Differences in intrinsic and extrinsic factors may exist between the US and the EU population of patients with PPD. The extrapolation to the EU population was discussed by the Applicant, based on several aspects. Pathophysiology of PPD is not different between EU and US populations; physiological and hormonal changes in the peripartum period are independent of ethnic background. In addition, despite differences in maternal support demonstrating beneficial effect in PPD prevention, prevalence of PPD is similar, and comorbidities in this population did not differ from EU. Intrinsic and extrinsic factors that may differ between EU and US populations, do not seem to impact efficacy and safety; treatment effects between subgroups were more or less comparable. Based on the metabolism profile of zuranolone, clinically relevant PK differences among different demographic groups are not expected, which was confirmed by popPK analysis. PPD risk factors in the study population are generally in line with data from EU countries, except the prevalence of psychiatric disorders; MDD was reported at 10.3% in US and 7.7% in Europe. Among study participants, 12% (pivotal study) and 34% (supportive study) had a history of MDD, the higher prevalence is comparable to what was observed in studies from Sweden and Hungary (both at 34%). Antidepressant use in the studies was 15% (pivotal study) and 19% (supportive study), reports from Sweden, Finland, and Denmark, indicate a variable percentage of PPD patients using antidepressants (5-24%), which may be dependent on the variable study conditions (cut-off time postpartum, history of depression). No specific aspect that would prevent extrapolation from the US population to the EU population was identified.

Treatment was 50 mg zuranolone (Autofill) or placebo to be taken with fat-containing food, once daily, for 14 days. A dose reduction to 40 mg was allowed, in case of tolerability issues. The applicant was requested to clarify whether a more treatment friendly dose formulation will be developed (such as 40+10 mg), accommodating the dose reduction to 40 mg in case of tolerability issues. The applicant does not intend to provide further oral formulation dosages beyond those presented.

Placebo is an acceptable comparator in a PPD study, since no appropriate active comparator is currently available and comparison with placebo is the main requirement for regulatory decision making (Guideline on clinical investigation of medicinal products in the treatment of depression; EMA/CHMP/185423/2010, Rev.3).

The primary endpoint was the change from baseline to end of treatment (day 15) in HAMD-17 total score. The HAMD-17 is a validated well-established outcome measure in depression trials and as such accepted.

Key secondary endpoints are mostly directly related to the primary outcome measure, i.e., changes from baseline in HAMD-17 at days 3, 28, and 45; and change from baseline in CGI-S at day 15. Other secondary endpoints were: HAMD-17 responders and remitters at day 15 and day 45, CGI-I responders at day 15; change from baseline in MADRS at day 15; and change from baseline in HAMD-17 subscale anxiety (HAM-A) at day 15. The defined endpoints can generally be agreed as they reflect the range of relevant, validated endpoints in the field of depression. However, the only PPD-specific scale, tested nominally, was the EPDS (Edinburgh Postnatal Depression Scale). To support the proposed PPD indication, formally tested disease-specific outcomes were not included in the study.

The chosen endpoints, at the end of treatment (day 15), and at one month after treatment has ceased (day 45), are considered adequate to establish short-term efficacy for a product with a rapid onset of action. However, the study duration is not appropriate to show maintenance of effect. The applicant included a warning to inform prescribers that no data are available on follow-up treatment after a relapse or insufficient response with zuranolone, in SmPC section 4.2.

The primary endpoint was met, the treatment effect (difference in HAMD-17 change from baseline to day 15) for zuranolone compared to placebo was statistically significant, with a difference of -4.0 points (95%CI -6.3, -1.7; p=0.0007) by MMRM. The difference in HAMD-17 change from baseline, was statistically significant from day 3 onwards, and this remained at days 28 and 45 (key secondary endpoint). The effect size of -4 difference in change in HAMD-17 total score, as found in the pivotal study, is considered clinically relevant. Previously, a difference of 2-points between test product and placebo has been considered sufficient to demonstrate efficacy of antidepressants in the regulatory setting (e.g. Spravato EPAR). Additionally, the average treatment effect by HAMD-17 was -3.0 (SD: 2.4) in depression studies conducted before 1995 and -1.8 (SD: 1.0) in studies conducted since 1995. The findings in this study exceed the commonly applied 2-3 point MCID threshold for MDD (Montgomery and Moller 2009), and is within the limit of the more conservative 3- to 5- point threshold (Hengartner and Plöderl 2022). The results are further supported by a clinically relevant difference of -5.1 in MADRS (95% CI: -8.4, -1.7, nominal p=0.003) at day 15, which exceeds the defined 2-point MCID threshold (Duru and Fantino 2008) and is within the limit of the more conservative 3- to 6- point threshold (Hengartner and Plöderl 2022).

Besides the difference in change of HAMD-17 total score over time, response and remission rates are important to adequately assess the clinical relevance of effect. Rates of response (HAMD-17 ≥50% improvement) and remission (HAMD-17 total score ≤7) at day 15 (other secondary endpoints); were 57% and 27% for zuranolone and 39% and 17% for placebo, respectively. The odds ratios for response (2.0, 95%CI: 1.1 – 3.7; p=0.02) and remission (1.8 (95%CI: 0.9-3.6; p=0.1) were presented. Relative risks for the response and remission rates were provided upon request. Relative risk and risk differences at Day 15 are also tabled in section 5.1 of SmPC.

Differences in responder and remitter rates, between zuranolone and placebo, support the clinical relevance of effect.

The only PPD-specific outcome, tested nominally, was the EPDS (Edinburgh Postnatal Depression Scale), a patient reported outcome measure of depressive symptoms, specific to the perinatal period. EPDS and PHQ9 were not included in the testing hierarchy, but both were nominally significant at day 15 and EPDS but not PHQ9 was also nominally significant at day 45. Although EPDS is a valid screening tool, the validity with regard to treatment response and the sensitivity to change are uncertain, and experience in the regulatory setting is absent. According to the limited information in literature, the nominal statistically significant 2-point difference in EPDS (95%CI -3.8, -0.1 p=0.0377) at day 15, between zuranolone and placebo is considered a medium decrease (Affonso D. J Psychosom Res, 2000) and below the MCID of 4 (Matthey S. J Affect Disord, 2004; Mao F. 2021 Asian J Psychiatr).

Given that the HAMD 17 results show a 4.0 point improvement compared to placebo which is within the limits of minimal important difference (MID) for the tool (3 to 5), but by day 45 the effect is in the lower limit of MID. Furthermore, the PRO tools used in the study were much more modest on favouring zuranolone as compared to the clinician based tools. Therefore, the possible benefit of speeding up recovery improving the mother – child relationship and the overall benefit on the mother may was questioned.

Relapse was defined by the applicant as: a 'HAMD-17 total score ≥20 for 2 consecutive assessments' after day 15. This definition seems rather strict, since moderate depression is defined by a HAMD-17 total score between 17 and 23 (Zimmerman 2013) and other signs of worsening were not included in the definition. In total 5 patients (3 zuranolone, 2 placebo) experienced a relapse, with unknown onset. The applicant concluded that the likelihood of a relapse is small, however, data are limited by the duration of the study. Alternative manifestations of disease reappearance, not defined as such by the Applicant, include the loss of response (19% zuranolone vs 12% placebo) and loss of remission (14% zuranolone vs 27% placebo) at day 45, among initial (day 15) responders and remitters. Missing data (not imputed) for initial responders and remitters treated with zuranolone (6 and 3) and placebo (2 and 0), were slightly imbalanced; reasons for missing data were discussed upon request and could not be found.

Supportive data

The primary analysis set for all efficacy analyses in clinical study 217-PPD-201 included all randomized participants who were administered the investigational product with valid baseline total score and at least 1 post-baseline total score (termed full analysis set and efficacy set). Overall, 7 of 9 participants who withdrew from the study (including one placebo participant) completed either a Day 21 Visit (which contained the required assessments for ET) or an ET Visit or were assessed out to Day 45. Only 2 remaining participants (1 zuranolone, 1 placebo) were not followed to Day 21/ET. Two participants (1 placebo and 1 zuranolone) both completed treatment and withdrew on Day 15.

The mean baseline HAMD-17 total score was comparable between zuranolone (29) and placebo (28). However, the number of participants with a HAMD-17 score ≤28, was relatively higher in the zuranolone group (40%), compared to placebo (30%). This may indicate a less severe PPD population in the zuranolone treatment group. The applicant was asked to discuss the impact of this difference on the efficacy results. The applicant acknowledged the observation of a relatively higher distribution of participants with a Hamilton Depression Rating Scale, 17 items (HAMD-17) score ≤28 in the zuranolone group relative to placebo. The randomisation schema in Study 217-PPD-201B was not stratified for HAMD-17 total score at baseline, and this distribution was a chance occurrence. Nonetheless, the mixed effect model for repeated measures (MMRM), utilised to analyse change from baseline in HAMD-17 total score, included baseline HAMD-17 total score as an explanatory covariate.

Thus, this difference is accounted for in the analysis and does not have an impact on the efficacy results.

Subgroups

Data in subgroups analysed, are rather consistent with the overall population. With the exception of patients who were using concomitant antidepressants during the study (see above). In several subgroups (e.g., lower BMI, HAMD-17 ≤28, onset during pregnancy, duration PPD episode ≥183 days, concomitant use of progestin-only contraceptive) the impact of zuranolone may be less pronounced, compared to the overall population. However, subgroup sizes were small, and confidence intervals were large; the direction of effect is generally consistent with the overall population.

Recommended dose

In two separate studies, zuranolone doses of 50 mg and 30 mg (see below), resulted in a treatment response of similar magnitude. Yet, the applicant recommends a dose of 50 mg zuranolone once daily for 14 days, for the treatment of PPD. This is primarily based on the mean treatment difference at day 3, which, according to the Applicant, is suggestive of a more rapid symptomatic improvement at the higher starting dose. In total 16 patients required dose adjustment to 40 mg, due to tolerability issues. The number of patients is too small, to assess the impact of dose reduction on efficacy.

The impact of impaired hepatic or renal function on zuranolone bioavailability was evaluated, using data from dedicated studies; based on these results the adjusted dose for patients with severe hepatic function or moderate/severe renal function is 30 mg zuranolone, once daily (refer to PK section).

It is recommended to take zuranolone with fat-containing food, to increase bioavailability, and studies indicate that the amount of fat content (low/medium/high) affect the exposure of zuranolone. The Applicant revised SmPC section 4.2 upon request. The applicant further specified the types of fat-containing food that could be taken together with zuranolone, including examples. Exposure of zuranolone increases when taken with food and (accidental) intake of zuranolone without food will result in lower (suboptimal) exposure. The applicant provided additional information in the PL to inform patients to mitigate this risk.

Supportive study 217-PPD-201B

Study 201B had a similar design to the pivotal study (301), which is considered to be appropriate.

No pre-planned interim analyses for futility were conducted. No estimands for the primary outcomes were defined, the Applicant stated that both the Protocol and the Statistical Analysis Plan were finalised before ICH E9(R1) (addendum on estimands). Missing data imputation was planned, but not performed, as <5% of HAMD-17 scores at day 15 were missing, which is below the predefined threshold of 10%, for a sensitivity analysis. The original protocol was updated 8 times. The most important updates concerned multiple changes to the sample size estimates, based on changes in the desired study power and placebo-adjusted treatment difference. These were triggered by new information from the brexanolone PPD and zuranolone MDD clinical programs. In line with this (per version 7), the study was upgraded from a phase 2a to phase 3 study. The number of major protocol deviations was considered very high (40% in the efficacy set); most efficacy deviations were attributed to out of window measurements for day 15, the applicant noted that no window was specified, in the pivotal study a window of 1 day was predefined; no major impact on efficacy results was noted.

In total 153 participants were randomized, and 91% zuranolone and 95% placebo completed the study. Three patients needed a dose reduction due to tolerability issues. The efficacy set included all patients dosed, with a valid baseline and at least 1 postbaseline efficacy assessment (76 zuranolone and 74 placebo). This was not a standard ITT analysis (ICH-E9 guidelines for statistical analyses).

However, the number of dropouts in the FAS is low. It is unlikely that amendments might have impacted results.

The mean age of study participants was 28.3 (range: 18 to 44 years) and BMI was 30.7 (SD 7.2) kg/m2. At baseline, 19% were treated with a stable dose of antidepressants. Most participants experienced their first PPD episode (83%) with onset of PPD within 4 weeks after delivery (58%). Per the inclusion criteria all patients were up to 6 months postpartum at baseline, this may indicate less chronic disease as compared to the population included in the pivotal study (with onset up to 12 months postpartum). The difference in mean duration of symptoms between studies 301 and 201B was discussed, upon request. As expected, participants in study 301 had a longer duration of symptoms compared to study 201B due to the difference in study eligibility (up to 12 months postpartum, and up to 6 months postpartum). Based on analysis of subgroups by duration of symptoms, it was concluded that the duration of a PPD episode did not significantly impact the efficacy of zuranolone. Although the mean baseline HAMD-17 total score was comparable between zuranolone (29) and placebo (28), the number of participants with a HAMD-17 score ≤28, was relatively higher in the zuranolone group (40%), compared to placebo (30%). This was evaluated as being a chance finding, which was accounted for in the MMRM.

The primary endpoint was met, the difference in change from baseline in HAMD-17 was statistically significant, with a mean difference of -4.2 (95%CI -6.9, -1.5, p=0.003) in favour of zuranolone. The magnitude of effect for the primary outcome, is similar to the results found in the pivotal study (PPD-301), and this is considered clinically relevant. Response and remission rates (although nominally tested) were supportive of the primary endpoint and the results found in the pivotal trial. Overall, higher percentages of patients in both groups had a HAMD-17 or CGI-I response or were in remission, when indirectly compared to the pivotal study, despite similar HAMD-17 total scores at baseline. In addition, differences between zuranolone and placebo were more pronounced in the supportive study. It is questioned whether there were any relevant differences between study populations, that could have impacted the treatment response, and that could explain differences between the two studies. An updated overview of demographics and baseline characteristics for adequate comparison of studies 301 and 201B was provided, upon request. Except for mean ± SD duration of symptoms (164±88 days in 301 vs 123±54 days in 201B), patient characteristics were generally comparable between studies.

According to the protocol of study 217-PPD-201B, patients with significant safety deviations should have discontinued treatment. Overall, safety deviations occurred in 29% zuranolone and 16% placebo treated participants, and it is unclear what these deviations were and how these were handled. An overview of major safety protocol deviations was provided upon request. In total 34 participants in the efficacy set had 46 major protocol deviations. The majority of these happened outside of the treatment period (at screening, day 1 or after day 15). Two participants in the placebo group were excluded from the per protocol set, due to major safety deviations (taking too many capsules, taking diazepam close to baseline). The impact of major protocol deviations on efficacy analyses is expected to be negligible.

2.6.8. Conclusions on the clinical efficacy

The Applicant has presented two studies with zuranolone for the treatment of PPD, one phase 2b study and a confirmatory phase 3 study. The phase 2b study was not conducted with the proposed dose for the treatment of PPD, so the sole main study is phase 3 study 217-PPD-301. The study showed a response to zuranolone on PPD, with the LS mean change from baseline in HAMD-17 at day 15 showing an improvement of 15.6, whilst placebo showed an improvement of 11.6. A difference between zuranolone and placebo, 4.0 points, is statistically significant (p value of 0.0007) and within the level of MID (3-5).

Relapses occurred in both groups (n=5), however detection of relapses was limited by the duration of the trial, and as such the maintenance of effect and durability of the response remain uncertain. Notwithstanding, given the relevance of a quick antidepressive response to the mother-child relation, the rapid onset of effect and attaining a reasonable response is considered very relevant in PPD. Since most PPD tend to resolve, maintenance of antidepressant effect of the product is thus less important in PPD than in MDD.

2.6.9. Clinical safety

2.6.9.1. Patient exposure

The safety profile for zuranolone has been characterised using data from the 36 clinical studies (33 completed and 3 ongoing) in the development programme. Overall, to examine the safety and tolerability of zuranolone, data were presented in pooled analysis (all based on data from completed studies), which included 25 studies. The primary analysis pool is the PPD PC Studies Pool, which includes the studies to support the intended indication. Secondary pools include the MDD PC Studies Pool and the Healthy Participants Pool. It is agreed that although PPD and MDD are different indications, the trials for MDD employed similar designs, doses, and durations, thereby enabling safety comparisons with the PPD studies.

Table 14. **Participant Enumeration in the Zuranolone Clinical Development Programme**

5119 Unique Participants in Clinical Development Programme (3048 Unique Participants in Pooled Analysis)								**3992 Unique Participants Exposed to Zuranolone** (1949 Unique Participants in Pooled Analysis)							
PPD Studies				**Phase 1 Studies**				**PPD Studies**				**Phase 1 Studies**			
Stat	**Study Number**	**Total** (n = 348)	**Pooled** (n = 347)	**Stat**	**Study Number**	**Total** (n = 899)	**Pooled** (n = 740)	**Stat**	**Study Number**	**Total** (n = 177)	**Pooled** (n = 176)	**Stat**	**Study Number**	**Total** (n = 807)	**Pooled** (n = 658)
COMPLETE	217-PPD-201A[a]	1	0	COMPLETE	217-CLP-101	94	82[b]	COMPLETE	217-PPD-201A[a]	1	0	COMPLETE	217-CLP-101	75	63[b]
	217-PPD-201B[a]	151	151		217-CLP-102	48	48		217-PPD-201B[a]	78	78		217-CLP-102	39	39
	217-PPD-301	196	196		217-CLP-103	21	21		217-PPD-301	98	98		217-CLP-103	21	21
MDD Studies (n = 3775 total; n = 1961 pooled)					217-CLP-105	8	8	**MDD Studies** (n =2911 total; n = 1115 pooled)					217-CLP-105	8	8
COMPLETE	217-MDD-201A	13	0		217-CLP-106	32	32	COMPLETE	217-MDD-201A	13	0		217-CLP-106	32	32
	217-MDD-201B	89	89		217-CLP-107	24	6[c]		217-MDD-201B	45	45		217-CLP-107	24	6[c]
	217-MDD-301A	570	570		217-CLP-108	24	6[c]		217-MDD-301A	380	380		217-CLP-108	24	6[c]
	217-MDD-301B	537	537		217-CLP-109	60	60		217-MDD-301B	268	268		217-CLP-109	60	60
	217-MDD-302	53	0		217-CLP-110	99[d]	0[e]		217-MDD-302	53	0		217-CLP-110	89	0[e]
	217-MDD-303A	1237[f]	0		217-CLP-111	49	49		217-MDD-303A	1238	0		217-CLP-111	47	47
	217-MDD-303B	0[g]	0		217-CLP-112	64	64		217-MDD-303B	57[h]	0		217-CLP-112	32	32
	217-MDD-304	86	86		217-CLP-113	60	60		217-MDD-304	43	43		217-CLP-113	60	60
	217-MDD-305	430	430		217-CLP-114	15	15		217-MDD-305	212	212		217-CLP-114	15	15
	1818A3731	249	249		217-CLP-115	36	36		1818A3731	167	167		217-CLP-115	36	36
ONGOING	2122A3734[i]	404[j]	0		217-CLP-116	49	49	ONGOING	2122A3734[i]	348[j]	0		217-CLP-116	48	48
	2207A3736[i]	107[j]	0		217-CLP-117	67	67		2207A3736[i]	87[j]	0		217-CLP-117	66	66
Other Indications (n = 97 total; n = 0 pooled)				COMPLETE	217-EXM-101	45	45	**Other Indications** (n = 97 total; n = 0 pooled)				COMPLETE	217-EXM-101	45	45
COMPLETE	217-PRK-201AB	28	0		1805A3711	92	92	COMPLETE	217-PRK-201AB	28	0		1805A3711	74	74
	217-BPD-201A	35	0	ONGOING	217-CLP-118[i]	12	0		217-BPD-201A	35	0	ONGOING	217-CLP-118[i]	12	0
	217-ETD-201[k]	34	0						217-ETD-201[k]	34	0				

[a] Study 217-PPD-201A and Study 217-PPD-201B are counted as one study in the number of total studies.
[b] Six participants who received a single dose of zuranolone 66 mg and 6 participants in the essential tremor cohort of Study 217-CLP-101 are not included in the Healthy Participants Pool.
[c] In Study 217-CLP-107, 18 participants with renal impairment were not included in the Healthy Participants Pool. In Study 217-CLP-108, 18 participants with hepatic impairment were not included in the Healthy Participants Pool.

[d] The number of participants included in each group (Placebo, All Zuranolone, Total) for Study 217-CLP-110 is based on participants in the treatment phase. Two participants who completed the qualification phase but received only alprazolam single doses in the treatment phase, are included in the Total group (n = 99) but not in the Placebo (n = 75) or All Zuranolone (n = 89) group.

[e] Study 217-CLP-110, conducted in nondependent, recreational CNS depressant users, assessed the abuse potential of a single oral zuranolone dose relative to placebo and alprazolam; these participants are not included in any pools.

[f] The total number of participants in Study 217-MDD-303A was 1238. One participant was enrolled in Study 217-MDD-201B (placebo) and Study 217-MDD-303A (zuranolone); this participant was only counted once towards the total unique participants.

[g] Participants in Study 217-MDD-303B are rollover participants from Study 217-MDD-305 and, therefore, are not included in the unique participant count.

[h] 57 participants in Study 217-MDD-305 were dosed with placebo, then later received zuranolone in Study 217-MDD-303B.

[i] Ongoing study which is not part of the pooled analysis.

[j] For Studies 2122A3734 and 2207A3736, participants in the Safety Population are being counted. For these studies, participants who were dosed but had no safety data collected after drug administration were excluded from the Safety Population. Two participants in Study 2122A3734 were excluded from the Safety Population for this reason. In addition, 5 participants who were dosed in Study 2122A3734 were excluded from the Safety Population due to GCP-noncompliance issues. In total, as 1 participant was excluded for more than one reason, 6 dosed participants are not included in the overall count for Study 2122A3734.

[k] Participants in more than one part of Study 217-ETD-201 are only counted once.

The studies that formed the pools are as follows

1) *PPD PC Studies Pool* - consisted of 2 studies (217-PPD-201B and 217-PPD-301), both randomised, double-blind, placebo-controlled studies of participants with PPD to support the intended indication;

2) *MDD PC Studies Pool*, which consisted of 6 studies, 5 of those were randomised, double-blind, placebo-controlled studies in participants with MDD (217-MDD-201B, 217-MDD-301A, 217-MDD-301B, 217-MDD-305, and 1818A3731) that shared similar inclusion/exclusion criteria (i.e. 14-day treatment period, a 28-day or longer follow-up period, and nearly identical safety assessments). The sixth study included in the latter pool analysis was the study 217-MDD-304, which was conducted in participants with MDD and comorbid insomnia. Given that insomnia is a symptom of MDD and insomnia disorder is often comorbid in patients with MDD, the applicant argues that the study design differences are not expected to influence the interpretation of the zuranolone safety profile, which can in principle be acceptable. According to the applicant, this study closed early due to reasons not related to safety; and

3) *Healthy Participants Pool* which consisted of 17 studies, primarily conducted in adult and elderly healthy participants but also included cohorts of participants (excluded from this pool) with hepatic or renal insufficiency or essential tremor.

As of the data cut-off date (03 February 2024) for this submission, the zuranolone clinical programme included 5119 unique participants, including Phase 1 study participants (899) and participants with PPD (348), MDD (3775), and other indications (97). There were 1703 participants exposed to placebo and 3992 participants exposed to zuranolone. Across the completed studies, 2653 participants with PPD or MDD were exposed to any dose of zuranolone (177 with PPD and 2476 with MDD), including 1231 participants exposed to 30 mg and 1227 participants exposed to 50-mg zuranolone.

PPD PC studies pool

Of the 347 participants in the PPD PC Studies Pool, the majority completed the 14-day course of treatment with IP (92.4% Placebo, 90.3% All Zuranolone) and the study (89.5% Placebo, 90.3% All Zuranolone). Lost to follow-up (6.4% Placebo, 3.4% All Zuranolone) and withdrawal by participant (2.9% Placebo, 3.4% All Zuranolone) were the most frequently reported reasons for premature discontinuation from the study. Total exposure duration (mean [median] exposure) was consistent across zuranolone dose groups and between the Placebo group (13.6 [14.0] days) and the All Zuranolone group (13.5 [14.0] days). A high percentage of participants in the Placebo (92.4%) and All Zuranolone (90.3%) groups received at least 14 days of IP, with some participants reporting IP exposure > 14 days. The majority of doses administered beyond the 14th day accounted for missed doses earlier in the treatment course. As required at study entry, all participants in the PPD PC Studies Pool were female and 18 to 45 years of age, inclusive. The mean (SD) age was 29.4(5.96) years in the placebo group and 29.6 (5.66) years in the All Zuranolone group. Overall, demographic and baseline characteristics were well-balanced across the Placebo and All Zuranolone dose groups.

MDD PC studies pool

Similar to the PPD PC studies pool, a high percentage of participants in the MDD PC Studies Pool completed the 14-day course of treatment with IP (86.3% Placebo, 86.5% All Zuranolone) and completed the study (83.1% Placebo, 81.9% All Zuranolone). Withdrawal by participant (8.3% Placebo, 9.9% All Zuranolone) and lost to follow-up (3.4% Placebo, 3.7% All Zuranolone) were the most frequent reasons for premature discontinuation from the study. Demographic and baseline characteristics were generally well-balanced between the placebo and All Zuranolone groups. The mean age of participants in the MDD PC Studies Pool was higher and there was a greater proportion of

Asian participants due to enrolment in Japan for Study 1818A3731 compared to the PPD PC Studies Pool. The mean age (SD) was 39.8 (12.25) years in the placebo group and 40.8 (12.54) years in the All Zuranolone group. A total of 544 (64.3%) and 732 (65.7%) participants were female in the placebo and in the All Zuranolone groups, respectively.

Healthy participants pool

Of the 1014 participants in the Healthy Participants Pool, a high percentage of participants completed the study (93.3% Placebo, 93.3% All Zuranolone). Withdrawal by subject (3.1% Placebo, 1.8% All Zuranolone), adverse event (1.1% Placebo, 1.7% All Zuranolone), and lost to follow-up (1.7% Placebo, 1.1% All Zuranolone) were the most frequent reasons for premature discontinuation from the study. The incidence of adverse events leading to premature discontinuation from the study increased with increasing zuranolone dose but was low overall at 1.7%.

Table 15. **Overall Patient exposure**

							Patients with long term safety data (Completed studies only)	
	Studies included	**Patients enrolled**	**Patients exposed to zuranolone**	**Patients exposed to blinded zuranolone**	**Patients exposed to open label zuranolone only [a]**	**Patients exposed to proposed dose range [b]**	**6 months follow-up [c]**	**12 months follow-up [d]**
Blinded studies (placebo controlled)		3526	2341	2103	238	785	93	0
PPD studies	217-PPD-201A, 217-PPD-201B, 217-PPD-301	348	177	177	NA	98	0	0
MDD studies	217-MDD-201B, 217-MDD-301A, 217-MDD-301B, 217-MDD-302, 217-MDD-304, 217-MDD-305, 1818A3731, 2122A3734 (ongoing), 2207A3736 (ongoing)	2525	1603	1377	226	480	93	0
Other indications	217-ETD-201 (Parts A and B)	16	16	4	12	0	0	0
Phase 1 studies	217-CLP-101 (Cohorts 1-10, 11A and 11B),	637	545	545	NA	207	0	0

	217-CLP-102 (Cohorts 1-3), 217-CLP-110, 217-CLP-111, 217-CLP-112, 217-CLP-113, 217-CLP-116, 217-CLP-117, 217-EXM-101, 1805A3711 (Parts A and C)							
Open studies		1871	1651	NA	NA	716	785	596
MDD studies	217-MDD-201A, 217-MDD-303A, 217-MDD-303B	1528	1308	NA	NA	649	785	596
Other indications	217-ETD-201 (Part C), 217-BPD-201A, 217-PRK-201	81	81	NA	NA	18	0	0
Phase 1 studies	217-CLP-101 (Cohort 12), 217-CLP-102 (Cohort 4), 217-CLP-103, 217-CLP-105, 217-CLP-106, 217-CLP-107, 217-CLP-108, 217-CLP-109, 217-CLP-114, 217-CLP-115, 1805A3711 (Part B), 217-CLP-118 (ongoing)	262	262	NA	NA	54	0	0
All studies		5119	3992	2103	NA	1506	878	596

[a] Only applies to placebo controlled blinded studies 217-MDD-302, 2122A3734, 2207A3736 and 217-ETD-201 (Parts A and B), which each contained an open label treatment phase in addition to the double-blind treatment phase.
[b] Patients exposed to at least one dose of 50 mg for PPD and MDD studies and to at least one dose ≥40 to <60 mg for all other studies.
[c] Includes studies 217-MDD-301A, 217-MDD-303A and 217-MDD-303B. For 217-MDD-303B, first dose of zuranolone may have been taken in 217-MDD-305.
[d] Includes studies 217-MDD-303A and 217-MDD-303B. For 217-MDD-303B, first dose of zuranolone will have been taken in 217-MDD-305.
Note 1: Studies 217-CLP-110, 217-CLP-111, 217-CLP-112, 217-CLP-113, 217-CLP-116 and 217-CLP-117 contain an active treatment but are counted in 'Blinded studies (placebo controlled)' as they are all placebo-controlled studies.
Note 2: For 217-MDD-303B, 'Participants enrolled' includes all enrolled participants but 'Participants exposed to zuranolone' includes only those not treated with zuranolone in 217-MDD-305.
Note 3: In Study 217-CLP-101, Cohort 10 was an open label zuranolone food-effect cohort, and in Study 217-EXM-101, Period 4 was an open label zuranolone PK cohort. However, all participants in Study 217-CLP-101 Cohort 10 and Study 217-EXM-101 Period 4 are counted in 'Blinded studies (placebo controlled)' because they had already also received double-blind zuranolone.

In summary and considering all patients overall data on zuranolone exposure, it is agreed that the safety database is adequate for safety assessment of zuranolone for the proposed indication, patient population, and the proposed dose. The duration of use, which corresponds to a single treatment course, is limited to 14 days. In addition, as mentioned above, long-term follow-up beyond 4 weeks has been evaluated in MDD studies with participants who received 14-day treatment cycles of zuranolone.

2.6.9.2. Adverse events

Overview of adverse events

PPD PC studies pool

Table 16. **Overview of TEAEs – PPD PC Studies Pool**

Category[a]	Number (%) of Participants			
		Zuranolone		
	Placebo (N = 171)	30 mg (N = 78)	50 mg (N = 98)	All Zuranolone (N = 176)
TEAE	90 (52.6)	47 (60.3)	65 (66.3)	112 (63.6)
On-treatment	75 (43.9)	43 (55.1)	59 (60.2)	102 (58.0)
Off-treatment	30 (17.5)	8 (10.3)	17 (17.3)	25 (14.2)
Extended Follow-up	15 (8.8)	7 (9.0)	10 (10.2)	17 (9.7)
Serious TEAE	1 (0.6)	1 (1.3)	2 (2.0)	3 (1.7)
Death[b]	0	0	0	0
On-treatment				
Serious TEAE	0	1 (1.3)	1 (1.0)	2 (1.1)
Death[b]	0	0	0	0
Off-treatment				
Serious TEAE	0	0	1 (1.0)	1 (0.6)
Death[b]	0	0	0	0
TEAE leading to IP discontinuation[c]	2 (1.2)	1 (1.3)	4 (4.1)	5 (2.8)
TEAE leading to study withdrawal	1 (1.0)	0[d]	1 (1.0)	1 (1.0) [d]
TEAE leading to IP dose reduction or interruption[c]	2 (1.2)	3 (3.8)	16 (16.3)	19 (10.8)
Dose reduction	1 (0.6)	3 (3.8)	16 (16.3)	19 (10.8)
Dose interruption	1 (0.6)	0	1 (1.0)	1 (0.6)
TEAE by maximum severity				
Mild	65 (38.0)	31 (39.7)	33 (33.7)	64 (36.4)
Moderate	21 (12.3)	13 (16.7)	29 (29.6)	42 (23.9)
Severe	4 (2.3)	3 (3.8)	3 (3.1)	6 (3.4)
On-treatment				
Mild	55 (32.2)	30 (38.5)	33 (33.7)	63 (35.8)
Moderate	17 (9.9)	11 (14.1)	24 (24.5)	35 (19.9)
Severe	3 (1.8)	2 (2.6)	2 (2.0)	4 (2.3)
Off-treatment				
Mild	26 (15.2)	6 (7.7)	9 (9.2)	15 (8.5)
Moderate	3 (1.8)	2 (2.6)	7 (7.1)	9 (5.1)
Severe	1 (0.6)	0	1 (1.0)	1 (0.6)

[a] For TEAE categories summarised by on-treatment and off-treatment (i.e., TEAEs, serious TEAEs, deaths, and TEAE by maximum severity), the total number of participants with at least 1 TEAE includes events during the Extended Follow-up Period. Therefore, on-treatment and off-treatment events do not sum to the total.
[b] TEAE with a fatal outcome, not limited to the PT of death.
[c] Data only available for on-treatment events.
[d] Percentage denominator excludes Study 217-PPD-201B, which did not collect action of study withdrawal due to an AE on the AE CRF. As a result, 1 participant in the 30 mg group who withdrew from the study due to a AE is not included here.

Table 17. **TEAEs with an incidence of ⩾ 3.0% of participants in either group by SOC and PT (overall) – PPD PC Studies Pool**

System Organ Class Preferred Term	Number (%) of Participants			
		Zuranolone		
	Placebo (N = 171)	30 mg (N = 78)	50 mg (N = 98)	All Zuranolone (N = 176)
At least 1 TEAE	90 (52.6)	47 (60.3)	65 (66.3)	112 (63.6)
Nervous system disorders	45 (26.3)	27 (34.6)	50 (51.0)	77 (43.8)
Somnolence	13 (7.6)	12 (15.4)	26 (26.5)	38 (21.6)
Dizziness	14 (8.2)	6 (7.7)	13 (13.3)	19 (10.8)
Headache	22 (12.9)	7 (9.0)	9 (9.2)	16 (9.1)
Sedation	1 (0.6)	4 (5.1)	11 (11.2)	15 (8.5)
Memory impairment	0	0	3 (3.1)	3 (1.7)
Gastrointestinal disorders	28 (16.4)	14 (17.9)	13 (13.3)	27 (15.3)
Diarrhoea	4 (2.3)	5 (6.4)	6 (6.1)	11 (6.3)
Nausea	12 (7.0)	3 (3.8)	5 (5.1)	8 (4.5)
Dry mouth	3 (1.8)	3 (3.8)	2 (2.0)	5 (2.8)
Infections and infestations	14 (8.2)	12 (15.4)	13 (13.3)	25 (14.2)
Urinary tract infection	4 (2.3)	1 (1.3)	5 (5.1)	6 (3.4)
Upper respiratory tract infection	3 (1.8)	6 (7.7)	0	6 (3.4)
COVID-19	0	0	5 (5.1)	5 (2.8)
Nasopharyngitis	2 (1.2)	3 (3.8)	1 (1.0)	4 (2.3)
Musculoskeletal and connective tissue disorders	9 (5.3)	5 (6.4)	9 (9.2)	14 (8.0)
Myalgia	0	0	3 (3.1)	3 (1.7)
General disorders and administration site conditions	8 (4.7)	5 (6.4)	11 (11.2)	16 (9.1)
Fatigue	2 (1.2)	3 (3.8)	3 (3.1)	6 (3.4)
Asthenia	1 (0.6)	0	4 (4.1)	4 (2.3)
Psychiatric disorders	14 (8.2)	2 (2.6)	10 (10.2)	12 (6.8)
Anxiety	1 (0.6)	0	3 (3.1)	3 (1.7)

Table 18. **Severe TEAEs by SOC and PT (Overall) – PPD PC studies pool**

System Organ Class Preferred Term	Number (%) of Participants			
		Zuranolone		
	Placebo (N = 171)	30 mg (N = 78)	50 mg (N = 98)	All Zuranolone (N = 176)
At least 1 severe TEAE	4 (2.3)	3 (3.8)	3 (3.1)	6 (3.4)
Nervous system disorders	1 (0.6)	2 (2.6)	0	2 (1.1)
Headache	1 (0.6)	0	0	0
Sedation	0	1 (1.3)	0	1 (0.6)
Migraine	0	1 (1.3)	0	1 (0.6)
Gastrointestinal disorders	0	0	2 (2.0)	2 (1.1)

System Organ Class Preferred Term	Number (%) of Participants			
	Placebo (N = 171)	Zuranolone 30 mg (N = 78)	Zuranolone 50 mg (N = 98)	Zuranolone All Zuranolone (N = 176)
Diarrhoea	0	0	1 (1.0)	1 (0.6)
Abdominal pain upper	0	0	1 (1.0)	1 (0.6)
Musculoskeletal and connective tissue disorders	2 (1.2)	0	0	0
Back pain	1 (0.6)	0	0	0
Muscle spasm	1 (0.6)	0	0	0
Muscular weakness	1 (0.6)	0	0	0
Psychiatric disorders	0	1 (1.3)	1 (1.0)	2 (1.1)
Confusional state	0	1 (1.3)	0	1 (0.6)
Perinatal depression	0	0	1 (1.0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0	0	0
Oropharyngeal pain	1 (0.6)	0	0	0
Reproductive system and breast disorders	1 (0.6)	0	0	0
Heavy menstrual bleeding	1 (0.6)	0	0	0

MDD PC studies pool

Table 19. **Overview of TEAEs – MDD PC Studies Pool**

Category[a]	Number (%) of Participants				
	Placebo (N = 846)	Zuranolone 20 mg (N = 273)	Zuranolone 30 mg (N = 362)	Zuranolone 50 mg (N = 480)	Zuranolone All Zuranolone (N = 1115)
TEAE	458 (54.1)	156 (57.1)	206 (56.9)	318 (66.3)	680 (61.0)
On-treatment	366 (43.3)	111 (40.7)	168 (46.4)	293 (61.0)	572 (51.3)
Off-treatment	146 (17.3)	36 (13.2)	59 (16.3)	80 (16.7)	175 (15.7)
Extended Follow-up	95 (11.2)	29 (10.6)	43 (11.9)	46 (9.6)	118 (10.6)
Serious TEAE	5 (0.6)	3 (1.1)	5 (1.4)	4 (0.8)	12 (1.1)
On-treatment	1 (0.1)	0	2 (0.6)	2 (0.4)	4 (0.4)
Off-treatment	2 (0.2)	0	2 (0.6)	1 (0.2)	3 (0.3)
After 14-day follow-up	2 (0.2)	3 (1.1)	1 (0.3)	1 (0.2)	5 (0.4)
Death[b]	0	1 (0.4)	0	0	1 (0.1)

TEAE leading to IP discontinuation	19 (2.2)	4 (1.5)	8 (2.2)	23 (4.8)	35 (3.1)
On-treatment	18 (2.1)	4 (1.5)	7 (1.9)	23 (4.8)	34 (3.0)
Off-treatment[c]	1 (0.1)	0	1 (0.3)	0	1 (0.1)
TEAE leading to study withdrawal	18 (2.2)	5 (1.8)	5 (1.6)[d]	17 (3.5)	27 (2.5)[d]
On-treatment	15 (1.9)	2 (0.7)	2 (0.6)	15 (3.1)	19 (1.8)
Off-treatment	3 (0.4)	0	2 (0.6)	2 (0.4)	4 (0.4)
TEAE leading to IP dose reduction or interruption	9 (1.1)	2 (0.7)	5 (1.4)	46 (9.6)	53 (4.8)
Dose reduction	7 (0.8)	0	5 (1.4)	43 (9.0)	48 (4.3)
Dose interruption	3 (0.4)	2 (0.7)	0	5 (1.0)	7 (0.6)
TEAE by maximum severity					
Mild	277 (32.7)	90 (33.0)	126 (34.8)	162 (33.8)	378 (33.9)
Moderate	169 (20.0)	61 (22.3)	77 (21.3)	140 (29.2)	278 (24.9)
Severe	12 (1.4)	5 (1.8)	3 (0.8)	16 (3.3)	24 (2.2)
On-treatment					
Mild	245 (29.0)	74 (27.1)	112 (30.9)	161 (33.5)	347 (31.1)
Moderate	114 (13.5)	37 (13.6)	54 (14.9)	122 (25.4)	213 (19.1)
Severe	7 (0.8)	0	2 (0.6)	10 (2.1)	12 (1.1)
Off-treatment					
Mild	100 (11.8)	22 (8.1)	35 (9.7)	46 (9.6)	103 (9.2)
Moderate	43 (5.1)	13 (4.8)	24 (6.6)	29 (6.0)	66 (5.9)
Severe	3 (0.4)	1 (0.4)	0	5 (1.0)	6 (0.5)

[a] For TEAE categories summarised by on-treatment and off-treatment (i.e., TEAEs, serious TEAEs, deaths, and TEAE by maximum severity), the total number of participants with at least 1 TEAE includes events during the Extended Follow-up and Long-term Follow-up Periods. Therefore, on-treatment and off-treatment events do not sum to the total.
[b] TEAE with a fatal outcome, not limited to the PT of death.
[c] These were events from Study 217-MDD-304, which started during the placebo run-out period but were off-treatment with respect to the double-blind period.
[d] Percentage denominator excludes Study 217-PPD-201B which did not collect action of study withdrawal due to an AE on the AE CRF. As a result, 1 participant in the 30 mg group who withdrew from the study due to an AE is not included here.

Table 20. **TEAEs with an incidence of ⩾ 3.0% of participants in any dose group by SOC and PT (overall) – MDD PC studies pool**

	Number (%) of Participants				
		Zuranolone			
System Organ Class Preferred Term	**Placebo (N = 846)**	**20 mg (N = 273)**	**30 mg (N = 362)**	**50 mg (N = 480)**	**All Zuranolone (N = 1115)**
At least 1 TEAE	458 (54.1)	156 (57.1)	206 (56.9)	318 (66.3)	680 (61.0)
Nervous system disorders	164 (19.4)	80 (29.3)	105 (29.0)	208 (43.3)	393 (35.2)
Somnolence	43 (5.1)	23 (8.4)	39 (10.8)	80 (16.7)	142 (12.7)
Dizziness	34 (4.0)	23 (8.4)	30 (8.3)	65 (13.5)	118 (10.6)
Headache	81 (9.6)	29 (10.6)	31 (8.6)	54 (11.3)	114 (10.2)
Sedation	15 (1.8)	12 (4.4)	12 (3.3)	32 (6.7)	56 (5.0)
Tremor	4 (0.5)	2 (0.7)	5 (1.4)	19 (4.0)	26 (2.3)
Gastrointestinal disorders	209 (24.7)	57 (20.9)	63 (17.4)	107 (22.3)	227 (20.4)
Nausea	85 (10.0)	16 (5.9)	18 (5.0)	30 (6.3)	64 (5.7)
Diarrhoea	52 (6.1)	15 (5.5)	17 (4.7)	21 (4.4)	53 (4.8)
Dry mouth	41 (4.8)	8 (2.9)	10 (2.8)	30 (6.3)	48 (4.3)

System Organ Class Preferred Term	Number (%) of Participants				
		Zuranolone			
	Placebo (N = 846)	20 mg (N = 273)	30 mg (N = 362)	50 mg (N = 480)	All Zuranolone (N = 1115)
Constipation	9 (1.1)	12 (4.4)	8 (2.2)	5 (1.0)	25 (2.2)
Psychiatric disorders	88 (10.4)	23 (8.4)	28 (7.7)	71 (14.8)	122 (10.9)
Insomnia	32 (3.8)	6 (2.2)	9 (2.5)	24 (5.0)	39 (3.5)
Infections and infestations	100 (11.8)	32 (11.7)	60 (16.6)	26 (5.4)	118 (10.6)
Nasopharyngitis	18 (2.1)	9 (3.3)	16 (4.4)	1 (0.2)	26 (2.3)
Upper respiratory tract infection	24 (2.8)	9 (3.3)	9 (2.5)	3 (0.6)	21 (1.9)
General disorders and administration site conditions	48 (5.7)	15 (5.5)	28 (7.7)	42 (8.8)	85 (7.6)
Fatigue	19 (2.2)	4 (1.5)	15 (4.1)	21 (4.4)	40 (3.6)

Table 21. **TEAEs With an Incidence of ⩾ 3.0% of Participants in Any Dose Group by SOC and PT (On-Treatment and Off-Treatment) – MDD PC Studies Pool**

System Organ Class Preferred Term	Number (%) of Participants				
		Zuranolone			
	Placebo (N = 846)	20 mg (N = 273)	30 mg (N = 362)	50 mg (N = 480)	All Zuranolone (N = 1115)
At least 1 TEAE					
On-treatment	366 (43.3)	111 (40.7)	168 (46.4)	293 (61.0)	572 (51.3)
Nervous system disorders	139 (16.4)	68 (24.9)	94 (26.0)	199 (41.5)	361 (32.4)
Somnolence	42 (5.0)	21 (7.7)	39 (10.8)	80 (16.7)	140 (12.6)
Dizziness	26 (3.1)	21 (7.7)	26 (7.2)	61 (12.7)	108 (9.7)
Headache	62 (7.3)	19 (7.0)	26 (7.2)	38 (7.9)	83 (7.4)
Sedation	15 (1.8)	11 (4.0)	12 (3.3)	32 (6.7)	55 (4.9)
Tremor	3 (0.4)	0	5 (1.4)	19 (4.0)	24 (2.2)
Gastrointestinal disorders	170 (20.1)	44 (16.1)	44 (12.2)	90 (18.8)	178 (16.0)
Nausea	65 (7.7)	10 (3.7)	13 (3.6)	25 (5.2)	48 (4.3)
Dry mouth	40 (4.7)	8 (2.9)	8 (2.2)	27 (5.6)	43 (3.9)
Diarrhoea	40 (4.7)	8 (2.9)	11 (3.0)	18 (3.8)	37 (3.3)
Constipation	8 (0.9)	11 (4.0)	6 (1.7)	3 (0.6)	20 (1.8)
Psychiatric disorders	65 (7.7)	11 (4.0)	17 (4.7)	58 (12.1)	86 (7.7)
Insomnia	26 (3.1)	2 (0.7)	0	18 (3.8)	20 (1.8)
General disorders and administration site conditions	41 (4.8)	7 (2.6)	22 (6.1)	36 (7.5)	65 (5.8)
Fatigue	16 (1.9)	3 (1.1)	13 (3.6)	19 (4.0)	35 (3.1)
At least 1 TEAE					
Off-treatment	146 (17.3)	36 (13.2)	59 (16.3)	80 (16.7)	175 (15.7)
Nervous system disorders	33 (3.9)	11 (4.0)	11 (3.0)	26 (5.4)	48 (4.3)
Headache	17 (2.0)	6 (2.2)	4 (1.1)	17 (3.5)	27 (2.4)

Healthy participants pool

In the Healthy Participants Pool, TEAEs were most frequently reported in the SOCs of nervous system disorders, general disorders and administration site conditions, gastrointestinal disorders, and psychiatric disorders (≥ 10.0% of participants in either the Placebo or All Zuranolone group). TEAEs with a higher incidence (≥ 5.0 percentage point difference) in the All Zuranolone group compared with the Placebo group belong to SOCs of nervous system disorders (49.1% vs. 18.0%), general disorders and administration site conditions (14.6% vs. 2.8%), investigations (5.9% vs. 0.3%), and psychiatric disorders (11.4% vs. 5.6%). TEAEs that occurred in ≥ 5.0% of participants in the Placebo group and All Zuranolone group were somnolence, dizziness, sedation, tremor, headache, fatigue, and nausea. Of these, the incidence of somnolence, dizziness, sedation, tremor, and fatigue was higher (≥ 5.0 percentage point difference) in the All Zuranolone group compared with the Placebo group. The incidence of somnolence, dizziness, and fatigue were higher in the in the ≥ 40-mg to < 60-mg group than in the > 20-mg to < 40-mg group, the ≤ 20-mg group, and the Placebo group. Among these TEAEs, severe events were limited to somnolence (6 [0.9%] participants in All Zuranolone group) and all somnolence events were nonserious. Overall, the types of TEAEs occurring in ≥ 5.0% of participants were generally consistent with those events seen in PPD and MDD. Notably, most events were mild or moderate and resolved without sequelae. The incidence of many TEAEs occurring in ≥ 5.0% of participants was higher compared with the PPD PC Studies pool, but these differences can be attributed to the differences in populations, duration and timing of administration (daytime vs. night-time), formulation (oral solution), and single higher doses ≥ 60 mg on the final day of dosing in driving studies/TQT studies.

Adverse drug reactions

In the PPD PC pool, the incidence of TEAEs assessed as related to IP by the Investigator was 30.4% and 40.9% in the Placebo and All Zuranolone groups, respectively. TEAEs assessed as related to IP with a higher incidence (≥ 5.0 percentage point difference) in the All Zuranolone group compared with the Placebo group were somnolence (20.5% vs. 7.6%) and sedation (8.5% vs. 0.6%). The incidences of somnolence, sedation, and dizziness assessed as related to IP in the zuranolone 50 mg group were higher than in the zuranolone 30 mg and placebo groups.

In the MDD PC studies pool, there was a higher incidence of TEAEs assessed as being related to IP by the Investigator in the All Zuranolone group (42.0%) than the Placebo group (29.8%), consistent with findings in the PPD PC Studies Pool. TEAEs assessed as being related to IP with a higher incidence (≥ 5.0 percentage point difference) in the All Zuranolone group compared with the Placebo group were similar to those in the PPD PC Studies Pool: somnolence (12.2% vs. 4.4%) and dizziness (9.3% vs. 2.6%). There was a dose-related trend with the incidences of somnolence, sedation, and dizziness assessed as related to IP, consistent with findings in the PPD PC Studies Pool.

2.6.9.3. Serious adverse event/deaths/other significant events

Deaths

No deaths were reported between the submission data cutoff date and the evaluation of the database as of 30 April 2024. Two participants died due to TEAEs, both of which were assessed as severe in intensity and not related to IP by the investigator. Both TEAEs occurred in MDD studies and more than 4 months after the last dose of IP.

One participant (TEAE: death, verbatim term: cause of death unknown), with a history of hypertension, chronic obstructive pulmonary disease and MDD, in the zuranolone 20 mg group died (during the extended follow-up period of Study 217MDD-301A) more than 4 months after the last dose of IP.

One participant died during the Observation Period in Study 217MDD-303A more than 150 days after completing 2 treatment cycles of zuranolone 30 mg (TEAEs haemorrhage intracranial and herpes simplex encephalitis).

Other treatment-emergent serious adverse events

A list of all TESAEs in the zuranolone clinical development programme as of the data cutoff date is provided in the Table below. There were 97 nonfatal TESAEs in 65 participants receiving zuranolone and 10 nonfatal TESAEs in 7 participants receiving placebo. Most of the nonfatal TESAEs in zuranolone participants occurred in open-label studies (Studies 217-MDD-303A and 217-MDD-303B). Most TESAEs were reported off treatment and were assessed as not related to IP by the Investigator.

Of the 97 nonfatal TESAEs in 65 participants receiving zuranolone, 28 TESAEs in 22 participants were on treatment and 69 TESAEs in 44 participants occurred after the on-treatment period (inclusive of all follow-up periods: off-treatment period, Extended Follow-up period, and Long-term Follow-up period). Of the 10 nonfatal TESAEs in 7 participants for placebo, 5 TESAEs in 2 participants were on treatment and 5 TESAEs in 5 participants were off treatment. Of the participants in the PPD and MDD PC Studies Pools, there was 1 participant in the Placebo group who had an on-treatment TESAE and 6 participants in the All Zuranolone group who had on-treatment TESAEs.

PPD PC Studies Pool: In the PPD PC Studies Pool, the incidence of TESAEs was low in the Placebo group (1 [0.6%]) and in the All Zuranolone group (3 [1.7%]). No TESAEs occurred in more than 1 participant. TESAEs assessed as related to IP by the Investigator occurred in 1 (0.6%) participant in the All Zuranolone group, with none in the Placebo group. One participant (30 mg) had a TESAE of confusional state assessed as related to IP.

MDD PC Studies Pool: In the MDD PC Studies Pool, the incidence of TESAEs was low in the Placebo (5 [0.6%] participants]) and All Zuranolone (12 [1.1%] participants) groups and across the zuranolone dose groups. No TESAE occurred in > 1 participant in either group. Five participants (1 [0.1%] in the Placebo group and 4 [0.4%] in the All Zuranolone group) experienced TESAEs that were assessed as related to IP by the Investigator: 1 participant (placebo) experienced ALT increased, AST increased, blood alkaline phosphatase increased, and gamma-glutamyltransferase increased; 1 participant (zuranolone 50 mg) experienced seizure-like phenomenon; 1 participant (zuranolone 50 mg) experienced psychotic disorder and slow speech; 1 participant (zuranolone 30 mg) experienced focal dyscognitive seizure; and 1 participant (zuranolone 30 mg) experienced suicide attempt.

Healthy Participants Pool: No participants in the Placebo group and 1 (0.4%) participant in the Zuranolone ≥40 mg to <60 mg group had a TESAE (substance-induced psychotic disorder). No participant had a TESAE assessed as related to IP by the Investigator.

Adverse events of special interest/significant events

- Somnolence

Table 22. **Incidence of somnolence overall and by preferred term**

Somnolence Preferred Term	Number (%) of Participants				
		Zuranolone			
	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	**(N = 171)**	**not applicable**	**(N = 78)**	**(N = 98)**	**(N = 176)**
At least 1 TEAE	13 (7.6)		12 (15.4)	27 (27.6)	39 (22.2)
Somnolence	13 (7.6)		12 (15.4)	26 (26.5)	38 (21.6)
Hypersomnia	0		0	1 (1.0)	1 (0.6)
MDD PC Studies Pool	**(N = 846)**	**(N = 273)**	**(N = 362)**	**(N = 480)**	**(N = 1115)**
At least 1 TEAE	43 (5.1)	23 (8.4)	40 (11.0)	81 (16.9)	144 (12.9)
Somnolence	43 (5.1)	23 (8.4)	39 (10.8)	80 (16.7)	142 (12.7)
Hypersomnia	0	0	1 (0.3)	1 (0.2)	2 (0.2)

Somnolence typically occurred during the on-treatment period, most frequently during the first 2 days, and declined over time during the treatment period.

Table 23. **Incidence of somnolence by time to onset**

Somnolence[a] Time Interval[b]	Number (%) of Participants With Event Within the Interval				
		Zuranolone			
	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	**(N = 171)**	**not applicable**	**(N = 78)**	**(N = 98)**	**(N = 176)**
1 to 2 days	12 (7.0)		10 (12.8)	22 (22.4)	32 (18.2)
3 to 7 days	1 (0.6)		2 (2.6)	8 (8.2)	10 (5.7)
8 to 15 days	1 (0.6)		2 (2.6)	2 (2.0)	4 (2.3)
>15 days	0		0	0	0
MDD PC Studies Pool	**(N = 846)**	**(N = 273)**	**(N = 362)**	**(N = 480)**	**(N = 1115)**
1 to 2 days	27 (3.2)	13 (4.8)	24 (6.6)	54 (11.3)	91 (8.2)
3 to 7 days	12 (1.4)	6 (2.2)	13 (3.6)	23 (4.8)	42 (3.8)
8 to 15 days	6 (0.7)	2 (0.7)	3 (0.8)	4 (0.8)	9 (0.8)
>15 days	3 (0.4)	3 (1.1)	1 (0.3)	1 (0.2)	5 (0.4)

[a] Somnolence includes PTs of somnolence and hypersomnia.

[b] Adverse events are classified into onset intervals according to each participant's length of exposure at the time when the AE started. Time to onset is calculated as AE onset date – first dose date + 1. For those who experienced the same event type multiple times and within different onset intervals, the event is counted once in each of the intervals in which it occurred. AEs with incomplete onset dates are excluded from these analyses.

- Sedation

Table 24. **Incidence of sedation**

Sedation	Number (%) of Participants				
		Zuranolone			
	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	(N = 171)	not applicable	(N = 78)	(N = 98)	(N = 176)
At least 1 TEAE	1 (0.6)		4 (5.1)	11 (11.2)	15 (8.5)
MDD PC Studies Pool	(N = 846)	(N = 273)	(N = 362)	(N = 480)	(N = 1115)
At least 1 TEAE	15 (1.8)	12 (4.4)	12 (3.3)	32 (6.7)	56 (5.0)

Sedation typically occurred during the on-treatment period, most frequently during the first 2 days, and declined over time during the treatment period (Table below).

Table 25. **Incidence of sedation by time to onset**

Sedation[a] Time Interval[b]	Number (%) of Participants With Event Within the Interval				
		Zuranolone			
	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	**(N = 171)**	**not applicable**	**(N = 78)**	**(N = 98)**	**(N = 176)**
1 to 2 days	0		3 (3.8)	7 (7.1)	10 (5.7)
3 to 7 days	1 (0.6)		1 (1.3)	4 (4.1)	5 (2.8)
8 to 15 days	0		1 (1.3)	1 (1.0)	2 (1.1)
>15 days	0		0	0	0
MDD PC Studies Pool	**(N = 846)**	**(N = 273)**	**(N = 362)**	**(N = 480)**	**(N = 1115)**
1 to 2 days	12 (1.4)	6 (2.2)	9 (2.5)	26 (5.4)	41 (3.7)
3 to 7 days	2 (0.2)	4 (1.5)	4 (1.1)	6 (1.3)	14 (1.3)
8 to 15 days	1 (0.1)	1 (0.4)	0	0	1 (0.1)
>15 days	0	1 (0.4)	0	0	1 (0.1)

[a] Sedation includes the PT of sedation.

[b] Adverse events are classified into onset intervals according to each participant's length of exposure at the time when the AE started. Time to onset is calculated as AE onset date – first dose date + 1. For those who experienced the same event type multiple times and within different onset intervals, the event is counted once in each of the intervals in which it occurred. AEs with incomplete onset dates are excluded from these analyses.

- Dizziness

Table 26. **Incidence of dizziness overall and by preferred term**

Dizziness Preferred Term	Number (%) of Participants				
		Zuranolone			
	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	**(N = 171)**	**NA**	**(N = 78)**	**(N = 98)**	**(N = 176)**
At least 1 TEAE					
Dizziness	14 (8.2)		6 (7.7)	13 (13.3)	19 (10.8)
Dizziness postural	NA		NA	NA	NA
MDD PC Studies Pool	**(N = 846)**	**(N = 273)**	**(N = 362)**	**(N = 480)**	**(N = 1115)**
At least 1 TEAE	35 (4.1)	24 (8.8)	30 (8.3)	66 (13.8)	120 (10.8)
Dizziness	34 (4.0)	23 (8.4)	30 (8.3)	65 (13.5)	118 (10.6)
Dizziness postural	1 (0.1)	1 (0.4)	0	1 (0.2)	2 (0.2)

Across both pools, dizziness typically occurred during the on-treatment period, most frequently during the first 2 days, and generally declined over time during the treatment period.

Table 27. **Incidence of dizziness by time to onset**

Dizziness[a] Time Interval[b]	Number (%) of Participants With Event Within the Interval				
		Zuranolone			
	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	**(N = 171)**	**NA**	**(N = 78)**	**(N = 98)**	**(N = 176)**
1 to 2 days	6 (3.5)		3 (3.8)	9 (9.2)	12 (6.8)
3 to 7 days	3 (1.8)		2 (2.6)	4 (4.1)	6 (3.4)

Dizziness[a]	Number (%) of Participants With Event Within the Interval				
		Zuranolone			
Time Interval[b]	Placebo	20 mg	30 mg	50 mg	All Zuranolone
8 to 15 days	2 (1.2)		1 (1.3)	1 (1.0)	2 (1.1)
>15 days	4 (2.3)		0	1 (1.0)	1 (0.6)
MDD PC Studies Pool	**(N = 846)**	**(N = 273)**	**(N = 362)**	**(N = 480)**	**(N = 1115)**
1 to 2 days	16 (1.9)	12 (4.4)	13 (3.6)	43 (9.0)	68 (6.1)
3 to 7 days	8 (0.9)	7 (2.6)	8 (2.2)	17 (3.5)	32 (2.9)
8 to 15 days	5 (0.6)	4 (1.5)	6 (1.7)	3 (0.6)	13 (1.2)
>15 days	10 (1.2)	2 (0.7)	5 (1.4)	4 (0.8)	11 (1.0)

[a] Dizziness includes PTs of dizziness, dizziness postural, and dizziness exertional.
[b] Adverse events are classified into onset intervals according to each participant's length of exposure at the time when the AE started. Time to onset is calculated as AE onset date – first dose date + 1. For those who experienced the same event type multiple times and within different onset intervals, the event is counted once in each of the intervals in which it occurred. Adverse events with incomplete onset dates are excluded from these analyses.

- Falls/Injuries

Table 28. **Falls/injuries reported by ≥ 2 participants in either the placebo or all zuranolone group overall and by preferred term**

Falls/Injuries	Number (%) of Participants				
		Zuranolone			
Preferred Term	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	**(N = 171)**	**NA**	**(N = 78)**	**(N = 98)**	**(N = 176)**
At least 1 TEAE	5 (2.9)		0	2 (2.0)	2 (1.1)
Concussion	2 (1.2)		0	0	0
MDD PC Studies Pool	**(N = 846)**	**(N = 273)**	**(N = 362)**	**(N = 480)**	**(N = 1115)**
At least 1 TEAE	24 (2.8)	6 (2.2)	13 (3.6)	15 (3.1)	34 (3.0)
Contusion	4 (0.5)	0	3 (0.8)	3 (0.6)	6 (0.5)
Ligament sprain	4 (0.5)	2 (0.7)	1 (0.3)	2 (0.4)	5 (0.4)
Road traffic accident	0	1 (0.4)	0	3 (0.6)	4 (0.4)
Muscle strain	3 (0.4)	1 (0.4)	2 (0.6)	0	3 (0.3)
Tooth fracture	0	1 (0.4)	2 (0.6)	0	3 (0.3)
Arthropod bite	2 (0.2)	0	1 (0.3)	1 (0.2)	2 (0.2)
Foot fracture	0	0	1 (0.3)	1 (0.2)	2 (0.2)
Post-traumatic neck syndrome	0	1 (0.4)	0	1 (0.2)	2 (0.2)
Ankle fracture	0	0	2 (0.6)	0	2 (0.2)
Cervical vertebral fracture	0	1 (0.4)	1 (0.3)	0	2 (0.2)
Epicondylitis	3 (0.4)	0	0	0	0

Unlike the other AEs of interest analysed above, the incidence of falls/injuries was higher off-treatment (i.e., after 15 days) than on-treatment for both the PPD and MDD PC Studies Pools, and there was no increased incidence of TEAEs of falls/injuries occurring concurrently with TEAEs of somnolence, sedation, and dizziness (***Table 29*** below).

Table 29. **Incidence of falls/injuries by time to onset**

Falls/Injuries[a] Time Interval[b]	Number (%) of Participants With Event Within the Interval				
		Zuranolone			
	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	**(N = 171)**	**NA**	**(N = 78)**	**(N = 98)**	**(N = 176)**
1 to 2 days	0		0	0	0
3 to 7 days	1 (0.6)		0	0	0
8 to 15 days	0		0	1 (1.0)	1 (0.6)
>15 days	4 (2.3)		0	1 (1.0)	1 (0.6)
MDD PC Studies Pool	**(N = 846)**	**(N = 273)**	**(N = 362)**	**(N = 480)**	**(N = 1115)**
1 to 2 days	0	0	0	0	0
3 to 7 days	5 (0.6)	0	2 (0.6)	2 (0.4)	4 (0.4)
8 to 15 days	3 (0.4)	2 (0.7)	0	4 (0.8)	6 (0.5)
>15 days	16 (1.9)	4 (1.5)	10 (2.8)	9 (1.9)	23 (2.1)

[a] Falls/injuries includes HLGT of Injuries NEC and HLGT of Bone and Joint Injuries.
[b] Adverse events are classified into onset intervals according to each participant's length of exposure at the time when the AE started. Time to onset is calculated as AE onset date – first dose date + 1. For those who experienced the same event type multiple times and within different onset intervals, the event is counted once in each of the intervals in which it occurred. AEs with incomplete onset dates are excluded from these analyses.

- Confusional State

Table 30. **Incidence of confusional state overall and by preferred term**

Confusional state Preferred Term	Number (%) of Participants				
		Zuranolone			
	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	**(N = 171)**	**NA**	**(N = 78)**	**(N = 98)**	**(N = 176)**
At least 1 TEAE	0		1 (1.3)	1 (1.0)	2 (1.1)
Confusional state	0		1 (1.3)	1 (1.0)	2 (1.1)
Disorientation	NA		NA	NA	NA
Delirium	NA		NA	NA	NA
MDD PC Studies Pool	**(N = 846)**	**(N = 273)**	**(N = 362)**	**(N = 480)**	**(N = 1115)**
At least 1 TEAE	0	1 (0.4)	1 (0.3)	6 (1.3)	8 (0.7)
Confusional state	0	0	1 (0.3)	5 (1.0)	6 (0.5)
Disorientation	0	0	0	1 (0.2)	1 (0.1)
Delirium	0	1 (0.4)	0	0	1 (0.1)

In the PPD PC Studies Pool, the 2 events of confusional state (pooled PTs) occurred in the 3 to 7 days interval in the All Zuranolone group (Table 31 below).

Table 31. **Incidence of confusional state by time to onset**

Confusional State[a] Time Interval[b]	Number (%) of Participants With Event Within the Interval				
		Zuranolone			
	Placebo	20 mg	30 mg	50 mg	All Zuranolone
PPD PC Studies Pool	**(N = 171)**	**NA**	**(N = 78)**	**(N = 98)**	**(N = 176)**
1 to 2 days	0		0	0	0
3 to 7 days	0		1 (1.3)	1 (1.0)	2 (1.1)
8 to 15 days	0		0	0	0
>15 days	0		0	0	0

Confusional State[a] Time Interval[b]	Number (%) of Participants With Event Within the Interval				
	Placebo	Zuranolone			
		20 mg	30 mg	50 mg	All Zuranolone
MDD PC Studies Pool	**(N = 846)**	**(N = 273)**	**(N = 362)**	**(N = 480)**	**(N = 1115)**
1 to 2 days	0	0	0	2 (0.4)	2 (0.2)
3 to 7 days	0	0	0	3 (0.6)	3 (0.3)
8 to 15 days	0	0	1 (0.3)	1 (0.2)	2 (0.2)
>15 days	0	1 (0.4)	0	0	1 (0.1)

[a] Confusional state includes preferred terms of confusional state, delirium, and disorientation.
[b] Adverse events are classified into onset intervals according to each participant's length of exposure at the time when the AE started. Time to onset is calculated as AE onset date – first dose date + 1. For those who experienced the same event type multiple times and within different onset intervals, the event is counted once in each of the intervals in which it occurred. Adverse events with incomplete onset dates are excluded from these analyses.

A brief narrative for the participant in the zuranolone 30 mg group of Study 217-PPD-201 with a TESAE of severe confusional state is presented below. The remaining TEAE of confusional state in the PPD PC Studies Pool was nonserious.

One participant had a TESAE of confusional state along with nonserious TEAEs of sedation and dizziness. The action taken with IP initially was dose interruption, followed by a dose reduction. The TESAE resolved on the same day. The Investigator assessed confusional state as related to zuranolone. The participant completed the treatment period on a reduced dose of 20 mg without any further symptoms during the study.

- Suicidal Ideation and Behaviour

The risk of suicidal ideation and behaviour was examined throughout the zuranolone development programme using the C-SSRS and analysis of TEAEs. For TEAEs in all study periods, the following PTs under the MedDRA High Level Term of Suicidal and self-injurious behaviour potentially related to suicidality were evaluated for all clinical studies in the PPD PC Studies Pool and MDD PC Studies Pool: Assisted suicide, Completed suicide, Intentional self-injury, Self-injurious ideation, Suicidal behaviour, Suicidal ideation, Suicide attempt, Suicide threat, Suspected suicide, and Suspected suicide attempt.

C-SSRS

Table 32. **Shift in C-SSRS From Baseline to Worst Postbaseline – PPD PC Studies Pool and MDD PC Studies Pool**

Baseline Assessment	Worst Postbaseline Assessment, n (%)		
	No suicidal ideation/behaviour	Suicidal ideation	Suicidal behaviour
PPD PC Studies Pool			
Placebo			
No suicidal ideation/behaviour (n = 122)	115 (94.3)	7 (5.7)	0
Suicidal ideation (n = 46)	31 (67.4)	15 (32.6)	0
Suicidal behaviour (n = 1)	0	1 (100.0)	0
Zuranolone 30 mg			
No suicidal ideation/behaviour (n = 58)	55 (94.8)	3 (5.2)	0
Suicidal ideation (n = 19)	16 (84.2)	3 (15.8)	0
Suicidal behaviour (n = 1)	1 (100.0)	0	0

Zuranolone 50 mg			
No suicidal ideation/behaviour (n = 60)	60 (100.0)	0	0
Suicidal ideation (n = 37)	22 (59.5)	14 (37.8)	1 (2.7)
Suicidal behaviour (n = 1)	0	1 (100.0)	0
MDD PC Studies Pool			
Placebo			
No suicidal ideation/behaviour (n = 489)	471 (96.3)	18 (3.7)	0
Suicidal ideation (n = 345)	187 (54.2)	157 (45.5)	1 (0.3)
Suicidal behaviour (n = 7)	6 (85.7)	1 (14.3)	0
Zuranolone 20 mg			
No suicidal ideation/behaviour (n = 177)	159 (89.8)	18 (10.2)	0
Suicidal ideation (n = 94)	37 (39.4)	55 (58.5)	2 (2.1)
Suicidal behaviour (n = 0)	0	0	0
Zuranolone 30 mg			
No suicidal ideation/behaviour (n = 252)	243 (96.4)	9 (3.6)	0
Suicidal ideation (n = 106)	45 (42.5)	60 (56.6)	1 (0.9)
Suicidal behaviour (n = 4)	2 (50.0)	2 (50.0)	0
Zuranolone 50 mg			
No suicidal ideation/behaviour (n = 268)	256 (95.5)	12 (4.5)	0
Suicidal ideation (n = 203)	112 (55.2)	90 (44.3)	1 (0.5)
Suicidal behaviour (n = 5)	3 (60.0)	2 (40.0)	0

TEAEs Potentially Related to Suicidality

- PPD PC Studies Pool

In the PPD PC Studies Pool, the incidence of TEAEs potentially related to suicidality was low: 0.6% in the All Zuranolone group and 0.6% in the Placebo group. None of the TEAEs related to suicidality were serious. One participant in the Placebo group had a TEAE of intentional self-injury and 1 participant in the All Zuranolone group (50 mg) had a TEAE of suicide attempt that occurred off treatment. This participant was ≥25 years of age and had also previously reported an on-treatment TEAE of suicidal ideation.

- MDD PC Studies Pool

The incidence of TEAEs potentially related to suicidality was 0.9% (8 participants) in the Placebo group and 1.4% (16 participants) in the All Zuranolone group. Serious TEAEs potentially related to suicidality include suicide attempt (1 participant [0.3%] in the zuranolone 30 mg group) and suicidal ideation (1 participant [0.1%] in the Placebo group). Three participants in the All Zuranolone group who experienced a TEAE potentially related to suicidality were < 25 years of age; the remaining 13 participants were ≥ 25 years of age.

TESAEs Potentially Related to Suicidality

Across the clinical programme, as of the data cutoff date, TESAEs potentially related to suicidality occurred in 7 participants (1 placebo, 6 All Zuranolone) and all occurred in MDD studies. Of the 6 TESAEs in zuranolone participants, 3 occurred off treatment. In Study 217-MDD-301A, 2 participants

(1 placebo, 1 zuranolone) had TESAEs relevant to suicidality. In Study 217-MDD-303A, 5 participants (3 zuranolone 30 mg, 2 zuranolone 50 mg) had TESAEs relevant to suicidality. Of the 5 events, 1 was assessed as related to IP by the Investigator; 1 (50 mg) was moderate and 4 were severe. Three of these 4 events required hospitalisation or prolongation of hospitalisation, 1 required hospitalisation or prolongation of hospitalisation and was life-threatening, and 1 was a medically important TESAE. All but 1 of these events occurred in participants age ≥25 years.

2.6.9.4. Laboratory findings

Clinical Laboratory Evaluations

Haematology

In the PPD PC Studies Pool, the percentage of participants with postbaseline PCS haematology parameter values was similar between the Placebo and All Zuranolone groups. In the MDD PC Studies Pool, the percentage of participants with postbaseline PCS haematology parameter values was similar between the Placebo and All Zuranolone groups.

Liver Function Tests

No participant in any analysis pool and 2 participants in ongoing MDD studies who received zuranolone had liver function test values that met Hy's law criteria (total bilirubin > 2 × ULN and ALT or AST > 3 × ULN and alkaline phosphatase < 2 × ULN). In the PPD PC Studies Pool, no clinically meaningful differences were observed between the Placebo and All Zuranolone groups for the percentage of participants with postbaseline PCS liver function test values. Consistent with the results from the PPD PC Studies Pool, there were no clinically meaningful differences observed between the Placebo and All Zuranolone groups for the percentage of participants with postbaseline PCS liver function test values in the MDD PC Studies Pool.

SAEs of Abnormal Liver Function Tests

Two participants who received zuranolone in ongoing MDD Studies 2207A3736 and 2122A3734 had liver function test values that met Hy's law laboratory criteria, but both had alternative causes, and both events were unlikely to be related to zuranolone. An additional participant enrolled in Study 2207A3736 reported an SAE of hepatic function abnormal, but this participant received placebo.

Liver Function Tests Shifts from Baseline

In the PPD PC Studies Pool, no clinically meaningful differences were observed between the Placebo and All Zuranolone groups for the percentage of participants with shifts from normal at baseline to high at the last on-treatment value for ALT, AST, bilirubin, and alkaline phosphatase. A similar pattern was observed between the Placebo and All Zuranolone groups in shifts from normal at baseline to high at the last on-study value for ALT, AST, bilirubin, and alkaline phosphatase. Shifts from baseline in LFT parameters for the Healthy Participants Pool are consistent with the PPD PC Studies Pool.

PCS Serum Chemistry Values

In the PPD PC Studies Pool, there was no clinically meaningful difference between the Placebo and All Zuranolone groups for the percentage of participants with postbaseline PCS serum chemistry parameter values. In the MDD PC Studies Pool, the percentage of participants with postbaseline PCS high potassium was 5.5% in the Placebo group and 5.1% in the All Zuranolone group. The incidence of other postbaseline PCS serum chemistry parameter values was low (< 2.0%) in the Placebo and All Zuranolone groups. In the Healthy Participants Pool, the incidence of postbaseline PCS serum chemistry parameter values was low (<2.0%) in the Placebo and All Zuranolone groups.

2.6.9.5. Safety in special populations

Renal Impairment

There were no participants with moderate or severe renal impairment in the PPD PC Studies Pool. There was not a ≥ 10.0% difference in TEAEs reported among participants in the All Zuranolone group with normal renal function (n = 85; 65.9%) and with mild renal impairment (n = 27; 57.4%).

In the MDD PC Studies Pool, there were 2 participants with severe renal impairment, both of whom reported at least 1 TEAE during the study. There was not a ≥ 10.0% difference in overall TEAE incidence in participants with mild (n = 308; 65.4%) and moderate (n = 12, 52.2%) renal impairment compared with participants with normal renal function (n = 358; 57.8%). There were no notable trends in any TEAE incidence between participants with normal renal function and participants with renal impairment.

Study 217-CLP-107 was a Phase 1 study of the PK, safety, and tolerability of a single dose of zuranolone (30 mg) in participants with renal impairment (N = 18) and participants with normal renal function (N = 6). Zuranolone AUC_{inf} increased by 33% to 42% in participants with renal impairment as compared with participants with normal renal function. There was no difference in the TEAE profile between renally impaired participants and participants with normal renal function. A single dose of 30 zuranolone mg was well tolerated when administered to adult participants with renal impairment or normal renal function.

Hepatic Impairment

Study 217-CLP-108 was a Phase 1 study of the PK, safety, and tolerability of a single dose of zuranolone in participants with hepatic impairment (n = 18) and participants with normal hepatic function (n = 6). Participants in the mild, moderate, and normal cohorts received a dose of zuranolone 30 mg and participants in the severe cohort received a dose of zuranolone 20 mg. Hepatic impairment was associated with an increased incidence of mild TEAEs (9 [37.5%]) with no trend observed by increasing severity of impairment. A single dose of zuranolone 30 mg was well tolerated when administered to adult participants with mild or moderate hepatic impairment or normal hepatic function and as a single dose of zuranolone 20 mg dose to adult participants with severe hepatic impairment.

Use in pregnancy and lactation

Pregnancy

The effects of zuranolone in pregnant women have not been studied, and the effects on labour, delivery, and the fetus are unknown. The outcomes of reported pregnancies by participants who received IP in a zuranolone clinical study are presented in the Table below. Twelve pregnancies in women exposed to zuranolone were identified in the safety database, all from studies in participants with MDD. A final outcome was reported for 10 of the pregnancies: 5 resulted in live births of healthy newborns, 1 resulted in stillbirth, and the other 4 participants had elective pregnancy terminations. The pregnancy outcome was not reported for 2 participants, 1 of whom was lost to follow-up and the other who withdrew due to a positive pregnancy test. One pregnancy was reported in the female partner of a male study participant exposed to zuranolone; the final outcome is unknown since this participant was lost to follow-up.

Lactation

Available data from a study in 15 healthy, lactating women indicate that the amount of zuranolone excreted in breast milk following daily administration of zuranolone 30 mg for 5 days was very low

when compared to the maternal dose, with an estimated mean RID of 0.217%, 0.357%, and 0.314% for Day 1, Day 5, and the entire study period (Days 1 to 11), respectively. In most participants, concentrations of zuranolone in breast milk were below the level of quantitation limit by 6 days after the last dose. The RID following a 50 mg maternal dose was also evaluated using a simulation approach in conjunction with a population PK model which characterised zuranolone distribution into breast milk. The expected mean RID associated with a 50 mg maternal dose was 0.738% for an infant with a milk intake of 150 mL/kg/day and 0.984% for an infant with a milk intake of 200 mL/kg/day. Lactation did not alter the PK profile, including the fraction unbound in plasma of zuranolone, in lactating women relative to other populations.

Zuranolone was generally well tolerated when administered as a 30 mg dose to healthy lactating female participants for 5 days. In clinical studies of zuranolone, female participants who were lactating or actively breastfeeding were required to stop giving breast milk to their infant starting on Day 1 until 7 days after the last dose of the IP. However, given the low transfer of zuranolone into breast milk, the theoretical maximum amount of drug ingestible by the infant could be minimal. In most participants, concentrations of zuranolone following 30 mg daily dose in breast milk were below the level of quantitation limit by 6 days after the last dose. All in all, there are no clinical data regarding the effects of zuranolone on the breastfed infant.

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

Although there is no clinical experience with CYP450 inhibitors, clinical pharmacology studies showed concomitant use of zuranolone with a strong CYP3A inhibitor increases the exposure of zuranolone. Systemic exposure (AUC_{inf}) to zuranolone is increased 62% when administered in combination with itraconazole. The dose of zuranolone should be reduced to 30 mg when used with a strong CYP3A inhibitor.

Psychotropic Medications of Interest

In the PPD PC Studies Pool, baseline use of ADT was 16.4% and 17.6% in the Placebo and All Zuranolone groups, respectively. During the study, no notable differences were observed between the Placebo and All Zuranolone groups for the percentage of participants using concomitant ADT (18.7% and 21.0%, respectively). In the PPD studies, benzodiazepines were restricted, and the use of anxiolytics and sedatives/hypnotics was low. Four participants in Study 217-PPD-301 and 8 participants in Study 217-PPD-201 took concomitant anxiolytic or sedative/hypnotic medications. Therefore, further interpretation is limited in the PPD PC Studies Pool.

In the MDD PC Studies Pool, baseline use of most psychotropic medications of interest aside from ADTs was low in the Placebo and All Zuranolone groups:

- Sedative/hypnotic (2.4% and 3.5%, respectively)
- Benzodiazepine (0.1% and < 0.1%, respectively)

Baseline use of ADT was similar between the Placebo and All Zuranolone groups (19.5% and 20.0%, respectively). Baseline use of ADTs was 22.0%, 23.2%, and 16.5% in the zuranolone 20-mg, 30-mg, and 50-mg groups, respectively. Per study design, existing use of ADTs at baseline was not permitted in Study 1818A3731 or Study 217 MDD-305, which was the only study in which participants (N = 218 [Placebo], N = 210 [All Zuranolone]) co-initiated ADT at baseline.

During the study period (including baseline and add-on use during the study), there were no notable differences observed between the Placebo and All Zuranolone groups for ADT use:

- ADT (22.7% and 22.8%, respectively)

A greater percentage of participants in the All Zuranolone group than in the Placebo group received concomitant administration with benzodiazepine/sedative/hypnotic medications, allowing for further analysis. Use of these medications was 4.8% in the Placebo group and 14.3%, 9.4%, 1.5%, and 7.2% in the zuranolone 20 mg, 30 mg, 50 mg, and All Zuranolone groups, respectively, during the study period. This finding may reflect differences in study design. Concomitant benzodiazepine use was prohibited in Studies 1818A3731 (zuranolone 20 mg and 30 mg), 217 MDD-301A (zuranolone 20 mg and 30 mg), 217 MDD 304 (zuranolone 30 mg), 217 MDD 301B (zuranolone 50 mg), and 217 MDD 305 (zuranolone 50 mg). Benzodiazepines were permitted in Study 217 MDD 201B (30-mg zuranolone) if they were stable from 14 days prior to baseline through the end of the treatment period.

All Concomitant Medications

In the PPD PC Studies Pool, the majority of participants took at least 1 concomitant medication (94.2% Placebo, 91.5% All Zuranolone). Use of ibuprofen was ≥ 10.0% in both the Placebo (14.0%) and All Zuranolone (13.6%) groups.

In the MDD PC Studies Pool, the majority of participants took at least 1 concomitant medication (79.9% Placebo, 77.4% All Zuranolone). Similar to the PPD PC Studies Pool, use of ibuprofen was ≥ 10.0% s in both the Placebo and All Zuranolone group (18.3% and 17.0%, respectively).

2.6.9.7. Discontinuation due to adverse events

The incidence of premature IP discontinuations due to a TEAE was low across the programme and generally similar between the placebo and all zuranolone groups. In general, there was a higher incidence of premature IP discontinuations at the higher dose range for zuranolone than at the lower dose ranges. The types of TEAEs leading to IP discontinuation were consistent across the pools, and most commonly included somnolence and sedation.

PPD PC studies pool

In the PPD PC Studies Pool, the incidence of premature discontinuations of IP due to a TEAE was low in the Placebo group (2 [1.2%] participants) and All Zuranolone group (5 [2.8%] participants). The most frequent TEAEs leading to IP discontinuation were in the Nervous system disorders SOC. Somnolence and sedation were the most frequently reported TEAEs leading to premature discontinuation of IP.

Table 33. **Table - TEAEs leading to IP discontinuation in ≥ 2 participants in the placebo or all zuranolone groups by SOC and PT – PPD PC studies pool**

	Number (%) of Participants			
		Zuranolone		
System Organ Class **Preferred Term**	**Placebo** **(N = 171)**	**30 mg** **(N = 78)**	**50 mg** **(N = 98)**	**All Zuranolone** **(N = 176)**
At least 1 TEAE	2 (1.2)	1 (1.3)	4 (4.1)	5 (2.8)
Nervous system disorders	2 (1.2)	1 (1.3)	3 (3.1)	4 (2.3)
Somnolence	0	0	2 (2.0)	2 (1.1)
Sedation	0	1 (1.3)	1 (1.0)	2 (1.1)

MDD PC studies pool

Similar to the PPD PC Studies Pool, in the MDD PC Studies Pool, the incidence of premature discontinuations of IP due to a TEAE was low in the Placebo (2.2% [19 participants]) and All Zuranolone (3.1% [35 participants]) groups. Consistent with the PPD studies, the most frequently reported TEAEs leading to IP discontinuation were also in the Nervous system disorders SOC.

Premature discontinuation of IP due to a TEAE was highest in the 50-mg treatment group, with the most frequent events being sedation (1.7%) and dizziness (1.5%).

Healthy participants pool

In the Healthy Participants Pool, the incidence of premature discontinuations of IP due to a TEAE was also low in the Placebo (0%) and All Zuranolone (1.5% [10 participants]) groups. TEAEs leading to IP discontinuation were higher in the ≥40-mg to <60-mg group (3.3%) than in the >20-mg to <40-mg group (0.5%) and the ≤20-mg group (0). Consistent with the PPD and MDD PC Studies Pools, the most frequent TEAEs leading to IP discontinuation were in the Nervous system disorders SOC. Of these, the most frequent TEAE in the ≥40-mg to <60-mg group was somnolence (1.2%).

TEAEs leading to dose reductions

The most frequently reported TEAEs leading to IP dose reduction or interruption were consistent across the pools and with the core safety profile of zuranolone, namely, somnolence, dizziness, and sedation. Seventeen of 19 participants in the All Zuranolone group of the PPD PC studies pool and 41 of 45 participants in the All Zuranolone group of the MDD PC studies pool completed the treatment regimen after dose reduction or interruption.

PPD PC Studies Pool

Table 34. **TEAEs leading to IP dose reduction or interruption in ≥ 2 participants in either the placebo or all zuranolone group by SOC and PT – PPD PC studies pool**

	Number (%) of Participants			
		Zuranolone		
System Organ Class Preferred Term	Placebo (N = 171)	30 mg (N = 78)	50 mg (N = 98)	All Zuranolone (N = 176)
At least 1 TEAE	2 (1.2)	3 (3.8)	16 (16.3)	19 (10.8)
Nervous system disorders	0	2 (2.6)	14 (14.3)	16 (9.1)
Somnolence	0	1 (1.3)	7 (7.1)	8 (4.5)
Dizziness	0	0	6 (6.1)	6 (3.4)
Sedation	0	1 (1.3)	3 (3.1)	4 (2.3)
Psychiatric disorders	1 (0.6)	1 (1.3)	1 (1.0)	2 (1.1)
Confusional state	0	1 (1.3)	1 (1.0)	2 (1.1)

MDD PC Studies Pool

Table 35. **TEAEs leading to IP dose reduction or interruption in ≥ 2 participants in either the placebo or all zuranolone group by SOC and PT – MDD PC studies pool**

	Number (%) of Participants				
		Zuranolone			
System Organ Class Preferred Term	Placebo (N = 846)	20 mg (N = 273)	30 mg (N = 362)	50 mg (N = 480)	All Zuranolone (N = 1115)
At least 1 TEAE	9 (1.1)	2 (0.7)	5 (1.4)	46 (9.6)	53 (4.8)
Nervous system disorders	4 (0.5)	0	4 (1.1)	35 (7.3)	39 (3.5)
Somnolence	3 (0.4)	0	1 (0.3)	13 (2.7)	14 (1.3)
Dizziness	2 (0.2)	0	2 (0.6)	12 (2.5)	14 (1.3)
Sedation	0	0	1 (0.3)	4 (0.8)	5 (0.4)
Headache	1 (0.1)	0	0	3 (0.6)	3 (0.3)
Tremor	1 (0.1)	0	0	3 (0.6)	3 (0.3)
Gastrointestinal disorders	2 (0.2)	0	1 (0.3)	7 (1.5)	8 (0.7)
Nausea	1 (0.1)	0	1 (0.3)	6 (1.3)	7 (0.6)
Vomiting	0	0	1 (0.3)	1 (0.2)	2 (0.2)
General disorders and administration site conditions	2 (0.2)	1 (0.4)	0	4 (0.8)	5 (0.4)
Fatigue	1 (0.1)	1 (0.4)	0	2 (0.4)	3 (0.3)
Feeling abnormal	0	0	0	2 (0.4)	2 (0.2)
Psychiatric disorders	2 (0.2)	1 (0.4)	0	4 (0.8)	5 (0.4)
Restlessness	1 (0.1)	0	0	2 (0.4)	2 (0.2)

Healthy Participants Pool

In the Healthy Participants Pool, 1 participant (0.3%) in the Placebo group and 3 participants (0.5%) in the All Zuranolone group had TEAEs leading to IP dose reduction or interruption. TEAEs leading to IP dose reduction or interruption in the All Zuranolone dose group were dizziness (50 mg, moderate, related), somnolence (50 mg, moderate, related), and urinary tract infection (30 mg, mild, not related). The TEAE leading to IP dose reduction or interruption in the Placebo dose group was erythema (mild, not related).

2.6.9.8. Post marketing experience

Zuranolone was first approved globally in the US on 04 August 2023. As of 30 April 2024, zuranolone is not authorised in any other country or region. From the International Birth Date, 04 August 2023, through 30 April 2024, zuranolone was prescribed to approximately 1133 patients, equivalent to 47.2 patient years in the postmarketing setting in the US. Estimated cumulative patient-months of exposure was calculated by summing the total number of sales patients each month from the start of marketing through the end of the period and multiplying that number by an assumed person-month contribution of 0.5 months. Patient-years of exposure was estimated by dividing the estimated cumulative patient-months by 12 months/year.

A total of 96 cases reporting 225 events were entered in the Biogen Global Safety Database from the postmarketing sources. Of these, 2 cases reported events with onsets in August 2020 and December 2020; however, zuranolone was approved on 4 August 2023. In addition, 1 literature report was received on 10 August 2023, which concerned a participant who received zuranolone during clinical

trials for PPD and reported that her depression returned after the trial ended. Therefore, these 3 cases were not considered for further discussion but are counted in the overall total.

Of the 225 events reported during the postmarketing period, the most commonly reported events (events with PTs ≥ 2%) were somnolence (n = 21, 9.3%), dizziness (n = 15, 6.7%), fatigue (n = 13, 5.8%), drug ineffective and sedation (n = 7, 3.1% each), feeling abnormal and tremor (n = 6, 2.7% each), nausea and suicidal ideation (n = 5, 2.2% each). The events reported include known ADRs with zuranolone, such as somnolence (including sedation), dizziness (including vertigo), fatigue (including asthenia), and tremor or are consistent with the background disease or patient population. Age was reported in 45 cases and ranged from 22 to 44 years old; age was not reported in the remaining 51 cases. Outcome was reported as resolved for 39 events (17.3%), not resolved for 29 events (12.9%), and unknown in the remaining 157 events (69.8%).

Of the 96 cases, zuranolone dose was not changed in 31 cases (32.3%), dose was reduced in 9 cases (9.4%), was interrupted in 2 cases (2.1%), and was discontinued in 17 cases (17.7%). There was no reported action taken for the remaining 37 cases (38.5%). The most frequently reported events where zuranolone dose was reduced were dizziness and fatigue (n = 2 each). Where zuranolone was discontinued, the most frequently reported events were dizziness and somnolence (n = 5 each), and feeling abnormal, sedation, and tremor (n = 2 each). Note: 1 case may contain more than 1 event.

Of the 225 reported events, 23 (10.2%) were reported as serious in 13 cases. Of the 23 serious events, the most frequently reported was the PT of suicidal ideation (n = 5, 21.7%), which was reported as life-threatening in 1 case and as an important medical event in the remaining 4 cases. The applicant was asked to thorough assess the causal relatedness of these events with zuranolone.

Of the 13 cases reporting 23 serious events, zuranolone dose was maintained in 2 cases, stopped temporarily in 1 case, discontinued in 3 cases, and action taken was unknown or not applicable in 7 cases. Possible confounding factors such as concurrent illnesses or concomitant medications were reported in 4 cases, and not provided in the remaining 9 cases.

A search for events related to the risk of impaired ability to drive or engage in other potentially hazardous activities due to CNS depressant effects identified 4 cases. In 3 cases the patients reported a perceived impaired ability to drive in the context of CNS depressant events, including PTs of brain fog, cognitive disorder, dizziness, fatigue, feeling abnormal, and somnolence. Limited information pertaining to driving impairment was available. It was unknown whether the patients attempted to drive. No adverse sequelae, such as motor vehicle accidents or injuries, were reported for these cases. The remaining case concerned a patient who experienced PTs of brain fog, falls, and injury, which were confounded by the concomitant administration of lorazepam. There was limited information around the circumstances of the falls or injury.

There were no events related to an abuse, misuse, or overdose with zuranolone reported in any patient in the post marketing setting in the US. There were no reports of use in pregnancy or withdrawal effects received from post marketing sources. One case concerned a patient who experienced an on-treatment event with a PT of seizure, which was confounded by a medical history of seizures.

Table 36. **Cumulative summary tabulation of serious adverse events from postmarketing sources**

MedDRA PT	HCP Confirmed	Consumer Reported	Total
Suicidal ideation	4	1	5
Affective disorder	1	0	1
Akathisia	1	0	1
Alanine aminotransferase increased	1	0	1*
Aspartate aminotransferase increased	1	0	1*
Blood alkaline phosphatase increased	1	0	1*
Blood pressure increased	0	1	1
Dizziness	0	1	1
Fatigue	1	0	1
Gamma-glutamyltransferase increased	1	0	1*
Heart rate decreased	0	1	1
Hypotension	0	1	1
Influenza like illness	1	0	1
Neurological symptom	1	0	1
Panic attack	0	1	1
Psychotic disorder	1	0	1*
Seizure	1	0	1
Slow speech	1	0	1*
Somnolence	1	0	1
Total	**17**	**6**	**23**

*Serious events with an onset on 11 August 2020 and 20 December 2020. Zuranolone was approved by the FDA on 04 August 2023 and is not marketed in any other country or region.

2.6.10. Discussion on clinical safety

The safety profile for zuranolone was characterised using data from the 36 clinical studies (33 completed and 3 ongoing) in the development programme. Data were presented in pooled analysis (all based on data from completed studies), which included 25 studies. The primary analysis pool is the PPD PC Studies Pool (two randomised, double-blind, placebo-controlled studies), which includes the studies to support the intended indication. Secondary pools include the MDD PC Studies Pool (6 studies, 5 of those were MDD randomised, double-blind, placebo-controlled studies) and the Healthy Participants Pool. Note that in some MDD studies, zuranolone was administered in repeated 14-day treatment courses (up to 5 repeated treatment courses per year), while in the PPD indication the proposed posology is one 14-day treatment course without chronic or chronic repetitive administration. In the target indication, exposure data is available for the intended treatment period of 14 days with a follow-up of up to Day 45. Data from the MDD studies is available with a follow-up period of up to 12 months, but as mentioned, with repetitive dosing. However, it can be agreed that although PPD and MDD are different indications, the trials for MDD employed overall similar designs, doses, and durations, thereby enabling safety comparisons with the PPD studies and thus supplement and support the safety profile of zuranolone for PPD.

Across the clinically complete studies, 2653 participants with PPD or MDD were exposed to zuranolone (177 with PPD and 2476 with MDD): 1227 participants exposed to 50 mg and 1231 participants exposed to 30 mg. A total of 401 participants who received zuranolone 50 mg as their first dose have been followed for 6 months and 284 have been followed for 12 months; 477 participants who received zuranolone 30 mg as their first dose have been followed for 6 months and 312 have been followed for 12 months. Of the 347 participants in the PPD PC Studies Pool, the majority completed the 14-day course of treatment (92.4% placebo, 90.3% zuranolone) and the study (89.5% placebo, 90.3% zuranolone). Lost to follow-up (6.4% placebo, 3.4% zuranolone) and withdrawal by participant (2.9% placebo, 3.4% zuranolone) were the most frequently reported reasons for premature discontinuation from the study. Considering all patients zuranolone overall data exposure, it is agreed that the safety database is adequate for safety assessment of zuranolone for the proposed indication, patient population, dose and short-term treatment. In addition, it should be noted that long-term follow-up beyond 4 weeks has been evaluated in MDD studies with participants who received 14-day treatment cycles of zuranolone.

In the pivotal studies, zuranolone was administered to patients' post-partum, within 6-12 months after delivery (depending on study protocol). As per exclusion criteria, pregnant women were excluded. The sought indication also specified the indication as postpartum depression. However, as depressive symptoms in this context often start already in the peripartum period i.e., including during pregnancy (up to ~40% of patients), and the current diagnostic criteria also define the disorder with peripartum onset, there is a risk that zuranolone could be prescribed to pregnant women. There are very limited data in humans (12 pregnancies in the MDD studies, exposure to zuranolone during gestation period unclear) and studies in animals show reproductive toxicity. Thus, the applicant thoroughly discussed the risk of zuranolone being prescribed to pregnant women in different trimesters of pregnancy and the associated risks to the foetus based on available non-clinical and clinical data (including post-marketing). In the responses provided by the applicant regarding the non-clinical data and taking into consideration the available data, there is evidence from 2 species in EFD studies, mouse and rat, that there is a risk for skeletal malformations. The applicant argued that a risk in the first trimester of pregnancy is low, since no adverse findings were seen in the FEED study. However, the outcome of the EFD studies is still relevant for the later stage of the human first trimester and beginning of second trimester. It cannot be excluded that women may become pregnant again whilst taking zuranolone. Although the risk is mitigated by the advice to women of childbearing potential to use contraception, the applicant, as requested, acknowledged the need for a contraindication during pregnancy taking into account the strength of the evidence available. Available human data is minimal. In addition, based on the data presented in pregnancies reported across the clinical development programme, exposure to zuranolone during pregnancy has been very short (if any) covering only the beginning of the 1st trimester. This is understandable as after a positive pregnancy test a subject was discontinued from zuranolone. Based on these very limited data, nothing can be concluded on the risk to the foetus. The same applies to post-marketing data provided by the applicant, which is limited to 2 spontaneous reports with incomplete data. All in all, considering the risk observed in the non-clinical studies and the non-existent human data, the introduced limitations to the SmPC are considered necessary. The proposed specification in the indication is accepted, to rule out exposure to zuranolone during the third trimester. The advice for use of effective contraception is also accepted. However, considering the strength of the evidence regarding malformations from animal studies, a contraindication was implemented (sections 4.3 and 4.6 of the SmPC have been adequately updated and section 2 of the PL is also considered adequate).

All patients in the pivotal PDD studies were female and 18 to 45 years of age, inclusive. It is questionable whether the upper limit of 45 years age was *per se* required as inclusion criterium considering the other inclusion criteria of the study. Given pregnancies and peripartum depression occur also in women above 45 years of age, the applicant was requested to discuss the lack of data in

women above 45 years of age and possible safety concerns in these patients, taking into account the adverse event profile of zuranolone. The Applicant provided additional analyses of efficacy and safety data for zuranolone in the PPD (and for safety also MDD) population. TEAEs in female patients >45 years of age, treated with zuranolone, were generally comparable to those in younger female patients (<45 years of age) in the MDD population. It is agreed that, in terms of age, the population in Study 301 is generally representative of EU women of child-bearing potential. However, there remains a small percentage of women who have a baby at higher age (>45 years). However, based on provided information, there is currently no reason to suspect differences in safety of zuranolone in patients with PPD >45 years of age.

There was consistency in the most frequently reported AEs across all analysis pools. Zuranolone appears to be well-tolerated at doses of 30 mg or 50 mg, with most TEAEs occurring on-treatment, reported as non-serious, and mild to moderate in severity. The TEAEs that were most frequently observed with zuranolone and reported at a higher incidence in the All Zuranolone group compared to the Placebo group were somnolence, dizziness, and sedation. A trend of increasing incidence with increasing zuranolone dose was observed, particularly pronounced for events of somnolence. Specifically, when considering the PPD PC studies pool only, it was observed that the Nervous system disorders SOC had the highest incidence of TEAEs reported overall for both the Placebo group (26.3%) and the All Zuranolone group (43.8%). Within this SOC, TEAEs that occurred in ≥ 5.0% of participants in the Placebo or All Zuranolone group were somnolence, dizziness, headache, and sedation, being all of these events (with exception of headache) more common in the All Zuranolone group than the Placebo group. These events are reflected in the product information. In the proposed dose of 50 mg zuranolone per day, somnolence occurred in 26.5% of patients, dizziness in 13.3%, headache in 9.2% and sedation in 11.2% of patients, as compared to 7.6%, 8.2%, 12.9% and 0.6% in the placebo group, respectively. The incidence in the 30 mg zuranolone group was 15.4%, 7.7%, 9.0% and 5.1% for somnolence, dizziness, headache and sedation, respectively. Overall, somnolence, dizziness, and sedation were each found to most frequently have onset within the first 2 days of treatment, rarely lasted longer than the period of dosing, and resolved spontaneously or with zuranolone dose reduction, interruption, or discontinuation. The incidence of somnolence and sedation was higher in the PPD PC Studies Pool than in the MDD PC Studies Pool, which may partly reflect the differences in the studied populations. The majority of confusional state events also occurred during the on-treatment period. Confusional state occurred in two patients (1.1%) in the zuranolone group as compared to none in the placebo group in the PPD PC pool. The incidence in the zuranolone group was somewhat lower (0.5%) in the MDD PC pool. Throughout the zuranolone development program, confusional state was reported as serious adverse event in five patients. The applicant was requested to discuss these cases more in detail, including temporal relationship to drug, action taken and time to resolution. The applicant stated that in four of these cases, the event was considered related to zuranolone, which is agreed. It is also reassuring that all cases resolved rather quickly. On the other hand, three of the four cases also occurred in patients older than the PPD population in general, which may indicate that the risk for serious confusional state is lower in the PPD population. It is concurred with the applicant that the proposed SmPC and PL adequately cover confusional state as adverse event of zuranolone.

Overall, participants treated with zuranolone in the PPD and MDD PC studies did not experience increased rates of falls/injuries compared to participants on placebo. Although no inability to care for the baby was reported the applicant was requested to clarify whether study subjects were systematically asked regarding this aspect or study investigators were instructed to monitor this, as spontaneous reporting may be unreliable. In the responses, the overall the impact of adverse events (nervous system and psychiatric) on ability to care for the baby was discussed by the applicant. Although it is acknowledged that no severe or serious cases of somnolence and sedation were reported, the experienced impact on somnolence can vary depending on many factors which influence

the overall wellbeing and restfulness of the mother, including the age of the infant and nightly awakenings, and the available support. The post-marketing data suggests that some patients experience uncertainty regarding taking care of the infant, in connection with the somnolence/sedation experienced while using zuranolone. However limited information is available regarding concomitant treatments, and it is unclear, whether the ability to care for the infant indeed was impaired. All in all, it is considered that in particular in the beginning of the treatment, somnolence and sedation may affect the patient's ability to take care of the infant, in particular during the night, since zuranolone is administered in the evening. Thus, the statement included in the PL regarding impact on daily activities was not considered sufficient to reflect this and was amended to include also 'taking care of your child' to stress this information.

In what concerns to the performed simulated driving studies, it was demonstrated that zuranolone adversely effects the ability to drive, and this effect remained after multiple dosing of 50 mg of zuranolone. It was also shown that subjects could not correctly estimate their ability to drive. It is also clear from the adverse event data that sedation, somnolence and dizziness persist to the next day after evening administration of zuranolone. While in the PPD studies no road traffic accidents were reported, four occurred during the MDD studies, thus the applicant was asked to elaborate further presenting the narratives and a discussion on relationship to zuranolone in the context of the proposed SmPC text regarding driving and operating machinery. From the data available, two cases occurred after IP was discontinued and in the other two cases patients did not experience CNS adverse events which may impact driving ability. It is agreed with the applicant that the current wording of the SmPC is considered adequate and no further recommendations around driving are needed. The incidence of TEAEs in the Gastrointestinal disorders SOC was similar in the Placebo group (16.4%) and All Zuranolone group (15.3%). Within this SOC, diarrhoea was the most common event reported among participants in the All Zuranolone group (6.3%), with a similar incidence by dose and most events occurred on-treatment. In the PPD PC studies pool diarrhoea was reported in 6.3% (n=6) of patients receiving zuranolone, as compared to 2.3% (n=4) in the placebo group, and the applicant has reported this adverse event as TEAE in the SmPC. In the MDD PC pool with considerably larger number of patients, however, there was no difference between the treatment groups, also when focussing on TEAEs occurring on-treatment.

The incidence of TEAEs in the Infections and infestations SOC was higher in the All Zuranolone group compared with the Placebo group (14.2% vs. 8.2%, respectively). Although, the applicant argued there was no apparent correlation with dose and Infections and infestations SOC, imbalances were found in what concerns to 'Urinary tract infection' (almost twice the cases, being the majority on the 50mg group), 'Upper respiratory tract infection' (twice the cases) and 'Nasopharyngitis' (twice the cases). The Applicant reviewed all the available information (non-clinical, clinical studies and literature) and, at the present time, it is agreed that the current evidence does not support a causal association between UTI, URTI, or nasopharyngitis and the use of zuranolone. Zuranolone's mechanism of action and pharmacology do not support the hypothesis of a suppressive effect on the immune system. No immunosuppressive effects were identified in nonclinical studies with zuranolone. All events of UTI were assessed as not related to zuranolone by the Investigator and there was no consistent time to onset in the MDD and PPD PC pools that could suggest a causal association with zuranolone. The majority of participants with events of UTI were female (except for 1 male participant in the MDD PC Pool) and it is recognized that events of UTI are more frequent in female patients and are common in the postpartum patient population: in PPD studies, the reported frequency of UTI in the All Zuranolone group (3.4%) was generally comparable to that reported in the postpartum patient population (2% to 4%). In what concerns to URTI, the incidence of participants reporting nasopharyngitis in the All Zuranolone group was overall similar in the PPD PC Pool (2.3%) compared with the Placebo group (1.2%) and in the MDD PC Pool (2.3%) compared with the Placebo group (2.1%). No dose-response

relationship was observed and none of the AEs collected during the clinical development phase were assessed as related to zuranolone by the Investigator.

Fatigue and asthaenia were reported in 10 patients receiving zuranolone (5.7%) as compared to three patients receiving placebo (1.8%) in the PPD PC pool and are included in the SmPC. In the PPD PC pool, tremor was reported in two patients (2.0%) in the zuranolone group as compared to none in the placebo group. The incidence of tremor was similar in the MDD PC pool 2.3% in the zuranolone group vs. 0.5% in the placebo group). In the zuranolone group five patients discontinued or lowered the dose due to this adverse event. It is agreed to include tremor in the listing of adverse events of zuranolone.

Memory impairment was reported in three patients (1.7%) in the zuranolone group (all 50 mg) as compared to none in the placebo group in the PPD PC pool. In the MDD PC pool, the incidence of memory impairment was lower (0.6% in the zuranolone group vs 0.1% in the placebo group). While the reported numbers are low, it is agreed that memory impairment is listed as a treatment-emergent adverse event, as neurosteroids such as zuranolone may play a role in memory function. This is also reflected in the Phase I studies which included assessment of cognitive effects, where higher doses of zuranolone (above 35 mg) resulted in decreased performance in working memory testing, among other tests evaluating complex attention and executive function. It is also possible that memory impairment is secondary to nervous system adverse events somnolence and sedation. No other adverse events related to cognition than memory impairment were reported in PPD studies. In the MDD PC pool, disturbance in attention was reported in 14 subjects receiving zuranolone (1.3%) (vs. 1 in the placebo group), other adverse events related to cognition were reported with an incidence <1%. All events were moderate severity at most.

The percentage of participants with at least one treatment-emergent adverse event during the follow-up period (planned Days 29-45, i.e., two weeks after stopping IP) was 8.8% and 9.7% in the placebo and zuranolone groups, respectively. No TEAE occurred in ≥2% of patients in either group. The available data from MDD PC pool was similar. The data suggest that there are no persistent adverse events after the initial 14-day treatment period.

As of the submission data cut-off date, 2 deaths were reported only in the MDD studies and assessed as not related to IP by the Investigator (occurred at least 128 days after the last dose of zuranolone), which is acceptable. There were 97 nonfatal TESAEs (all studies as date cutt-off) in 65 participants receiving zuranolone and 10 nonfatal TESAEs in 7 participants receiving placebo. Most of the nonfatal TESAEs in zuranolone participants occurred in open-label studies (Studies 217-MDD-303A and 217-MDD-303B). Most TESAEs were reported off-treatment and were assessed as not related to IP by the Investigator. Out of the 97 nonfatal TESAEs in 65 participants for zuranolone, 28 TESAEs in 22 participants were on-treatment and 69 TESAEs in 44 participants occurred after the on-treatment period. In the PPD PC Studies Pool, the incidence of TESAEs was low in the Placebo group (1 [0.6%]) and in the All Zuranolone group (3 [1.7%]), although the database was limited in its size. One participant (zuranolone 30 mg) had a TESAE of confusional state assessed as related to IP. Similarly, the incidence of TESAEs was low across the MDD PC Studies Pool and the Healthy Participants Pool.

In what concerns to suicide related events, imbalances were found between placebo and zuranolone arms. Plus, since MDD studies were supportive in what concerns to safety data, events that occurred in those clinical studies cannot simply be neglected, so the argument raised by the applicant to not consider suicidal events because this imbalance was not found in the very limited safety database size PPD pool is not acceptable. Further, suicide behaviour events were reported during post-marketing phase (please see below). The applicant was therefore requested to provide a thorough discussion on the causality assessment for all reported cases of suicidal ideation/attempt/behavior (serious and non-serious). In the responses, the applicant mentioned that in the 36 clinical studies, a total of 11 TESAEs related to suicidality were reported, all from MDD studies and none from PDD. In addition, there were

27 non-serious events related to suicidality reported in 21 participants. Regarding the serious cases, 2 of the 11 serious cases were from the placebo-controlled study 217-MDD-301A, with 1 participant identified as being on placebo. The remaining 9 cases were reported from open-label, long-term studies: 7 from 217-MDD-303A and 2 from Study 217-MDD-303B. The Investigator assessed 3 of the cases with events of suicidality as related to zuranolone; but the applicant assessed the 3 cases as unlikely related. The remaining 6 cases were assessed as not related by the Investigator and unlikely related by the applicant. The applicant provided a through causal assessment of all these cases. It is concurred with the applicant that in these cases, causality could be confounded by previous history of suicidality, comorbid psychiatric conditions and/or psychosocial stressors given the narratives provided. Regarding the non-serious cases, it should be also noted that there was no consistent temporal pattern with AEs of suicidal ideation that suggested a causal association, as 10 occurred on-treatment and 17 occurred off-treatment. In addition, it was reported by the applicant that these nonserious events have more limited information, including detailed psychiatric history, treatment history, and circumstances around suicidal ideation or behaviour. It is agreed that the current evidence is insufficient to establish a causal relationship between zuranolone and suicidality events to further warrant an update of the section 4.8 of the SmPC at present time. Nevertheless, given the slight imbalances found in the MMD clinical studies, the small database size of the clinical studies for the PPD indication, and the information retrieved from post-marketing data regarding the use of zuranolone for PPD (where one case was classified as possible according to the WHO-UMC classification; please see below), these events should be closely monitored through routine pharmacovigilance activities and presented in the future PSURs.

No safety signal was observed in the clinical laboratory evaluation results. No clinically significant differences were observed between the Placebo and All Zuranolone groups for the percentage of participants with any postbaseline PCS vital sign value, including blood pressure, heart rate, and oxygen saturation. The performed thorough QTc study was negative and QTcF abnormalities were rare across PPD PC and MDD PC pools, with one subject with post-baseline QTcF of >500 msec. One participant each in the placebo group and zuranolone group had a postbaseline QTcF > 480 to 500 msec in the PPD PC pool. Four participants (1 placebo, 3 zuranolone [1 participant per dose]) in the MDD PC pool experienced events of electrocardiogram QT prolonged (all QtcF >450 to 480 msec), these were not associated with cardiovascular TEAE. Altogether, the available data does not raise concerns on cardiovascular safety.

Subgroup analyses were performed to evaluate drug-demographic, drug-disease, and drug-drug interactions. In the PPD PC Studies Pool and MDD PC Studies Pool, there were no clinically meaningful differences for the incidence of specific PTs when categorised by age, sex, race, ethnicity, BMI, baseline ADT use, concomitant ADT use, or concomitant benzodiazepine/sedative/hypnotic use. Overall, the Applicant mentioned that no new safety concerns for zuranolone were identified in Phase 1 studies of healthy participants with renal impairment or hepatic impairment; the safety profiles were comparable to those without renal or hepatic impairment. However, the applicant stated that zuranolone 30 mg dose should be used for patients with severe hepatic impairment or moderate to severe renal impairment because of the increased zuranolone exposure observed in this population. In what concerns to drug-drug interactions, the overall incidence of nervous system adverse events was somewhat higher in patients with concomitant use of ADTs as compared to those without (45.0% vs. 40.3%). Sedation occurred more often in those patients with concomitant antidepressants (18.9% vs. 5.8%). Interaction studies with alprazolam and ethanol are discussed under the pharmacodynamics section. Based on the results obtained in the studies: 217-CLP-111 and 217CLP116, a dose reduction of zuranolone is recommended when administered concomitantly with CNS depressants ethanol or alprazolam, according to medical assessment/decision. This position is reflected in sections 4.4 and 4.5 of the SmPC.

Zuranolone is excreted into breast milk and based on popPK simulations, the mean relative infant dose is expected to be <1% (of the maternal dose). The applicant stated that the effects on breast-fed newborns/infants are unknown. The effects seen in animal studies point towards ineffective nursing and sedation of the offspring. Postnatal mortality was also reported with unclear causality to zuranolone. Thus, the applicant was requested to further discuss the available non-clinical and clinical data on lactation (e.g., post-marketing) and to propose an unambiguous SmPC section 4.6 text on lactation according to the EMA guidance (EMEA/CHMP/203927/2005).

It is acknowledged that breastfeeding is important for the relationship of mother and child, however it is considered that patients should be adequately ensured of safety of breastfeeding. Importance of this aspect was also reflected in the contributions received from Patients and Healthcare Professionals Organisations (see section 2.6.6). As requested, the applicant discussed the available non-clinical and PK data and presented the available post-marketing data on lactation. While zuranolone is excreted into breast milk, the concentrations are low and the simulated infant doses are minimal. The provided post-marketing data indicate that some mothers continue nursing during zuranolone treatment, and for the majority of cases no adverse events were reported. In two cases adverse events which due to their nature (increased sleepiness, sedation) could be related to zuranolone, too little details are presented for making any conclusions on causality to zuranolone and the full nature of the events. It is agreed that any inconvenience around breast-feeding (e.g. pumping breast milk and discarding it) should be avoided as much as possible in this fragile patient population. The applicant proposed to advise discontinuing breastfeeding unless in the judgement of the healthcare professional, the benefits of breast-feeding outweigh the possible risks for the child. This is agreed, considering the demonstrated excretion of zuranolone to breast milk, unknown effects in breastfed newborns/infants and the adverse event profile of zuranolone (CNS depressant effects on the infant cannot be fully excluded; there are uncertainties on the potency and PK of zuranolone in a newborn infant due to immaturity of the CYP metabolic system, potential difference in protein binding (the presence of fetal proteins and endogenous substrates known to interfere with drug binding can lead to unexpected effetcs due to higher than expected free drug fraction), immature blood brain barrier and a highly developing CNS).

From August 2023 to April 2024, zuranolone was prescribed to approximately 1133 patients in USA. A total of 225 events were reported during the post marketing period, the most commonly reported events were somnolence, dizziness, fatigue, drug ineffective, and sedation feeling abnormal and tremor, nausea, and suicidal ideation. Generally, the events reported are in line with the known AEs reported during the development program or are consistent with the target population background incidence of events. Nevertheless, 5 (2.2%) suicidal behaviour events (including suicidal ideation) were reported and the applicant was asked to provide an update of post-marketing data. Furthermore, these post-marketing cases demand a thorough causality assessment discussion given the seriousness of the event and the relevant number of the cases reported during the short period of time of the post-marketing safety (9 months) together with the low number of exposed patients of zuranolone within this timeframe.

In the responses, the applicant provided an update of the post-marketing information setting. A cumulative search up to 13 December 2024 identified 28 initial cases (including the 5 previously reported suicidal ideation post marketing cases in the applicant’s dossier application) reporting 31 events using the Standardised Medical Dictionary for Regulatory Activities (MedDRA) query Suicide/self-injury (narrow). There were 20 healthcare professional (HCP)-confirmed cases and 8 consumer-reported cases. Twenty-six cases were serious and 2 were nonserious. Of the 20 HCP-confirmed cases, 4 cases were assessed as related, 4 were not assessed, and 12 were unknown as assessed by the reporter. Among HCP reported cases, one case was considered WHO-UMC possibly

related, based on onset and noting that no confounders were present. The remainder cases were classified as follows: a total 11 of HCP cases were considered WHO-UMC unlikely and 8 cases were considered WHO-UMC unassessable. Regarding consumers' reports, a total of 8 cases containing 9 events were reported. Of the 8 cases, 7 cases contained events reported while on treatment with zuranolone; all cases included limited information, and 2 cases contained confounders such as medications that have suicidal-related events. Among consumer cases, 3 were considered WHO-UMC unlikely and 5 were considered WHO-UMC: unassessable. In addition, the applicant conducted a literature review (up to 13 December 2024), where no case reports concerning zuranolone and suicidality were identified. All and all, based on the data provided and the causality assessment performed by the applicant, it is concurred that at present time, the existing data does not provide sufficient evidence to establish a causal relationship between suicidality and zuranolone. Nevertheless, it is acknowledged that underlying conditions and risk factors limit a thorough causality assessment, especially among cases with limited information. Given the slight imbalances found in the MMD clinical studies, the small database size of the clinical studies for the PPD indication, and the overall information retrieved from post-marketing data regarding the use of zuranolone for PPD (where one case was classified as possible according to the WHO-UMC classification), these events should be closely monitored through routine pharmacovigilance activities and reported in the following PSURs.

Abuse potential of zuranolone was demonstrated in a dedicated Phase I study. There were no reported cases of abuse, misuse or overdose across the zuranolone clinical study program or post-marketing. Withdrawal symptoms were not detected in study 217-PPD-301 as assessed by PWC-20 at day 21. No participant in the zuranolone group in PPD studies experienced rebound after treatment discontinuation.

2.6.11. Conclusions on the clinical safety

Overall, across the clinical development programme, the safety profile of zuranolone at the PPD indication at the proposed recommended dose of 50 mg was generally well tolerated, with most AEs being of mild or moderate severity. Most adverse events were those of the central nervous system – somnolence, dizziness and sedation. Data suggests that dose reduction can mitigate adverse events.

Clear information and advice regarding use during pregnancy and lactation is of utmost importance in this target patient population. Risks associated with use during pregnancy and appropriate wordings in the product information regarding contraindication in pregnancy is implemented and recommendation to not breastfeed is included.

2.7. Risk Management Plan

2.7.1. Safety concerns

None.

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

None.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 04 August 2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zurzuvae (zuranolone) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

The target indication is the treatment of Postpartum depression (PPD). Postpartum depression is characterised as a major depression episode occurring during pregnancy or up to 12 months postpartum.

The aim of the treatment is to quickly improve depression as measured by HAMD 17, in a condition which tends to improve with time in the majority of the patients.

The proposed posology is oral administration of 50 mg zuranolone once daily in the evening for a single 14-day period.

Zuranolone is a synthetic neuroactive steroid (NAS). The mechanism of action in the treatment of PPD is not fully understood, but zuranolone is considered a positive allosteric modulator of the gamma-aminobutyric acid type A ($GABA_A$) receptor. Zuranolone may exert antidepressant effects by enhancing GABAergic inhibition.

If approved, zuranolone will be the first registered medicinal product with a specific PPD indication.

Postpartum depression (PPD) is the most common psychiatric condition following childbirth. In the DSM-5, postpartum depression is diagnosed under "depressive disorder with peripartum onset", in which "peripartum onset" is defined as either any time during pregnancy or within the four weeks following delivery. Cases of PPD are often not identified, and women may seek psychiatric care at various timepoints postpartum.

Evidence on the natural history of PPD is limited, and in particular severe cases of a major depressive episode are generally, in MDD, not considered to be self-limiting.

The estimated prevalence of PPD varied widely across studies but is approximately 10-15% in Western countries. The pathogenesis of PPD is unknown. It is not clear whether PPD represents a distinct subtype of depression. The cause of PPD may include a combination of factors, e.g., genetic susceptibility, hormonal changes, and psychosocial events. The clinical features of PPD are comparable to those of a major depressive episode (MDE), and include depressed mood (dysphoria), anhedonia, worthlessness or excessive guilt, impaired concentration and decision making, and suicidal ideation and behaviour. Untreated PPD can result in adverse consequences for the mother and infant.

3.1.2. Available therapies and unmet medical need

The Applicant claims that PPD is related to specific characteristics such as the neuroendocrine turmoil around the partum and the impact that the mothers' depression may have in the mother-child relationship.

Postpartum depression has dedicated recommendations from national and European organisations. However, in the EU there are no specific treatments for PPD alone, and the available antidepressants take weeks to show a clinically significant improvement. Therefore, a quickly acting agent may have its role in the treatment of PPD.

Treatment approaches in PPD are primarily based on MDD studies, rather than specific PPD studies. Initial pharmacological treatment for moderate to severe PPD includes the use of antidepressants. These usually involve selective serotonin reuptake inhibitors (SSRIs), as those have been used in pregnant and breastfeeding patients, in line with practice guidelines (American College of Obstetricians and Gynecologists). Reasonable alternatives to SSRIs include serotonin-norepinephrine reuptake inhibitors (SNRIs). These conventional treatments, target monoamine neurotransmitters, and require about 4-6 weeks before the onset of clinical effect. In addition, they are often associated with long-term use, which may increase the risk of (ongoing) adverse events.

Zuranolone may fulfil the unmet need for a rapid onset (within days) of symptomatic improvement for patients with PPD, without the requirement for continued treatment.

3.1.3. Main clinical studies

The clinical development program for PPD included two placebo-controlled phase 3 studies, to evaluate the efficacy and safety of zuranolone in adults with severe PPD.

Pivotal study (217-PPD-301) evaluated the recommended dose and formulation of zuranolone and is considered pivotal. In this study, 196 participants were randomized (1:1) to 50 mg oral zuranolone or matching placebo, once daily. A dose reduction to 40 mg, was allowed in case of tolerability issues.

Treatment consisted of a single 14-day period, and the total study duration was 45 days. A PPD diagnosis was determined during the 28-day screening period, according to DSM-5 criteria. Participants with onset of symptoms in the 3rd trimester or within the first 4 weeks following delivery, up to 12 months postpartum and with a HAMD-17 total score of ≥26 were eligible to enter the study. Stable use of antidepressants was permitted. The primary endpoint was change from baseline in HAMD-17 total score at day 15. Key secondary endpoints included change from baseline in HAMD-17 at days 3, 28 and 45.

At baseline, 15% of participants were treated with a concomitant stable dose of antidepressants, most participants experienced their first PPD episode (86%) with the onset of PPD within 4 weeks following delivery for the majority of participants (67%). The baseline HAMD-17 total score was 29 in both groups and the mean duration of symptoms was ~5 months.

Additional PPD study (217-PPD-201B) with similar design was presented as pivotal study by the applicant. However, this study was considered supportive, because it evaluated a lower dose of zuranolone (30 mg), in another capsule formulation, with higher bioavailability. In addition, the design of the study was not fully adequate, secondary endpoints were not hierarchically tested, and uncertainties remain with regards to the handling of discontinued participants. In this study, 151 participants were randomized 1:1 to 30 mg oral zuranolone or matching placebo, once daily, with a dose reduction to 20 mg in case of tolerability issues. Study design, objective, population and primary endpoint were overall similar to the pivotal study; except that patients at start of the study were at ≤6 months postpartum. No secondary endpoints were predefined for this study.

3.2. Favourable effects

Primary endpoint result in pivotal study 217-PPD-301: LS mean treatment difference (95% CI) in HAMD-17 at day 15 between placebo and 50 mg zuranolone of -4.0 (-6.3, -1.7); p-value= 0.0007. The mean change in HAMD-17 total score in the 50 mg zuranolone group was -15.6 versus -11.6 in the placebo group; which was statistically significant and clinically relevant, demonstrating a difference greater than 4 points.

The onset of clinical response was shown at day 3, and the response was remained throughout the study. The LS mean difference (95% CI), in change of HAMD-17 total score, was -3.4 (-5.4, -1.4; p=0.0008) at day 3, -2.9 (-5.4, -0.5; p=0.02) at day 28 and -3.5 (-6.0, -1.0; p=0.005) at day 45 (secondary endpoints).

The proportion of patients with an improvement in HAMD-17 total score ≥50%, defining response (other secondary endpoint), was 57% in the zuranolone group and 39% in the placebo group at day 15. (OR: 2.0; 95% CI: 1.1, 3.7; nominal p=0.02). The proportion with a HAMD-17 total score ≤7,

defining remission (other secondary endpoint), was 27% in the zuranolone group and 17% in the placebo group at day 15 (OR: 1.8; 95% CI: 0.9, 3.6; nominal p=0.1).

CGI-I response rates (much/very much improved) at day 15 supported the primary endpoint: 67% and 47% of patients treated with zuranolone and placebo, respectively, had much/very much improved (odds ratio: 2.2, 95%CI: 1.2, 4.1, nominal p=0.009).

Although the importance of PROs is acknowledged, EPDS and PHQ9 are not validated for the use in clinical trials and both outcomes were not included in the hierarchical testing strategy. Therefore, EPDS and PHQ9 are not considered critical to the B/R of zuranolone for the treatment of PPD.

Subgroups

In general, consistent results were found in subgroups as compared to the overall population, with the exception of concomitant use of antidepressants: no impact of zuranolone treatment, on the primary endpoint, was shown in this subgroup (LS mean difference: 0.8; 95%CI: -5, 6.7; p=0.7).

Consistency of findings

Supportive study 217-PPD-201B showed a consistent effect with 30 mg zuranolone (in another capsule formulation) on change from baseline in HAMD-17 total score.

3.3. Uncertainties and limitations about favourable effects

In this application two randomised, double-blind, placebo-controlled, multicentre studies were performed in patients with PPD. Although study designs were overall similar, only study 301 tested the 50 mg zuranolone dose, and as such this study is considered pivotal. Due to variable treatment effects in depression studies, in principle two convincing pivotal studies are expected to assess the therapeutic efficacy. In this specific sub-population of PPD patients, one pivotal study, supported by results of additional study 201B are considered sufficient, since the results of the pivotal study are statistically compelling and clinically relevant. Limited number of patients were included from EU in the studies and differences in intrinsic and extrinsic factors may exist between the US and the EU population of patients with PPD. This was elaborated to confirm that there were no cultural or EU clinician treatment behaviour difference between Europe and US that might challenge the results; European centres were: a) opened late during the study; b) during COVID-19 pandemics in countries greatly affected at the time of study enrolment. Overall, no specific aspect that would prevent extrapolation from the US population to the EU population was identified.

To support the durability of response for zuranolone, the applicant provided an overview of efficacy results in MDD patients treated with zuranolone for 14 days, and re-treated if needed (HAMD-17 total score ≥20). The time to first repeat treatment was 281 days for patients initially treated with 50 mg zuranolone. Overall, 54% of patients did not need additional treatment courses (up to 48 weeks). Although, extrapolation to the PPD situation is not justified and differences between MMD and PPD study populations are not taken into account, these MDD data do provide supportive information regarding the sustained response of zuranolone during an episode of depression.

Zuranolone has a rapid onset of action with a short course of active treatment, and PPD has significant consequences for the mother and baby. Therefore, it may be considered that rapid improvement in symptoms of depression, may be more important than sustained efficacy in this vulnerable population of patients. It remains uncertain whether this is the most optimal treatment duration. However, the data indicate a beneficial effect of zuranolone without major safety issues. In addition, despite uncertainties in applicability for the PPD population, the results in the MDD population do support the ability of a durable response to zuranolone.

No relevant uncertainties remained for the efficacy of zuranolone for the treatment of women with PPD after comprehensive discussions.

3.4. Unfavourable effects

Zuranolone appears to be well-tolerated, with most TEAEs occurring on-treatment, reported as non-serious, and mild to moderate in severity. In the PPD pivotal studies, the TEAEs most frequently observed with zuranolone and reported at a higher incidence compared to placebo were somnolence (21.6%), dizziness (10.8%), and sedation (8.5%). A trend of increasing incidence with increasing zuranolone dose was observed, particularly pronounced for events of somnolence. Overall, somnolence, dizziness, and sedation were found to have an onset within the first 2 days of treatment, rarely lasted longer than the period of dosing, and resolved spontaneously or with zuranolone dose reduction, interruption, or discontinuation. These events are reflected in the product information.

Within the Gastrointestinal disorders SOC, diarrhoea was the most common event reported among participants in the zuranolone group (6.3%), with a similar incidence by dose and most events occurred on-treatment; these events are labelled in the product information, although a further discussion is needed. The incidence of TEAEs in the Infections and infestations SOC was higher in the zuranolone group compared with placebo (14.2% vs. 8.2%, respectively) and imbalances were found in what concerns to 'Urinary tract infection' (almost twice the cases), 'Upper respiratory tract infection' (twice the cases) and 'Nasopharyngitis' (twice the cases).

Although there was no signal for suicidal ideation and behaviour in the PPD studies, imbalances were found between placebo and zuranolone arms in the MDD studies, which cannot be neglected and required further discussion. Noteworthy, five post-marketing suicidal behaviour cases (including suicidal ideation) were reported in the US (August 2023 to April 2024). The existing data do not provide sufficient evidence to establish a causal relationship between suicidality and zuranolone.

In the PPD pivotal studies, nearly all zuranolone participants with TEAEs had events that were mild (36.4%) or moderate (23.9%) in severity. There was a higher incidence of moderate TEAEs in the zuranolone 50 mg group (29.6%) than in the zuranolone 30 mg group (16.7%). The incidence of TESAEs in the zuranolone group (1.7%). One participant (zuranolone 30 mg) had a serious event of confusional state assessed as related to zuranolone. The incidence of discontinuations due to a TEAE was 2.8%. Somnolence and sedation were the most frequently reported TEAEs leading to discontinuation. No deaths were reported between the submission data cutoff date and the evaluation of the database as of 30 April 2024.

In addition to the commonly reported nervous system adverse events, also psychiatric adverse events memory impairment and confusional state were reported in a higher incidence in the zuranolone 50 mg group as compared to placebo group; 1.7% vs. 0% and 1.1% vs. 0%, respectively.

Fatigue and asthenia were reported in 10 patients receiving zuranolone (5.7%) as compared to three patients receiving placebo (1.8%) in the pivotal PPD trials, as well as tremor in two patients (2.0%) in the zuranolone group as compared to none in the placebo group.

Due to CNS depression, zuranolone causes driving impairment. In two driving simulation studies, the driving ability of healthy adults was impaired in a dose-dependent manner lasting up to 12 hours after dose administration. This risk is addressed in the warnings and precautions section of the product information. With respect to driving ability, it should be mentioned that the impairment in ability remained after multiple dosing of 50 mg of zuranolone and the subjects could not adequately estimate their ability to drive.

Three serious adverse events occurred in patients receiving zuranolone during the pivotal PPD trials as compared to one patient receiving placebo. The serious adverse events in the zuranolone group were confusional state, upper abdominal pain and perinatal depression, from which the latter occurred off-treatment.

3.5. Uncertainties and limitations about unfavourable effects

The PPD safety database included 176 subjects with PPD who were exposed to zuranolone, which is limited in size concerning the ability to detect uncommon and rare adverse events for this specific target indication. Furthermore, patients have been exposed to different doses (30 and 50 mg) different from those proposed for marketing. There are limited clinical data available on pregnancies in the zuranolone development programme and the effect of zuranolone on breastfed newborns/infants is unknown.

The risk of zuranolone being prescribed to pregnant women and the associated risks to the foetus are unclear. There are very limited data in humans and studies in animals show reproductive toxicity. Considering that depressive symptoms in this context often start during pregnancy, as also reflected in the current diagnostic criteria, zuranolone could be seen as a treatment option during late pregnancy. A contraindication during pregnancy was requested, considering the evidence of skeletal malformations in rats and mice, and the risk of PPD women becoming pregnant while taking zuranolone.

3.6. Effects table

Table 37. **Effects table for zuranolone in postpartum depression (data cut-off: 3 February 2024)**

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
HAMD-17 D15	LS mean change (SE) from baseline HAMD-17 total score at Day 15	Mean change (SE)	-15.6 (0.817)	-11.6 (0.823)	Studied population, duration of treatment, magnitude of difference in an improving condition (95% CI -6.3, -1.7; P=0.0007)	Study 217 PPD 301
HAMD-17 D3	LS mean change (SE) from baseline HAMD-17 total score at Day 3	Mean change (SE)	-9.5 (0.704)	-6.1 (0.710)	Studied population, magnitude of difference in an improving condition (95% CI -5.4, -1.4; P=0.0008)	Study 217 PPD 301
HAMD-17 D28	LS mean change (SE) from baseline HAMD-17 total score at Day 28	Mean change (SE)	-16.3 (0.884)	-13.4 (0.875)	Studied population, magnitude of difference in an improving condition (95% CI -5.4, -0.5; P=0.0203)	Study 217 PPD 301
HAMD-17 D45	LS mean change (SE) from baseline HAMD-17 total score at Day 45	Mean change (SE)	-17.9 (0.903)	-14.4 (0.902)	Studied population, duration of treatment, magnitude of difference in an improving condition. Maintenance of effect beyond D45. Extent of effect in pts on antidepressants. (95% CI -6.0, -1.0; P=0.0067)	Study 217 PPD 301

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
CGI-I	CGI of improvement percentage of responders (much / very much improved) by day 15	%	66.7	46.7	OR (95%CI) 2.23 (1.22 – 4.07) p=0.0089 in support of clinical relevance, but almost 50% improvement in placebo treated patients. Maintenance of effect beyond D45	Study 217 PPD 301
EPDS	Day 15 EPDS percent improvement compared to baseline	%	49.6	40	Significance of the difference in improvement between placebo and zuranolone Patient reported outcome	Study 217 PPD 301
PHQ9	Day 15 PHQ9 percentage of patients improved compared to baseline	%	85.7	76.7	Significance of the difference in improved patients between placebo and zuranolone Patient reported outcome	Study 217 PPD 301
Unfavourable Effects						
Somnolence	Nervous system disorders	n (%)	38 (21.6)	13 (7.6)	**Unc**: relation to road traffic accidents and ability to care for the baby	PPD PC studies pool
Dizziness	Nervous system disorders	n (%)	19 (10.8)	14 (8.2)	**Unc**: relation to road traffic accidents and ability to care for the baby	PPD PC studies pool
Sedation	Nervous system disorders	n (%)	15 (8.5)	1 (0.6)	**Unc**: relation to road traffic accidents and ability to care for the baby	PPD PC studies pool
Confusional state	Psychiatric disorders	n (%)	2 (1.1)	0	**Unc**: SAE in 5 patients in zuranolone programme, details and impact unclear	PPD PC studies pool

Abbreviations: PPD PC (postpartum depression placebo controlled) pool data

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Postpartum depression (PPD) is a special population of MDE, since it may have a significant impact on the baby.

In the pivotal study, the primary endpoint, change from baseline in HAMD-17 total score at day 15 was met; a statistically significant mean treatment difference was shown at day 15, in favour of zuranolone. The mean difference in HAMD-17 improvement between groups was observed at day 3, the earliest post-baseline timepoint of measurement, and remained throughout the study (at days 28 and 45). These results were further supported by rates of response (HAMD-17 and CGI-I) and remission, and consistent results were found in the supportive study.

Rapid onset in the improvement of depressive symptoms is an important outcome, especially because PPD patients are considered a vulnerable population, and depressive symptoms have adverse consequences for both mother and infant. The observed improvement in depressive symptoms, based on a mean difference of 4.2 points in HAMD-17 change from baseline to day 15, is considered clinically relevant. The threshold for a mean difference in change of HAMD-17 to be clinically relevant is 2 points. Further, upon a single treatment period of 14 days with zuranolone, the beneficial effect of treatment on depressive symptoms, could be maintained throughout the study, up to day 45.

The applicant proposed a broad PPD indication, which is in line with the analyses provided across severities and the guideline for the treatment of depression (EMA/CHMP/185423/2010, Rev.3). It is also reassuring that there is a possible slightly better safety B/R balance in the severe population (65.9% TEAEs) than in the moderate population (54.1%).

The indication does not specify mono- or add-on use of zuranolone, instead this is included in the section 4.2 of the SmPC. Use of zuranolone alone or with stable background ADTs can be accepted. Although the extent of treatment benefit of zuranolone in combination with ADTs remains uncertain, mechanistically there is no reason to suspect altered efficacy compared to zuranolone monotherapy. No differences in safety profile were identified for zuranolone mono- or combination therapy.

It remains uncertain, whether the single 14-day treatment period with zuranolone results in sustained clinical benefit, throughout the depressive episode. Maintenance of effect is usually shown with a relapse prevention study, for which a randomised withdrawal study is the preferred design. However, this type of design would not be adequate, to study a single 14-day treatment regimen with no repeat treatment. Extended follow-up of the zuranolone group, could be of relevance, however, the optimal follow-up duration is uncertain. Depending on the natural course of a depressive episode, a relatively shorter follow-up may be sufficient, for a rapid acting antidepressant. In addition, the rapid onset of effect may be more important than the risk of not maintaining response to treatment, in this vulnerable population of patients. This is highly dependent, however, on the severity of remaining depression in patients who relapsed and recommendations for follow-up care. The applicant added a warning to inform prescribers that no data are available on follow-up treatment after a relapse or insufficient response with zuranolone.

The short treatment regimen of zuranolone may be of added value over the continued administration of (off-label) antidepressants. Especially for new mothers, who may have concerns regarding the impact of a continued treatment on their infant and for whom a rapid effect of treatment is warranted.

Zuranolone is mainly associated with nervous system adverse events, namely somnolence, sedation and dizziness. These effects are dose-dependent and persist to the following day after evening administration. Importantly, most CNS adverse events are mild in severity and diminish after first two days of dosing.

A contraindication to the use in pregnant women was implemented, given the associated risks to the foetus, and recommendation to not breastfeed was included.

3.7.2. Balance of benefits and risks

The benefit/risk balance is positive.

The unmet medical need for a treatment with rapid onset of effect in patients with PPD is recognised, as currently no approved treatments are available for this specific indication, and standard antidepressants (used off-label) have a delayed onset of effect.

A statistically significant and clinically relevant improvement in depressive symptoms was shown for zuranolone over placebo. The onset of effect was rapid, and could be maintained throughout the study, up to day 45. Rates of response and remission were supportive of the primary endpoint.

In this vulnerable population of patients, a rapid effect on depressive symptoms, after a short period of active treatment, may be more important than the risk of not maintaining response to treatment. However, handling of relapses in clinical practice, and recommendations for follow-up care, should be discussed.

Most adverse events were those of the central nervous system – somnolence, dizziness and sedation. These were in general mild in severity and the incidence diminished after multiple days of dosing. Data suggests that dose reduction can mitigate adverse events.

Clear information and advice regarding use during pregnancy and lactation is of utmost importance in this target patient population, as also highlighted in the input received from the Patients and Healthcare Professionals Organisations. Risks associated with use during pregnancy were addressed with contraindication included in the product information and recommendation to not breastfeed was included.

3.7.3. Additional considerations on the benefit-risk balance

There are no additional considerations for the B/R balance of zuranolone for the treatment of women with PPD after overall discussions.

3.8. Conclusions

The overall benefit/risk balance of Zurzuvae is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zurzuvae is favourable in the following indication(s):

> *Zurzuvae is indicated for the treatment of postpartum depression (PPD) in adults following childbirth (see section 5.1).*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that zuranolone is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).