24 October 2013
EMA/699150/2013
Committee for Medicinal Products for Human Use (CHMP)

Brintellix

vortioxetine

Procedure No. EMEA/H/C/002717

Applicant: H. Lundbeck A/S

Assessment report for an initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

AMS Accelerated Mass Spectrometry
ANOVA analysis of variance
ANCOVA analysis of covariance
APTS all-patients-treated set
ASEX Arizona Sexual Experience Scale
BA bioavailability
BE bioequivalence
BMI body mass index
Cav average plasma concentration at steady state
CGI-I Clinical Global Impression – Global Improvement
CGI-S Clinical Global Impression – Severity of Illness
CHMP Committee for Medicinal Products for Human Use (European Union)
CI confidence interval
C-CASA Columbia Classification Algorithm for Suicide Assessment
CPFQ Cognitive and Physical Functioning Questionnaire
C-SSRS Columbia Suicide Severity Rating Scale
%CV percentage coefficient of variation
CYP cytochrome P450 isoenzyme
DDI drug-drug interaction
DESS Discontinuation Emergent Signs and Symptoms
DMC Data Monitoring Committee
DSM-IV-TR™ Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DSST Digit Symbol Substitution Test
ECG electrocardiogram
EM extensive metaboliser
EMA European Medicines Agency
ESRD end-stage renal disease
F absolute bioavailability
Frel relative bioavailability
FAS full-analysis set
FDA United States Food and Drug Administration
FTIR Fourier transform infrared spectroscopy
GAD Generalised Anxiety Disorder
GC gas chromatography
HAM-A Hamilton Anxiety Rating Scale
HAM-D24 Hamilton Depression Rating Scale 24-item
HDPE high density polyethylene
HPLC high-performance liquid chromatography
HRQoL health-related quality of life
HSQ-12 12 Item Health Status Questionnaire
ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP investigational medicinal product
IR immediate-release
IS internal standard
ISR incurred sample reanalysis
IV intravenous
KF Karl-Fischer
LLOQ lower limit of quantification
LOCF last observation carried forward
LSC liquid scintillation counting
LREG logistic regression
MAA Marketing Authorisation Application
MADRS Montgomery and Åsberg Depression Rating Scale
MCS mental component summary
MDD Major Depressive Disorder
MDE Major Depressive Episode
MedDRA Medical Dictionary for Regulatory Activities
MF matrix factor
NIR near infrared spectroscopy

MMRM mixed model repeated measures
MR metabolic ratio
MRI magnetic resonance imaging
OC observed cases
PBO placebo
PCS potentially clinically significant
PD pharmacodynamic(s)
PET positron emission tomography
PK pharmacokinetic(s)
PM poor metaboliser
PMI placebo-mean imputation
PYE patient years of exposure
Q-LES-Q (SF) Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form
QTc heart-rate corrected QT interval
RAVLT Rey Auditory Verbal Learning Test
RoW rest of the world
SAE serious adverse event
SDS Sheehan Disability Scale
SMQ Standardised MedDRA Query
SNRI serotonin norepinephrine reuptake inhibitor
SOC system organ class
SSRI selective serotonin reuptake inhibitor
TEAE treatment-emergent adverse event
TESD treatment-emergent sexual dysfunction
tmax time to maximum observed concentration
ULOQ upper limit of quantification
UM ultra-fast metaboliser
UV Ultra Violet spectroscopy
VAS visual analogue scale
WHO World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant H. Lundbeck A/S submitted on 24 August 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Brintellix, 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 15 March 2012.

The applicant applied for the following indication.

Treatment of major depressive episodes in adults

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that vortioxetine was considered to be a new active substance.

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 tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/282/2011 on the agreement of a paediatric investigation plan.

At the time of submission of the application, the PIP P/282/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did no> submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18-03-2012 (EMEA/H/SA/1503/1/2010/PED/II) and 15-12-2011 (EMEA/H//SA/1503/3/2011/III). The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Brintellix has been given a Marketing Authorisation in USA on 30th Septebmer 2013.

A new application was filed in the following countries: Canada, Switzerland, Australia, Brazil, Mexico, Turkey, South Africa and Korea.

1.2. Manufacturers

Manufacturer responsible for batch release

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

1.3. Steps taken for the assessment of the product

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

Rapporteur: Bart Van der Schueren (replacing Walter Janssens)

Co-Rapporteur: Martina Weise

CHMP Peer reviewer: Piotr Fiedor

- The application was received by the EMA on 24 August 2012.
- The procedure started on 19 September 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 December 2012 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 December 2012.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 January 2013.
- During the meeting on 17 January 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 January 2013 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 May 2013.
- The Rapporteurs circulated the Joint updated Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 May 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 13 June 2013.
- During the CHMP meeting on 27 June 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 3 September 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 2 October 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 October 2013.

- The Rapporteurs circulated the Final Joint Assessment Report to all CHMP members on 18 October 2013.
- During the meeting on 21-24 October 2013, 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 Brintellix.

2. Scientific discussion

2.1. Introduction

Problem statement

Major Depressive Disorder (MDD) is reported to be **the most common mood disorder**. Depressive disorders tend to be chronic and both relapse and recurrence are seen frequently.
A worldwide lifetime prevalence of approximately 15%, and as high as 25% in women, has been reported for depression.

In Europe, depression affects 13% of the population at some point in life and 6 to 8% in any one year. This corresponds to more than 20 million women and men of working age in Europe suffering each year from depression. Furthermore, the burden is expected to grow over the coming years. The World Health Organization (WHO) predicts that depression will become the single most important illness in Europe and worldwide by 2030.

Depression is **recurrent** in 75 to 80% of patients, becomes chronic (that is, lasts 2 years or longer) in 15 to 20% of depressed patients, and can lead to substantial impairments in an individual's ability to take care of his/her everyday responsibilities. Furthermore, depression may lead to suicide; worldwide estimates indicate that approximately 60 to 70% of those who committed suicide had recently suffered from (mostly untreated) depressive episodes. Therefore, early recognition and sufficient treatment of depression can save lives.

Depression is associated with considerable **co-morbidity**. More than 70% of patients with lifetime MDD also meet the criteria for at least one other DSM-IV disorder; for example, approximately 60% have anxiety disorders. Furthermore, more than half of the patients have a somatic illness, with the most common being hypertension (30%) and diabetes mellitus (10%). Co-morbid depression impairs the quality of life and several aspects of functioning of patients with chronic diseases and aggravates the course of their mental or somatic illness, resulting in increased health care utilisation and costs compared to non-depressed patients with chronic diseases.

Depression poses an **economic burden** on the patients, on their families and friends, and on society. The ability of the depressed patients or their caregivers to work and make productive contributions to society is reduced, whereas the utilisation of treatment and support services is increased. In Europe, the tangible cost of depression was estimated to 113 billion euro in 2011. The health-care costs for older adults with depression, who have typically left the work force, are approximately 50% higher than those for older adults without depression. From the above, it is clear that depression is a major public health challenge, both with respect to its prevalence and the severity of its consequences in terms of mortality, chronicity, co-morbidity, and disability, and with respect to the economic burden on society.

Antidepressant medications are the **first-line treatment** for people meeting current diagnostic criteria for MDD. The presumed mechanism of action of the majority of antidepressants is thought to be via inhibition of neuronal reuptake of monoamines (mainly serotonin and noradrenaline), with a resultant increase in monoamine neurotransmission in the central nervous system (CNS). Vortioxetine is claimed to bring a new concept into the antidepressant treatment area. The vortioxetine molecule is presented

as possessing a new and multimodal pharmacological mechanism of action. *In vitro* studies indicated that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_1D receptor antagonist, a 5-HT_1B receptor partial agonist, a 5-HT_1A receptor agonist, and an inhibitor of the 5-HT transporter.

Data from serotonergic receptor and transporter occupancy studies coupled with neuronal firing and microdialysis studies in rats suggest that the targets interact in a complex fashion, leading to modulation of neurotransmission in several systems, including the serotonin, norepinephrine, dopamine, histamine, and acetylcholine systems within the rat forebrain. These **multimodal** pharmacological actions are thought to be responsible for the antidepressant effects of vortioxetine. In addition, vortioxetine shows anxiolytic and cognitive enhancing properties and analgesic potential in animal models.

The recommended dose proposed by the Applicant in the SmPC is 10 mg once daily (taken with or without food). Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily or reduced to a minimum of 5 mg daily. After the depressive symptoms resolve, treatment for at least 6 months is recommended for consolidation of the antidepressive response.

The **clinical development** programme focused on showing safety and efficacy of vortioxetine 1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg against placebo in the rather wide MDE indication. Supportive studies were performed to demonstrate efficacy in the elderly, relapse prevention, and maintenance of the therapeutic effect during long-term treatment.

About the product

Vortioxetine (1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine) belongs to a new chemical class of psychotropics, the bis-aryl-sulfanyl amines, which is structurally different from all currently known psychotropics.

The mechanism of action of Vortioxetine is thought to be related to its multimodal activity which is a combination of two pharmacological modes of action: direct modulation of receptor activity and inhibition of the serotonin transporter. Non-clinical data indicate that Vortioxetine is a 5-HT3, and 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the 5-HT transporter, leading to modulation of neurotransmission in several systems, including predominantly the serotonin but probably also the norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate systems. This multimodal activity is considered responsible for the antidepressant and anxiolytic-like effects and the improvement of cognitive function, learning and memory observed with vortioxetine in animal studies. However, the precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to man.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate-release film-coated tablets containing 5, 10, 15 or 20mg of Vortioxetine (as hydrobromide salt) as the active substance and as oral drops containing 20mg/ml of Vortioxetine (as the lactate salt) as the active substance.

Other ingredients in the film-coated tablets are mannitol (E421), microcystalline cellulose, hydroxypropylcellulose, sodium starch glycolate (type A) and magnesium stearate which are present in the tablet core and hypromellose, macrogol 400, titanium dioxide (E171) and iron oxide red (E172) and/or iron oxide yellow (E172) present in the tablet coating.

Other ingredients in oral drops are hydroxypropylbetadex, ethanol (96 %) and purified water.

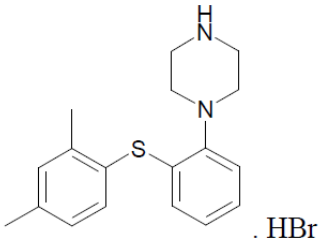
The tablets are available in PVC/PVdC blisters or white HDPE bottles with child-proof closure and tamper-evident seal. The oral drops are packed in amber glass bottles with dropper applicator (low density polyethylene), and child-proof screw cap (polypropylene) as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Vortioxetine has been qualified as a new active substance. Its salts, Vortioxetine hydrobromide and Vortioxetine DL-lactate have been used to manufacture the immediate-release film-coated tablets and the oral drops respectively.

Vortioxetine hydrobromide

The chemical name of Vortioxetine hydrobromide is 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide and has the following structure:



. HBr

The molecular formula is $C_{18}H_{22}N_2S.HBr$ and its relative molecular mass is 298.45 mg/mol as a free base and 379.36 mg/mol as the hydrobromide salt.

Vortioxetine hydrobromide appears as a white to very slightly beige powder, non-hygroscopic, soluble in methanol and ethanol and slightly soluble in water and aqueous solutions at pH 2.0 to 8.3. Its pKa is 9.1 as the free base and 3.0 as the salt.

Vortioxetine exhibits polymorphism and appears in four polymorphs. The most thermodynamically stable polymorphic form has been determined and the crystallisation process is designed to consistently deliver this form.

Vortioxetine has a non-chiral molecular structure.

Manufacture

Vortioxetine hydrobromide is manufactured in two well defined synthetic steps, followed by recrystallization and milling. The starting materials used are well defined and commercially available with acceptable specifications. Two sites are involved in the manufacture of Vortioxetine hydrobromide.

The route of synthesis has been described in sufficient detail and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Information about the formation, presence, origin and fate of impurities during manufacture has been satisfactorily discussed.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Representative batch analysis data provided for the two proposed manufacturing sites produced with the proposed synthetic route show that the active substance can be manufactured reproducibly.

Specification

The active substance specification includes tests for identification (HPLC, FTIR and NIR), assay (HPLC), impurities (HPLC and GC), residual solvents (GC), residue on ignition, heavy metals and particle size. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data for a number of commercial and development batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

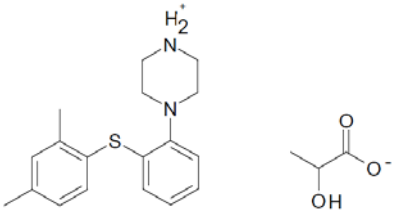
Stability data were provided on 2 pilot and 9 production scale batches of Vortioxetine hydrobromide active substance from the proposed manufacturers stored in a container closure system representative of that intended for the market. According to the ICH guidelines the samples were stored up to 48 months under long term conditions at 25ºC/60% RH and for up to 6 months under accelerated conditions at 40ºC/75% RH.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions 60°C/80% RH were also provided on one batch.
The following parameters were tested*:* description, assay and impurities. The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

Vortioxetine DL-lactate

Vortioxetine DL-lactate is a lactate salt of vortioxetine and its chemical name is 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (RS)-2-hydroxypropanoate and has the following structure:



The molecular formula is $C_{18}H_{22}N_2S.C_3H_6O_3$ and its relative molecular mass as the lactate salt is 388.52 mg/mol. The lactate salt of vortioxetine is used for the oral drops formulation due to its increased solubility in polar solvents.

Vortioxetine lactate appears as a white to beige powder, non-hygroscopic, soluble in polar solvents and water. Its pKa is 9.1 as the free base and 3.0 as the salt.

Vortioxetine exhibits polymorphism and appears in three polymorphs. The most thermodynamically stable polymorphic form has been determined and the crystallisation process is designed to consistently deliver this form.

Manufacture

Vortioxetine DL-lactate is manufactured from the milled Vortioxetine hydrobromide via the non-isolated free base. One site is involved in the manufacture of the lactate salt of Vortioxetine.

The route of synthesis has been described in sufficient detail and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Information about the formation, presence, origin and fate of impurities during manufacture has been satisfactorily discussed.

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.

Representative batch analysis data provided for the proposed manufacturing site produced with the proposed synthetic route show that the active substance can be manufactured reproducibly.

Specification

The active substance specification includes tests for identification (HPLC, FTIR), assay (HPLC), impurities (HPLC and GC), residual solvents (GC), residue on ignition, heavy metals and particle size. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.
Batch analysis data for four commercial and development batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on three pilot batches of Vortioxetine DL-lactate active substance from the proposed manufacturer stored in the intended commercial package. According to the ICH guidelines the samples were stored up to 48 months under long term conditions at 25ºC/60% RH and for up to 6 months under accelerated conditions at 40ºC/75% RH.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions 60°C/80% RH were also provided on one batch.
The following parameters were tested*: description, assay and impurities.* The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Film-coated tablets

Pharmaceutical Development
Vortioxetine immediate-release film-coated tablets contain 5, 10, 15 or 20 mg of the Vortioxetine (as hydrobromide salt).

During the pharmaceutical development the applicant evaluated different formulations to find the most appropriate combination of excipients and physicochemical and biological properties of the formulation/blend to manufacture the tablet with the best possible tablet characteristics and dissolution rate. The dissolution rate is influenced by the particle size and therefore the active substance is milled to obtain the required particle size distribution throughout the blend.

The compatibility of the active substance with the excipients has been evaluated using binary mixtures in stability studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulation used during clinical studies is the same that the used for marketing. The development of the manufacturing process of film-coated tablets 5 mg, 10 mg, 15 mg and 20 mg was performed at pilot scale on similar equipment used for production scale.

The film-coated tablets are packed in polyvinyl chloride/polyvinylidene chloride/aluminium (PVC/PVdC/alu) blisters and in high density polyethylene (HDPE) containers. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

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

Manufacture of the product

The manufacturing process of the immediate release dosage form involves the following steps: blending, fluid bed granulation, drying, blending, compression and film coating.

The process is considered to be a standard manufacturing process.

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

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, UV and FT-IR), uniformity of dosage units, assay (HPLC), degradation products (HPLC), dissolution, water content and microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for three pilot scale batches for each strength, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three pilot scale batches of finished product stored under long term conditions for 24 months at 25ºC/60% RH and intermediate conditions at 30°C/75% RH, and for up to 6 months under accelerated conditions at 40ºC/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.

Samples were tested for tablet description, assay, degradation products, dissolution, water content and microbiological quality. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products and also to a humidity stress test during 3 months at 25°C/93% RH.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Oral drops

Pharmaceutical development

The aim was to develop an oral drops formulation with a concentration of 20 mg vortioxetine per ml to be administered with a dropper device corresponding to 20 drops for a dose of 20 mg vortioxetine. Unlike the film-coated tablets where a hydrobromide salt of the active substance is used, the oral drops formulation contains vortioxetine DL-lactate as the active substance which shows higher solubility in polar solvents. The solubility is further increased due to the presence of hydroxypropylbetadex in the formulation. The substitution degree and the temperature necessary for interaction with the active substance were investigated and taken into consideration during the development. Both parameters were not found critical for the interaction between hydroxypropylbetadex and vortioxetine.

The other excipient, ethanol 96%, increases the number of drops per ml and at the same time serves as preservative. Various ratios were investigated and a concentration of 8.5% (w/v) gave the desired drop number of 20 drops/ml. The oral drops formulation is self-preserving which is confirmed with a test for efficacy of antimicrobial preservation. Purified water serves as vehicle for the formulation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulation used in the clinical bioequivalence study was the same as the formulation used for marketing. The study also showed bioequivalence between the oral drops solution, 20 mg/ml and the 20 mg film-coated tablet formulation.

The primary packaging is an amber glass bottle with dropper applicator and child-proof screw cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

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

Manufacture of the product

The manufacturing process consists of three main steps: preparation of the bulk solution, filtration and subsequent filling of the amber bottles. The manufacturing process is carried out protected from light. The process is considered to be a standard manufacturing process.

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

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and include description (visual), identification (HPLC, UV), assay vortioxetine (HPLC), assay ethanol 96% (GC), degradation products (HPLC), dose and uniformity of dose of oral drops, pH (Ph. Eur.) and microbial quality(Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for three batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of two production scale and one pilot scale batches of finished product stored under long term conditions for 18 months at 25ºC/60% RH and intermediate conditions at 30°C/75% RH, and for up to 6 months under accelerated conditions at 40ºC/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.

Samples were tested for description, vortioxetine assay, ethanol assay, degradation products, dose and uniformity of dose of oral drops, pH, colour of solution and microbiological quality. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products and in–use stability studies were performed on two batches stored for up to 8 weeks after first opening of the bottles at 25°C/60% RH.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable 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.

2.3. Non-clinical aspects

2.3.1. Introduction

In the nonclinical program VOR was administered orally, subcutaneously (SC), intraperitoneally, and/or intravenously (IV) in aqueous solutions of hydroxypropyl-betacyclodextrin (vehicle) (HP-β-CD) to mice, rats, dogs, and rabbits.

Pivotal nonclinical toxicology studies were conducted with the hydrobromide (HBr) salt of VOR. Nonclinical pharmacology studies were conducted with the HBr salt, except for the human ether-à-go-go-related gene (hERG) assay, where the hydrochloride salt was used. Since VOR was used in solution, no differentiation was made between salts. Thus, in this EPAR the term VOR (VOR) will be used, irrespective of the salt form used.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The in vitro studies in recombinant cell lines showed that Vortioxetine acts as an antagonist at 5-HT3, 5-HT7, and 5-HT1D receptors, a partial agonist at 5-HT1B receptors, an agonist at 5-HT1A receptors, and as an inhibitor of the 5-HTT both in human and rats. When taking into account the unbound plasma concentration at doses of 20 mg of Vortioxetine attained in healthy volunteers following repeated administration (Cmax unbound = 1.3 nmol/L), the binding affinities for the h5-HT3 receptor and the h5-HTT are the only ones to be considered therapeutically relevant. At 10-fold higher free plasma concentration, however, 5-HT1A agonistic and 5-HT7 antagonistic effects come into play. In the in vitro functionality assays IC50/EC50 levels are several fold higher than the unbound plasma concentration at doses of 20 mg of Vortioxetine attained in healthy volunteers following repeated administration:

- the IC50 for the h5-HT3A antagonist activity is 7.7-fold higher
- the Kb for the h5-HT7 antagonist activity is still 346-fold higher
- the Kb for the h5-HT1D antagonist activity is 19-fold higher
- the in vitro partial agonist activity at the h5-HT1B receptor is observed at concentrations that are 92- up to 354-fold higher
- the in vitro EC50 for the h5-HT1A agonist activity is 153-fold higher
- the in vitro inhibitory activity of h5-HTT is seen at clinically relevant unbound plasma concentrations.

Vortioxetine has comparable potency at the human and rat 5-HTT, and 5-HT1B receptors, it is more potent (4- to 10-fold) as 5-HT3 and 5-HT1D receptor antagonist in the rat as compared to human and less potent (approximately 10-fold) as 5-HT1A receptor agonist and 5-HT7 receptor antagonist in the rat as compared to human. This may imply that the in vivo activities measured in the rat may be somewhat overestimated with respect to impact of 5-HT3 and 5-HT1D receptor antagonism and somewhat underestimated with respect to impact of 5-HT1A receptor agonism and 5-HT7 receptor antagonism as compared to effects in humans.

Vortioxetine did not reveal clinically relevant interaction with other targets when a broad panel of receptors was tested at concentration up to or above 1000 nM.

The pharmacologically active doses in acute mechanistic and behavioural studies are in general in the range of 2.5 to 20 mg/kg SC (plasma concentrations approximately 170-900 ng/mL according to Study 929-300 2111 042) corresponding to >50% occupancy at the 5-HTT. In the low end of the dose range, inhibition of r5-HT3 receptors and r5-HTT is likely to account for the net pharmacological effects while inhibition of r5-HT1B and stimulation of r5-HT1A receptors and likely also inhibition of r5-HT1D and 5-HT7 receptors contribute to the net effect in the high end of the dose interval.

The ED50's for receptor occupancy are either at plasma exposures below (5-HT3), equal (5-HTT) or above (5-HT1B: 2- fold, 5-HT1A 27-fold at ED43.8) plasma concentration at doses of 20 mg of Vortioxetine attained in healthy volunteers (Cmax = 33 ng/mL). As such, the in vivo target profile of Vortioxetine is compatible with the notion of a multimodal mode of action involving 5-HT3 antagonism, 5-HT1B partial agonism and 5-HTT inhibition.

As can be concluded from the in vivo mechanistic studies, acute i.v. dosing of Vortioxetine suppressed the firing activity of dorsal raphe 5-HT neurons in rats (ED50 548 µg/kg). The effect is mediated via a 5-HT1A receptor-dependent mechanism and involving contribution of 5-HT3 receptor antagonism to the net effect of Vortioxetine in this assay.

Administration of Vortioxetine at a dose corresponding to 40%-50% 5-HTT occupancy produced a significant reduction in the firing activity of rat dorsal raphe neurons 5 to 10 hours following continous drug delivery by an implanted minipump. There is a rapid recovery from the neuronal suppression (recovery of the firing frequency to control levels at 24 hours and maintenance at these levels at 3, 7 and 15 days). Co-administration of Vortioxetine and the 5-HT3 receptor agonist SR57227 counteracted the acute inhibitory effect of vortioxetine on dorsal raphe nucleus firing and delayed recovery thus pointing to the involvement of 5-HT3 antagonistic activity.

Vortioxetine also showed an antidepressant or anxiolytic-like profile in following in vivo behavioural assays:

- Novelty-induced suppression of feeding in 129SvEvTac mice (MED = 5 mg/kg/day p.o., no effect at 20 mg/kg/day), accompanied by enhanced cell proliferation and maturation in the hippocampus
- Mouse (NIH Swiss mice) forced swim test (15.8 mg/kg s.c.)
- Rat (SD) foot shock-induced ultrasonic vocalization (MED=3.9 mg/kg s.c.)
- Rat (SD) social interaction test (1 mg/kg p.o. → 3 ng/ml).

Except for the rat social interaction test, the active doses are in the high end of the dose range, where more targets in addition to 5-HT3 receptor and the 5-HTT are expected to be involved in the pharmacological effects. Plasma exposures are available only for the rat social interaction test and they are slightly lower than the plasma exposures attained following a single clinical dose of 20 mg of Vortioxetine in healthy volunteers (Cmax = 8.03 ng/mL). Vortioxetine is active in the rat social interaction test at doses where the occupancy at the 5-HTT is less than 20%, which may be regarded as negligible, hence the effect is most likely mediated through 5-HT3 receptor antagonism.

The mouse marble burying test in CD-1 mice (s.c.) and the olfactory bulbectomised test in SD rats (p.o.) are considered failed tests as the respective positive controls failed to exhibit an effect.

Vortioxetine also failed to reverse the stress-induced hedonic deficit measured as intake of a sucrose solution in the rat chronic mild stress test (Wistar rats, i.p., 5 weeks), whereas the positive control compound, imipramine, 10 mg/kg/day, IP, was active.

Vortioxetine showed memory enhancing effects in a rat contextual fear-conditioning paradigm (5 mg/kg s.c.) and novel object recognition model (10 mg/kg s.c.) at doses corresponding to 5-HTT occupancies of about 90%. The SSRI, escitalopram, is also active in these assays in normal rats at 5-HTT occupancies greater than 90%.However, Vortioxetine unlike escitalopram and duloxetine recovers cognitive deficits in rats following 5-HT depletion even at doses as low as 0.1 mg/kg (corresponding to a 5-HTT occupancy less than 20%, 5-HT3 receptor mediated).

Secondary pharmacodynamic studies

Vortioxetine demonstrates analgesic potential in models of pain with central sensitization (the mouse formalin model) and neuropathic pain (the rat chronic constriction nerve injury model), whereas there is no activity against inflammatory pain as assessed in the carrageenan paw model. Hence Vortioxetine shows potential as treatment of centrally mediated pain.

Most SSRIs and SNRIs cause treatment related sexual dysfunction. Consequently, Vortioxetine was tested in a sexual behaviour study in male rats. Unlike the SSRI fluoxetine, Vortioxetine did not significantly influence male rat sexual behaviour (noted a transient decrease in anticipatory level in the low-dose group and a slight non-statistically significant decrease in the number of ejaculations) in spite of high levels of 5-HTT occupancy with both drugs (70% for Vortioxetine as compared to 98% for fluoxetine), 8-9 hours after the last dose. In concert with the lack of fertility effects in reproduction toxicity investigations or on reproductive organs in multiple dose toxicity studies, these findings suggest a lower risk of sexual side effects of Vortioxetine than for SSRI or SNRI antidepressants (see below).

Safety pharmacology programme

Vortioxetine did not impair central nervous system function as evident by an Irwin test and the rotarod performance in rats. In behavioural studies in dogs, only sedation was noted at clinically relevant plasma exposures. This sign is consistent with observations noted in the toxicity studies.

In in vitro cardiovascular studies, Vortioxetine had a minor effect on currents of hERG (IC50 2538-fold higher than human unbound plasma exposure) and cloned human cardiac SCN5A sodium ion channels (IC50 715-fold higher than human unbound plasma exposure).

Vortioxetine administered to dogs in with single or sequential IV infusions induced minor prolongation of the PR intervals. As such, in the definitive study in conscious restrained male and female Beagle dogs at NOEL, plasma levels and AUC were, respectively, 1.4-fold higher and 7.5 fold lower than the values measured at doses of 20 mg of Vortioxetine attained in healthy volunteers (Cmax = 33 ng/mL). At the NOEL of 0.94(initial)/0.08(maintenance) mg/kg iv. dose in the anesthetised female dog study, plasma levels were 14-fold higher than the plasma exposures measured at doses of 20 mg of Vortioxetine attained in healthy volunteers.

Likewise, PR-prolongations were observed upon oral vortioxetine administration in dog toxicity studies over 4 weeks (plasma exposure at the no-observed effect level=101/84 ng/mL for males/females, plasma levels are 3/2.5(M/F)-fold higher than the plasma exposures measured at doses of 20 mg of Vortioxetine attained in healthy volunteers) and 13 weeks. The effects on PR interval are noted at plasma exposures exceeding human the plasma exposures measured at doses of 20 mg of Vortioxetine attained in healthy volunteers by 4.6/6.3(M/F)-fold. PR-prolongations were however not observed in the clinical program. In anesthetized guinea pigs, no effects on pulmonary resistance or compliance were observed with IV doses up to 20 mg/kg. In freely moving rats, no biologically significant adverse effects were seen on respiratory parameters with doses up to 20 mg/kg (PO, gavage). No bronchoconstrictive effects of Vortioxetine were observed at PO doses ≤40 mg/kg. At 40 mg/kg, a significant reduction in the peak expiratory flow was observed.

Respiratory measurements in IV dosed conscious dogs showed that the pH of the arterial blood was reduced with a NOEL of 1.5 mg/kg (plasma levels are 3-fold higher than the plasma exposures measured at doses of 20 mg of Vortioxetine attained in healthy volunteers (Cmax = 33 ng/mL)). No statistically significant effects were observed in pCO2 and pO2 at plasma exposures below 210 ng/mL.

Vortioxetine had no pharmacodynamic renal effects in male and female rats at 20 mg/kg twice daily (BID) in a renal function study where Vortioxetine was administered for 5 days at oral doses up to 40 mg/kg BID. At 40 mg/kg BID, changes in sodium and chloride excretion and in urine osmolarity and albumin levels were noted. No changes in creatinine clearance were observed. At NOEL (20 mg/kg BID), plasma levels are 5.6/8.7(M/F)-fold higher than the plasma exposures measured at doses of 20 mg of Vortioxetine attained in healthy volunteers (Cmax = 33 ng/mL).

A gastrointestinal transit study in rats showed that VOR, 20, 40, and 100 mg/kg, PO, corresponding to respective average plasma levels of 198, 497, and 749 ng/mL, caused a dose-dependent decrease in

gastric emptying but only a marginal reduction in charcoal transit in the small intestine. At these dose levels, plasma exposures are 1.4 up to 6.4-fold higher than the plasma exposures measured at doses of 20 mg of Vortioxetine attained in healthy volunteers (Cmax = 33 ng/mL).

In dogs, presumed abdominal pain (manifested by hunched back and discomfort during abdominal palpation) was observed at IV doses ≥1.5 mg/kg, corresponding to plasma exposures that are 3.2-fold higher than the plasma exposures measured at doses of 20 mg of Vortioxetine attained in healthy volunteers (Cmax = 33 ng/mL).

Consequently, gastrointestinal effects can be expected in the clinical setting and this is reflected in section 4.8 and 4.9 of the SmPC.

Pharmacodynamic drug interactions

Conduct of nonclinical pharmacodynamic drug interaction studies with Vortioxetine were considered not to be relevant as pharmacodynamic drug interactions were addressed in clinical pharmacology studies.

This was considered acceptable.

2.3.3. Pharmacokinetics

Pharmacokinetic properties of vortioxetine were predominantly investigated in mice, rats and dogs, i.e. species tested in toxicology studies, and were further compared using plasma and hepatocytes from rabbits, guinea pigs and Cynomolgus monkeys.

The oral absolute bioavailability was approximately 10% in the rat, 48% in the dog and 75% in patients, with terminal elimination half-life values of 3.0, 7.9 and 66 hours, respectively. In patients, the absorption was relatively slow (Tmax from 6 to 10h). Both in dogs and in rats there is a disproportionate increase in AUC after oral administration while in patients pharmacokinetics were dose-proportional. Consistent with the elimination half-life, Vortioxetine accumulates 5- to 6-fold in patients after multiple dosing. Gender differences in plasma Cmax and AUC were observed in rats and in mice after oral administration. Gender differences were first observed in one clinical study, however after normalisation to weight no more gender differences were observed in patients.

After repeated oral administration in rats and dogs, the half-life of Vortioxetine very significantly increased with dose which could suggest some kind of accumulation. However, PK data from a four-week toxicology study in dogs resulted in a mean half-life similar to single dose administration. No accumulation was seen after single dose oral administration in the distribution study in rats. In patients, the half-life of Vortioxetine did not vary with oral dose after single or repeated administration.

Pharmacokinetics of two metabolites of Vortioxetine were studied in dogs. Lu AA34443 is the major metabolite in all species and in patients. Lu AA34994 is an intermediate that was identified in vitro but never detected in vivo. Lu AA34994 metabolism further leads to Lu AA34443.

Distribution studies with [^{14}C]Vortioxetine and drug-related material in male rats showed fast absorption and distribution to all organs and tissues. Vortioxetine binds to melanine and concentrations of drug-related material were higher in melanin containing tissues. Elimination of radioactivity over time occurred more rapidly in the albino Wistar Han rat as compared to the pigmented Lister Hooded rat, with approximately half the number of tissues being below the limit of quantification after 24 hours. At 504 hours after dose administration, radioactivity was only quantifiable in the pigmented skin and uveal tract of the Lister Hooded rat. In vitro protein binding of [^{14}C]Vortioxetine in human plasma

was high (98.8%) and similar to the plasma protein binding in mice, rats, rabbits, and dogs (between 99.1% to 99.8%).

All metabolites detected in human hepatocytes were also present in dogs, mice and rats (plasma and/or urine) in vivo, except for a glucuronide conjugate of monohydroxy-Vortioxetine which was not found in mice or rats. Among all species tested, rabbit hepatocytes appeared to have the metabolite profile closer to human hepatocyte metabolite profile.

Vortioxetine and/or metabolites inhibited the following CYPs: CYP2C19, CYP2C9, CYP3A4, CYP2B6 and CYP2C8 at high concentrations. Clinical trials assessing drug-drug interaction of Vortioxetine with regard to CYP2C19, CYP2C9, CYP3A4 and CYP2B6 did not demonstrate an inhibitory activity of the treatment on these enzymes.

Vortioxetine and related material was mainly excreted by faeces in mice (84 %), rats (69 %) and dogs (59-65 % in two separate studies), whereas humans showed prominent urinary excretion (59 %) compared to faeces (26 %). In excretion studies, the recovery of [^{14}C]Vortioxetine and related material was close to 100% in rodents. Dogs and humans exhibited a protracted excretion and the recovery was approximately 90% and 85% after 168 hours and 360 hours, respectively. Excretion in maternal milk was demonstrated in rats. This was included in the SmPC section 5.3, with a cross-reference in section 4.6.

Studies were conducted to determine the composition and solubility of the crystalline material observed in the kidney and liver of rats and in the liver of mice in repeat-dose studies. The crystals were found to be composed of the carboxylic acid metabolite Lu AA34443 and M3 (glucuronide of Lu AA39835). It is concluded that the crystal formation was due to exceeded solubility of these metabolites. The M3 metabolite is only found in trace amounts in human feces and urine, in contrast to the high concentrations found in rodents. The mean concentration of Lu AA34443 in human urine is clearly below the determined solubility of this metabolite in human urine. It is thus considered that crystal formation is unlikely to occur in patients.

2.3.4. Toxicology

Toxicity studies with Vortioxetine ranging from single-dose studies up to 26- or 52-week repeat-dose toxicity studies were conducted. The rat and dog were used as the primary rodent and non-rodent species, respectively.

A standard set of in vitro and in vivo genotoxicity studies was performed and the carcinogenic potential of Vortioxetine was investigated in two 2-year carcinogenicity studies in mice and rats, respectively. Potential effects on fertility and pre- and postnatal development were assessed in the rat and embryo-fetal developmental toxicity studies were conducted in the rat and the rabbit.

Other studies included immunotoxicity (as part of the 13-week rat toxicity study), intravenous (IV) 7- and 14-day toxicity studies in rats and dogs, a local lymph node assay (LLNA) for assessment of skin sensitization in mice, and mechanistic toxicity studies in dogs (to address the convulsive episodes seen in this species) and rats (mechanistic evaluation of crystalline materials in liver and kidney).

Vortioxetine was administered orally to dogs and twice daily to rabbit, rat and mouse due to its relatively short plasma half-life in these species. Due to severe toxicity the dosing regimen was changed to once daily dosing for the mouse.

HP-β-CD was chosen as the vehicle for the formulations of Vortioxetine in order to enhance solubility and oral bioavailability. In the rabbit studies, vehicle-mediated effects on bodyweight, food consumption, and faeces were seen and in the rat carcinogenicity study, vehicle-mediated effects were seen in the large intestines. According to the literature, the main effects of oral administration of high doses of HP-β-CD are related to the large load of poorly digestable, osmotically active carbohydrates which leads to soft and/or loose faeces in rats and dogs and effects on bodyweight, food consumption, and faeces in rabbits. In addition, oral administration of HP-β-CD has effects on haematological and clinical chemistry parameters and induces histological changes in the gastrointestinal tract, liver, pancreas, and urinary tract.

Toxicokinetic (TK) profiling or proof of systemic exposure measurements of vortioxetine were performed in all pivotal studies. Additional TK measurements of metabolites were performed in selected studies.

All pivotal toxicity studies were conducted in compliance with GLP principles. GLP compliance is not claimed for all dose range-finding studies.

The bioanalytical phases of 10 nonclinical toxicity studies were affected by a case of misconduct during the conduct of the bioanalyses at a contract research organization. The misconduct resulted in 10 deficiencies relating to the bioanalytical work. GLP compliance cannot be claimed for the bioanalytical phases of the 10 nonclinical studies. However, based on the investigation and the remedial work of the Applicant, the overall conclusions of the studies are adequate.

Single dose toxicity

Single dose toxicity studies were performed in the mouse and in the rat following oral or iv administration of LUAA21004. In both species, clinical signs related to CNS effects occurred rapidly after oral dosing and included marked sensitivity to touch, tremor, partly closed eye, rapid breathing, hypoactivity and perinasal staining. Clinical signs observed at doses higher than the MTD resulted in convulsions in both sexes after single oral or iv administration of LuAA21004. The MTD were 300 mg/kg (mouse) and 500 mg/kg (rat) after oral administration and between 20 and 30 mg/kg in both species following iv dosing.

Repeat dose toxicity

Repeat-dose toxicity studies were conducted ranging up to 26- or 52-weeks in mouse, rat and dog. The main findings during the repeat-dose toxicity studies were clinical signs associated with the effect of Vortioxetine on the central nervous system (CNS) in all species and changes in the liver and kidneys of rodents.

<u>CNS effects</u>

Clinical signs of convulsions were seen in the mouse in the non-pivotal repeat-dose toxicity studies at dose of 200mg/kg/day. No convulsions and no other CNS clinical sign (except sporadic overactivity in female) were seen during 26 week treatment at daily dose up to 50 mg/kg and 200 mg/kg in the male and female mouse, respectively.

No sign of convulsions were seen during repeat-dose toxicity in the rat up to 26 weeks at oral dose of 40 mg/kg/BID that corresponded to a safety margin of 17 and 15 for male and female, respectively, as compared to the exposure in human at the maximum daily recommended dose (20 mg).

In the dogs, following oral administration of Vortioxetine, episodes of convulsions were observed in two females at 10 and 15 mg/kg/day doses, respectively, within the first days of treatment in the 13-week toxicity study. A no effect level for convulsions was established at 7.5 mg/kg/day in the 52-week dog study. This corresponded to a plasma exposure level 4.7 -fold the human exposure at the maximum recommended therapeutic dose of 20 mg/day Vortioxetine (AUC for single dose: 645.51, AUC for multiple dose: 646 ng.h/mL). A mechanistic study confirmed that the major metabolite of LuAA21004, LuAA34443, was not responsible for the convulsions seen in the dog following oral administration of LuAA21004. Taking into account the narrow dose range between the NOEL and the occurrence of convulsions (7.5 mg/kg/day vs 10 mg/kg/day) in this species and the fact that two episodes of convulsions were reported during clinical trial (although being of alternative ethiology), arisk of convulsions in human cannot be excluded and is reflected in the SmPC and followed up in the RMP.

In addition to convulsions, other LUAA21004-related CNS effects were seen in all the species used during repeat-dose toxicity studies. In the mouse, the principal clinical signs were tremor, hypoactivity, abdominal distension, noisy respiration, piloerection, ungroomed coat, and vocalization occurring at doses ≥ 50 mg/kg/day. In the rat, salivation was seen at all the doses tested. In the dogs, pupil dilatation/incomplete pupil contraction, was noted in both male and female at ≥ 3.75 mg/kg/day.

Kidney toxicity

Pale appearance and increase kidneys weight were observed in the mouse. With daily regimen increased kidneys weight was only seen during the 13 week study without any related-findings in blood chemistry/urinalysis parameters and histopathological examination.

In contrast, renal toxicity was found in the rat in the MTD, 13- and 26-week toxicity studies at 40 mg/kg BID and above. The toxic findings included glomerulonephritis and kidney changes indicative of renal tubular obstruction by crystals. There was evidence of an effect upon renal function as indicated by alteration of the urinary composition (production of higher volume of diluted urine, presence of blood, and variations of plasma and urinary electrolytes). After a 12-week treatment-free recovery period, kidney findings similar to those detected at the end of the 26-week treatment period were present in 1/6 males that received 40 mg/kg BID.

The risk to human is considered low, however, the non-clinical finding is considered a potential risk and followed up in the RMP

Liver toxicity

In mice, repeat oral administration of LuAA21004 resulted in liver toxicity characterized by hepatocyte necrosis, presence of inflammatory cells, bile duct hyperplasia, crystalline material in bile ducts, and an increase in hepatocyte mitotic activity predominantly in the males. In female, cytoplasmic hepatocyte vacuolation was seen at dose of 200 mg/kg/day. With regard to liver toxicity the NOAEL for male mice was 50 mg/kg/day whereas it was 200 mg/kg/day in females.

Liver toxicity was also noticed in the rat. This included hepatocellular hypertrophy, hepatocyte necrosis, bile duct hyperplasia and presence of crystal material in the duct. With regards to liver necrosis the NOAEL was 10 mg/kg/BID in the rat. Based on this values a safety margin of LuAA21004 exposure levels was only 1.6-2.2 when compared to the human exposure following repeat oral administration of LuAA21004 at the maximum daily recommended dose of 20 mg.

Liver changes characterized as mild hepatocellular vacuolation were observed in dogs in the 4-week study, but were not confirmed in studies of longer duration. Changes in plasma aspartate amino-transferase activity and glucose and protein concentrations suggesting an effect upon the liver were observed in the 13-week toxicity study but these were not related to any histopathological changes.

The liver findings in rodents (focal hepatocyte necrosis) are considered related to the crystalline precipitation of the metabolites Lu AA34443 and M3 at dosages of 20 mg/kg BID (rats) and 100 mg/kg/day (mice) and above.

Since focal hepatocyte necrosis is very common in mice and rats and since they also occur following bile duct obstruction in rats (Kountouras et al., 1984), the focal necrosis may be viewed as part of the other histopathological changes. Furthermore, crystal precipitation is considered not likely to occur in humans at therapeutic dose levels the liver findings in rodents are considered only to pose a low risk to humans. The aetiology of the hepatocellular vacuolation observed in dogs in the 4-week study at a dose of 15 mg/kg is not known. However, these changes were mild and no histopathology changes have been observed in the 13- and 52-week study in dogs. Furthermore, they were observed at exposure levels which are approximately 8-fold to the human exposure at the recommended clinical dose. Therefore, the relevance to humans is limited.

A wording is proposed for section 5.3.

Crystal formation containing LuAA34443 and M3 was confirmed in the rat renal tubules and bile ducts. These were considered to represent major routes of excretion of Vortioxetine and/or a metabolite. In rats, the concentration of Lu AA34443 in urine occasionally exceeded the solubility limit explaining the crystal formation in rats, while the concentration of Lu AA34443 in urine in dogs was below the solubility limit; no renal crystal formation was noted in dogs. In human urine, the concentration of Lu AA34443 was 10-fold lower than the solubility limit. All together these data suggested a rodent-specific effect for the crystal formation that is unlikely to occur in patients with normal renal function.

Other effects

In the 4-week repeat dose toxicity study in rats (Study 10194) histopathological investigation indicated findings in the salivary glands (degranulation of the striated ducts, acinar degranulation and/or acinar atrophy) in animals receiving 20 or 40 mg/kg b.i.d. and, to a lesser extent, 10 mg/kg b.i.d. These findings were considered to have been induced by the increased incidence of salivation noted in the treated groups rather than a result of systemic toxicity. The Applicant therefore considers these histopathological and clinical findings to be of no toxicological importance. However, degranulation of striated submandibular salivary gland ducts and acinar athrophy of the sublingual salivary glands were also noted in the 14-day toxicity study in rats after i.v. administration of vortioxetine (Study 10305) with no clinical signs of salivation. The morphology of the salivary gland changes in the 4-week and 14-day studies points towards a functional response of the glands induced by release of neurotransmitters more than a direct toxic effect of the treatment with vortioxetine. This is also in agreement with data from the literature. As such, increased levels of 5-HT due to the pharmacological effect of vortioxetine may have augmented the changes in the salivary gland epithelium. The lack of salivary gland changes in the 13- and 26-week oral toxicity studies in rats is a possible adaption to the dosing procedure and subsequent disappearance of the changes in the salivary gland. This has been confirmed by incidences of salivation recorded in the studies. In the 4-week and 13-week studies maximal incidences were observed in weeks 2-4 and 3-4, respectively, thereafter the incidences decreased in the 13-week study.

Genotoxicity

Vortioxetine (Lu A21004) was tested in a standard battery according to ICH S2 guidelines. There was no evidence for any genotoxic potential of Vortioxetine.

Carcinogenicity

In the mouse carcinogenicity study, once daily oral administration of Vortioxetine at 50 mg/kg/day in males produced an increased incidence of benign neoplastic change in terms of hepatocellular adenomas in the liver. At this dose in males and, to a lesser extent, at 100 mg/kg/day in females there was crystalline material in the lumen of the biliary system, which caused a range of secondary inflammatory changes, as a result of irritancy, in the hepatobiliary system. The increased incidence of benign neoplastic changes in the high dose males was considered likely to be mediated by a non-genotoxic mechanism of persistent hepatotoxicity. There was a clear no-effect level for tumour-formation related to treatment with Vortioxetine at 15 mg/kg/day in males and 100 mg/kg/day in females. The NOAEL in this study, considering both neoplastic and non-neoplastic changes, was 15 mg/kg/day in males and 30 mg/kg/day in females.

In the rat carcinogenicity study, neoplastic findings related to oral administration of LuAA2100 were observed in the liver and mesenteric lymph node.

In the liver, a slight increase of hepatocellular adenomas was observed in the high dose groups. The treatment had no effect on the incidence of hepatocellular carcinomas, and there was a clear no-effect-level for the hepatocellular adenoma (7 mg/kg b.i.d. in males and 15 mg/kg b.i.d. in females) thus suggesting a non-genotoxic mechanism of persistent hepatotoxicity.

In the mesenteric lymph node, males given 7 or 20 mg/kg b.i.d. showed an increased incidence of benign neoplastic lesions (benign haemangioma), and angiomatous hyperplasia was also reported for the high dose males. There was no effect in females. This could potentially be attributed to the hydroxypropyl-β-cyclodextrin-induced increase in cholecystokinin, a peptide that can act locally as a mitogen in rats, but not in mice, non-human primates and man. Moreover, a role is also being attributed to gastrointestinal mucosal inflammation also due to hydroxypropyl-β- cyclodextrin. It could thus be hypothesized that angiogenic factors from the inflamed intestinal mucosa or increased levels of cholecystokinin has stimulated endothelial cell proliferation locally in the mesenteric lymph node and thereby played a role in the development of the haemangiomas. Whilst mesenteric lymph node haemangioma is a well described spontaneous tumour in rats that is most common in males with incidences up to 73 % in male rats in life-time studies; lymph node angiomas in humans are extremely rare, not reported in mesenteric lymph nodes, more common in females than males. There is no evidence to support that the occurrence of mesenteric lymph node angiomas in rats are relevant for humans. Vortioxetine is non-genotoxic, no proliferative vascular lesions have been observed in the chronic toxicity studies and there is no increase in malignant vascular neoplasms in rodent studies. However, benign haemangiomas were seen to occur dose dependently in male rats only. In the absence of a clear clinical correlate, therefore, these findings are considered to be of low clinical relevance.

Non-neoplastic findings related to LUAA21004 identical to that observed in general toxicity studies were found in the liver, kidneys, bile duct, as well as in the stomach (dilated glands), and the mesenteric lymph node (sinus histiocytosis, hyperplasia). In the rat, considering both neoplastic and non-neoplastic findings, the NOAEL was 2 mg/kg b.i.d. in males and 15 mg/kg b.i.d. in females.

All of the treatment-related increases in tumor incidences seen in mouse or rat were small and involved only benign lesions and none of the findings noted indicate a carcinogenic potential for Vortioxetine in humans.

Reproduction toxicity

Vortioxetine had no effect on fertility, mating performance, reproductive organs or on sperm morphology and motility. However, a study in rats on sexual behavior showed that vortioxetine mildly impact male rat sexual behavior (decreased anticipatory sexual excitement and slightly decreased

number of ejaculations). At high dose (60 mg/kg/bid), a decreased in food consumption was seen in dams. The NOAEL for the male fertility was 60 mg/kg/b.i.d. This represented a safety margin of 24 following repeat oral administration of Vortioxetine at the daily maximum human recommended dose (20 mg). The NOAEL for female fertility and early embryonic development was 60 mg/kg/b.i.d, that represented a safety margin of 16 following repeat oral administration of Vortioxetine at the daily maximum human recommended dose (20 mg). Nevertheless, as vortioxetine comparably affects serotonin levels as the pharmacologically related class of SSRIs, it seems reasonable to include a warning for a potentially impaired sperm quality in section 4.6 of the SmPC in accordance with the recently adopted requirements of the PhVWP.

Embryo-foetal development studies were performed in both rat and rabbit following oral administration of Lu AA21001 (from 5 up to 80 mg/kg/bid in the rat, from 1 up to 30 mg/kg/bid in the rabbit).

In the rat, Vortioxetine was found to reduce maternal body weight gain during gestation and to elicit body weight loss and decreased foetal weight at doses ≥ 60 mg/kg/bid. In the rabbit, maternal toxicity characterized by marked body weight losses and reduction in food consumption was seen at all doses tested (≥ 1mg/kg/bid) and decreased foetal weight was observed at doses ≥ 15 mg/kg/bid.

Meningoceles were seen in 3 foetuses from different litters of the 10 mg/kg/bid mid dose group and the incidence of this finding (2.5%) was above the historical foetal rabbit background data (0.0-1.3%). This occurred at levels exposures comparable to that measured in human at maximum daily recommended dose of 20mg. The NOAEL with regard to meningocele occurrence was 5mg/kg/bid in the rabbit and a safety margin was absent. Moreover, a case of meningocele was also seen in a rat foetus from a low dose group, which was not found in historical background data for foetal rat abnormalities. The relevance of these rare findings for humans is questionable taking into account that this finding is not dose dependent and that pharmacological and toxicological data (including results from the pre- and postnatal toxicity study) do not suggest a bell-shaped dose response curve in animals.

Significant increase in the incidence of dilated ureters was seen in the rat foetuses starting at low dosed group. This is considered a transient effect on development and not to a related treatment effect, and it occurred in the absence of maternal toxicity. In addition, increased incidence of bilobed gall bladders was also seen in rabbit foetuses. This finding is considered incidental and unrelated to treatment although the incidence at the HD level in one study exceeds historical control incidence by more than 2-fold. A subsequent rabbit embryofoetal development study has failed to demonstrate a similar increase at a higher dose level.

An increased incidence of minor skeletal abnormalities and variants, predominantly associated with the state of ossification (incomplete and/or non-ossification), mainly concerning the sternum, cervical and thoracic vertebrae and the bone skull, was observed in foetuses of both species. These skeletal findings appeared correlated with the disruption in maternal bodyweight performance.

Based on the above findings, a potential risk of delayed foetal development in humans cannot be excluded. This was reflected in the SmPC.

Pre- and postnatal study with Vortioxetine was performed in the rat. Bodyweight and bodyweight gain were reduced in pups from dams treated with 60 mg/kg BID. Vortioxetine (≥ 5 mg/kg/bid) showed adverse effects on pup development at doses which did not result in maternal toxicity.

The findings included increased pup mortality, reduced bodyweight gain, and delayed eye opening. The effect of Vortioxetine on pup mortality was achieved at exposures similar to those achieved in human at the daily recommended dose (20mg). Based on these findings, a potential risk to humans cannot be excluded.

In all repeat-dose toxicity studies, NOAELs have been established and the systemic exposures at these NOAELs with regard to the human exposure at the maximum therapeutic dose (20 mg/day) were determined. Following concerns regarding the NOAELs established for some reproduction toxicity studies the Applicant has recalculated the NOAELs of the embryo-fetal developmental studies in rats and rabbits and in the pre-postnatal study in rat and a wording for section 5.3 is proposed.

A toxicity study following oral administration of Vortioxetine was done in juvenile rats from day 21 to day 91 of age. There were no treatment-related findings on reproductive parameters. Both liver and kidneys were identified as major target organs. Histopathological changes were seen in the liver and kidneys in terms of minimal hepatocellular centrilobular hypertrophy and vacuolation and minimal corticomedullar mineralization, respectively. Corticomedullary mineralization was mainly seen in female .rats but this finding was not evident in studies where adult rats were previously treated with Vortioxetine. The reduction in incidence in the high dose female group following cessation of treatment suggested a partial reversal of this finding. The precise mechanism underlying this observation was unclear and may be associated with a change in hormone levels in the females.

The survival and clinical condition of the offspring born to parents previously treated at high dose of Vortioxetine were clearly inferior to those of offspring in the control group and those born to parents previously treated at 20 or 10 mg/kg/ b.i.d. In addition, such offspring showed clinical sign (cold to touch, no milk in the stomach) that was not observed in the offspring of animals treated with the control vehicle. In term of exposure levels this corresponded to a safety margin of only 4. A treatment related effect cannot be ruled out and this finding was described under section 5.3 of the SmPC, even if the current indication only concerns adult population and BRINTELLIX is not recommended in children under 18 years of age.

Local tolerance

Since the intended route for administration of BRINTELLIX in patients is oral, data from local tolerance studies are irrelevant.

Other toxicity studies

The repeated dose toxicity studies studies did not indicate potential immunotoxicity studies in mouse, rat and dog. Therefore, no specific studies are required to assess potential immunotoxic effects of Vortioxetine.

Nonclinical studies show that Vortioxetine at a high dose produced an increase in extracellular dopamine in the medial prefrontal cortex, but failed to activate other parts of the mesolimbic dopamine pathway including the nucleus accumbens. These findings support that Vortioxetine is devoid of dependence liability. Furthermore, no discontinuation symptoms were observed in animal studies. No specific non-clinical studies have been performed or are to be performed. This issue has been addressed from a clinical point of view. Consequently the Applicant will monitor the occurrence of drug discontinuation symptoms as part of the routine pharmacovigilance activities. The newly released SMQ for Drug Abuse, Dependence and Withdrawal (MedDRA 15.0, section 2.22) will be used to identify cases." This is considered sufficient.

2.3.5. Ecotoxicity / environmental risk assessment

Table 1. Summary of main study results

Substance (INN / Invented Name): Brintellix			
CAS-number (if available): 508233-74-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 122	logD: 3.1 (pH 7.4)	Potential PBT (N) Potential B (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	N/A	B/not B
	BCF	2032-2121	B
Persistence	DT50 or ready biodegradability	stable/persistent in sediment (Dt_{50} not calculable)	P
Toxicity	NOEC or CMR	0.000116 mg/l (HBr-salt); 0.000091 mg/l (free base)	T
PBT-statement :	The compound is considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.1	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	mean Koc= 10481	Terrestrial studies triggered. Sand : 5433 Loamy sand : 9001 Sandy loam 1 : 16153 Sandy loam 2 : 6818 Clay : 14998
Ready Biodegradability Test	OECD 301	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ =2.1-3.7 days $DT_{50,\ sediment}$ =not calculable $DT_{50,\ whole\ system}$ =7.2-50.1 days % shifting to sediment (d100) = 90.7% / 86.7%	SFO, 20°C;

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	2.98	µg/L	Species:Pseudokirchneriella subcapita Free base
Daphnia sp. Reproduction Test	OECD 211	NOEC	4.02	µg/L	Free base
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	0.091	µg/L	Species: Fathead Minnow (Pimephales promelas). Free base; risk for fish PEC/PNEC > 1
Activated Sludge, Respiration Inhibition Test	ISO 8192	EC	3147	µg/L	Free base
Phase IIb Studies					
Bioaccumulation	OECD 305	BCFkinetic BCF steady state	2032-2121 1804-1918	L/kg	%lipids: 5% total radioactivity Species: Rainbow trout
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2	32,3-43,3d 3,3-4,4%		two aerobic soils; 20°C, SFO Chelmorton = a silt clay loam pH6.3, at d 32.3 Bromsgrove = a sandy loam pH7.3, at d43.3 organic carbon 1.2%
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect<25 %	0.0531	mg/kg	1xPEC Soil = sandy loam ph6.4, organic carbon 1.1%
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC for all 3 species	78.5	mg/kg	Value corresponds to free base. Spring barley (*Hordeum vulgare*) Oil seed rape (*Brassica napus*) Tomato (*Lycopersicon esculentum*)
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	96.8	mg/kg	Free base Eisenia fetida
Collembola, Reproduction Test	OECD 232	EC10	28.7	mg/kg	Free base *Folsomia candida* The lowest test

					concentration of the submitted OECD 232 with Folsomia candida showed already a clear effect so that no NOEC effect could be determined but only an extrapolation of EC_{10}.
Sediment dwelling organism		NOEC measured NOEC standard sediment	904 3172	mg/kg	Chironomid (*Chironomus riparius*) Free base

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of vortioxetine to the environment. The CHMP recommends the following points for further investigation:

1. Submission of Koc values derived from at least one sludge in a batch equilibrium method according to OECD 106 or OPPTS 835.1110. Furthermore, the PECsoil and the PECsw-refined (Tier B) should be recalculated taking into account Koc values derived from at least one sludge to conclude on the risk for the terrestrial environment.
2. Submission of a valid and plausible test for collembolan (OECD 232) with test concentrations allowing the determination of a NOEC.

2.3.6. Discussion on non-clinical aspects

The mechanism of action of vortioxetine is thought to be related to its direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter. Non-clinical data indicate that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter, leading to modulation of neurotransmission in several systems, including predominantly the serotonin and also the norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate systems. This multimodal activity is considered responsible for the antidepressant and anxiolytic-like effects and the improvement of cognitive function, learning and memory observed with vortioxetine in animal studies. However,the precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to man.

Administration of vortioxetine in the general toxicity studies in mice, rats and dogs was mainly associated with CNS-related clinical signs. These included salivation (rat and dog), pupil dilatation (dog), and two incidences of convulsions were noted in dogs during the general toxicity study program. A no-effect level for convulsions was established with a corresponding safety margin of 5 considering the maximum recommended therapeutic dose of 20 mg/day. Target organ toxicity was restricted to kidneys (rats) and liver (mice and rats). The changes in the kidney in rats (glomerulonephritis, renal tubular obstruction, crystalline material in renal tubule) and in the liver of mice and rats (hepatocellular hypertrophy, hepatocyte necrosis, bile duct hyperplasia, crystalline material in bile ducts) were seen at exposures more than 10-fold (mice) and 2-fold (rats) the human exposure at the maximum recommended therapeutic dose of 20 mg/day. These findings were mainly attributed to

rodent-specific vortioxetine-related crystalline material obstruction of the renal tubules and the bile ducts, respectively, and considered of low risk to humans.

Vortioxetine was not genotoxic in a standard battery of *in vitro* and *in vivo* tests.

Based on results from conventional 2-year carcinogenicity studies in mice or rats, vortioxetine is not considered to pose a risk of carcinogenicity in humans.

Vortioxetine had no effect on rat fertility, mating performance, reproductive organs, or sperm morphology and motility. Vortioxetine was not teratogenic in rats or rabbits, but reproductive toxicity in terms of effects on foetal weight and delayed ossification were seen in the rat at exposures more than 10-fold the human exposure at the maximum recommended therapeutic dose of 20 mg/day. Similar effects were seen in the rabbit at sub-therapeutic exposure.

In a pre- and post-natal study in rats, vortioxetine was associated with increased pup mortality, reduced bodyweight gain, and delayed pup development at doses that did not result in maternal toxicity and with associated exposures similar to those achieved in humans following administration of vortioxetine 20 mg/day.

Vortioxetine-related material was distributed to the milk of lactating rats.

In juvenile toxicity studies in rats, all vortioxetine treatment-related findings were consistent with those noted in adult animals.

On the available ERA data provided the CHMP concluded that Brintellix is expected to pose a risk for the environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of Brintellix have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2: Overview of Clinical Pharmacokinetics and Biopharmaceutic Studies

Study	Type of Study	Lu AA21004 Treatment Duration[a]	Dose Route of Administration[b]	No. of Subjects Exposed to Lu AA21004
Single- and Multiple-dose PK Studies				
10272	PK in men	Single dose	10, 20, 30, 50, or 75mg	36
10467	PK in young women (SD and MD), young men (MD), and elderly men and women (SD and MD)	Single dose 10, 12, or 25 days	SD: 20 or 60mg MD: 2.5, 5, 10, 20, 40, or 60mg	56
Japanese Single- and Multiple-dose PK Studies				
CPH-001	PK in Japanese men (SD and MD) and women (MD)	Single dose 12 days	SD: 2.5, 5, 10, 20, or 40mg MD: 5, 10, or 20mg (men); 5 or 10mg (women)	60
CPH-002[c]	Relative bioavailability enteric-coated formulation	2 × 7 days	10 and 20mg or 20 and 30mg	42
CPH-003	PK in Japanese elderly subjects	Single dose	10mg	16
Mass Balance Study				
10477	Mass balance in healthy men	Single dose	50mg	6
Absolute and Relative Bioavailability Studies				
10982	Absolute bioavailability	Single dose	5 or 9mg i.v. or 20mg p.o.	26
123	Food effect and relative bioavailability	Single dose	20mg	24
106	Food effect and relative bioavailability	Single dose	10mg	24
13921A	Relative bioavailability, oral drops solution	Single dose	20mg	26
13138A[c]	Relative bioavailability, enteric-coated formulation	Single dose	20 and 30mg	24
13119A[c]	Food effect and relative bioavailability, enteric-coated formulation	14 days Single dose	Part A: 20 or 30mg Part B: 20mg	66
Intrinsic Factor Studies				
111	Effect of age, sex, and race	Single dose 14 days	10mg	48
114	Effect of hepatic impairment	Single dose	10mg	33
112	Effect of renal impairment	Single dose	10mg	66
Extrinsic Factor Studies – Cytochrome P450 Interaction Studies				
117	DDI (bupropion)	14 or 28 days	10mg	58
115	DDI (rifampicin)	Single dose	20mg	14
103	DDI (ketoconazole and fluconazole)	Single dose	10mg	36
11826A	DDI (omeprazole)	15 days	10mg	18
101	DDI (drug cocktail)	15 days	10mg	24
102	DDI (oral contraceptives)	21 days	10mg	26
109	DDI (warfarin)	14 days	10mg	27
113	DDI (diazepam)	21 days	10mg	44
Extrinsic Factor Studies – Other Interaction Studies				
110	DDI (ethanol)	Single dose	20 or 40mg	69
116	DDI (aspirin)	20 days	10mg	28
118	DDI (lithium)	14 days	10mg	16

CSF = cerebrospinal spinal fluid; DDI = drug-drug interaction; i.v. = intravenously; MD = multiple dose; PK = pharmacokinetics; PET = positron emission tomography; p.o. = orally; SD = single dose

a Treatment duration for co-administered drugs is in Table 1.

b Oral dose of Lu AA21004, unless otherwise indicated

c The PK data for the enteric-coated formulations are not presented in this MAA, since the sponsor is not seeking marketing authorisation for these formulations. The PK data for the IR tablet formulation that were collected in these studies are presented in Tables 2 to 4.

Table 2a: Overview of Biopharmaceutic and Clinical Pharmacology studies completed after MAA submission or ongoing as of 31 August 2013

Study	Type of Study	Lu AA21004 Treatment Duration	Dose (Oral)	Number of Lu AA21004-treated Subjects[a]	Status[b] / (Expected Date of CSR)
Relative Bioavailability					
14520A	Bioavailability (4×5mg tablets *versus* 20mg tablet)	2 single doses	20mg	30	Completed
PK and Tolerability in Children & Adolescents					
12708A	Open-label; stratified by age (7 to <12 years old; 12 to <18 years old)	14, 16, 18, or 20 days	5mg/day 10mg/day 15mg/day 20mg/day	10 6 4 –	Ongoing (Q3/2015)
Pharmacodynamic Studies					
14029A	Effect on polysomnographic parameters	2×3 days[c]	20 and 40mg	24	Completed
14137A	Effect on cognition (BOLD fMRI)	13-14 days	20mg	23	Ongoing (Q2/2014)
Chinese Single-dose PK Studies					
14077A	PK and safety in young Chinese	Single dose	10mg	16	Ongoing (Q4/2013)
Studies in the Japanese Clinical Development Programme					
CPH-004	PK and food effect in Japanese	2 single doses	10mg	20	Completed

BOLD = blood-oxygen-level-dependent; CSR = *Clinical Study Report*; fMRI = functional magnetic resonance imaging; PK = pharmacokinetics

a As of 31-Mar-2013 for ongoing studies (data cut-off date for the most recent DSUR [dated 23 May 2013])

b As of 31-Aug-2013; *Clinical Study Reports* are available for "completed" studies

c Total treatment duration was 4×3 days (including placebo and active-comparator treatment).

Table 3: Overview of Phase II / III studies (short-term)

Study nr.	APTS[1]	Type of study	Region	Main objective	Patients completed/patients withdrawn (% withdrawn in APTS)							
					VOR 1	VOR 2.5	VOR 5	VOR 10	VOR 15	VOR 20	PBO	VLF/DUL[2]
11492A	360/66 (15.5)	6-week + 1-week VOR /2-week VLF taper down	EU, CA, AU, Asia	Change from baseline in MADRS at Week 6			108/98 (10)	100/82 (18)			105/87 (18)	113/93 (18) VLF
11984A	605/161 (21)	8-week + 1-week DUL taper down	EU, CA, AU, Asia	Change from baseline in MADRS at Week 8		115/130 (16)	157/122 (22)	151/117 (22)			148/123 (27)	155/113 (27) DUL
305	505/54 (9.6)	8-week	EU, AU, Asia, ZA	Change from baseline in HAM-D24 at Week 8	140/127 (10)		140/129 (8)	140/122 (13)			140/127 (9)	
13267A	506/101 (16.6)	8-week +1-week taper up + 1-week DUL taper down	EU, ZA	Change from baseline in MADRS at Week 8					151/117 (22)	151/125 (17)	158/133 (16)	147/131 (11) DUL
315	470/144 (23.5)	8-week +1-week taper up + 1-week DUL taper down	US	Change from baseline in MADRS at Week 8					147/113 (23)	154/113 (27)	161/129 (20)	152/115 (24) DUL
316	385/77 (16.7)	8-week +1-week VOR 20 taper up	US	Change from baseline in MADRS at Week 8				155/124 (20)		150/122 (19)	157/139 (11)	
303	480/117 (19.5)	6-week	US	Change from baseline in HAM-D24 at Week 6			300/244 (19)				300/236 (21)	
304	451/152 (24.9)	8-week + 1-week DUL taper down	US	Change from baseline in HAM-D24 at Week 8		153/99 (35)	153/122 (20)				153/120 (21)	152/110 (28) DUL
12541A	392/60 (13)	8-week + 1-week DUL taper down	EU, CA, US	Change from baseline in HAM-D24 at Week 8			156/136 (13)				145/128 (11)	151/128 (15) DUL

[1] Patients completed/patients withdrawn (%withdrawn in APTS)
[2] Active comparators: VLF: venlafaxine, DUL: duloxetine

Table 4: Overview of Phase II/III studies (long-term)

Study nr.	APTS[1]	Type of study	Region	Main objective	Patients completed/patients withdrawn (% withdrawn in APTS)						
					VOR 1	VOR 2.5	VOR 5 / VOR 10	VOR 15	VOR 20	PBO	VLF/DUL[2]
11985A Part A	492/147 (23)	12-week open label flexible dose	EU, AU, Asia, ZA	Time to relapse			639/492 (23)			-	-
Part B	229/171 (43)	24-64-week double blind fixed dose	EU, AU, Asia, ZA	Time to relapse			204/125 (39)			192/104 (46)	-
11492C	54/20 (27)	52-week Flexible dose	EU, CA, AU, Asia	(*Long-term safety*)			74/54 (27)			-	-
11984B	328/207 (39)	52-week Flexible dose	EU, CA, AU, Asia	(*Long-term safety*)			535/328 (39)			-	-
301	526/310 (37)	52-week Flexible dose	EU, AU, Asia, ZA, US	(*Long-term safety*)			836/526 (37)			-	-

[1]Patients completed/patients withdrawn (%withdrawn in APTS)
[2]Active comparators: VLF: venlafaxine, DUL: duloxetine

Table 5: Overview of phase III studies in MDD completed between MAA submission and 31 August 2013

Study	Study Design and Duration	Number of Patients in Safety Population			CSR Issue Date
		PBO	Lu AA21004	AGO	
Short-term Studies					
317	Randomised, DB, parallel-group, PBO-controlled, fixed-dose[a] (10 or 15mg/day) 8 weeks	160	10mg: 154 15mg: 151	–	30-Aug-2012
14122A	Randomised, DB, parallel-group, PBO-controlled, fixed-dose[a] (10 or 20mg/day) 8 weeks	196	10mg: 195 20mg: 207	–	21-Aug-2013
14178A	Randomised, DB, parallel-group, active-comparator (AGO 25 or 50mg/day), flexible-dose[b] (10 or 20mg/day) 12 weeks	–	10/20mg: 253	242	05-Jul-2013
Open-label Extension Studies					
13267B	Open-label, flexible-dose[c] (15 or 20mg/day), 1-year extension study (to Study 13267A)	–	71	–	28-Jun-2013
Short-term Studies in the Japanese Clinical Development Programme					
CCT-002[d]	Randomised, DB, parallel-group, PBO-controlled, fixed-dose[a] (5, 10, or 20mg/day) 8 weeks + 2-week discontinuation period[e]	151	5mg: 144 10mg: 148 20mg: 150	–	11-Apr-2013

AGO = agomelatine; CSR = *Clinical Study Report*; DB = double-blind; PBO = placebo

a Patients on Lu AA21004 15 or 20mg/day received Lu AA21004 10mg/day during the first week.
b Patients on Lu AA21004 received a fixed dose (10mg/day) during the first week; patients on agomelatine received a fixed dose (25mg/day) during the first 2 weeks.
c Fixed dose (10mg/day) during the first week. Thereafter, the dose was increased to 15 or 20mg/day.
d Including patients from Japan, other parts of Asia, and Europe
e All patients received placebo during the discontinuation period.

Table 5a: Overview of Phase III studies (ongoing) as of 31 August 2013

Study	Study Design and Duration	Number of Patients Enrolled[a]	Expected Date of CSR
Short-term Studies			
202	Randomised, DB, parallel-group, PBO-controlled, active-reference (DUL 60mg/day), flexible-dose[b] (10 or 20mg/day) 8 weeks + 1-week DB down-taper[c]	320	Q4/2014
13926A	Randomised, DB, parallel-group, active-comparator (VLF extended release 150mg/day), fixed-dose (10mg/day) 8 weeks + 1-week DB down-taper[d]	170	Q1/2014
318	Randomised, DB, parallel-group, active-comparator (ESC 10 or 20mg/day), flexible-dose[e] (10 or 20mg/day) 8 weeks + 1-week DB down-taper[f]	331	Q2/2014
Open-label Extension Studies			
314	Open-label, flexible-dose[g] (15 or 20mg/day), 1-year extension study (to Studies 315, 316, and 317)	1073	Q4/2013
Studies in the Japanese Clinical Development Programme			
CCT-003[h]	Randomised, DB, parallel-group, PBO-controlled, fixed-dose (5 or 10mg/day) 8 weeks + 2-week discontinuation period[i]	366	Q4/2013
OCT-001[h]	Open-label, flexible-dose[j] (5, 10, or 20mg/day), 1-year extension study (to Study CCT-003)	119	Q4/2014

CSR = *Clinical Study Report*; DB = double-blind; DUL = duloxetine; ESC = escitalopram; PBO = placebo; VLF = venlafaxine

2.4.2. Pharmacokinetics

Introduction

The pharmacokinetic properties of vortioxetine have been characterised across studies using both non-compartmental pharmacokinetic analysis and population PK analysis.

The clinical pharmacology package for vortioxetine consists of 10 human biomaterial studies and 31 clinical pharmacology studies evaluating the pharmacokinetics and/or pharmacodynamics of vortioxetine in humans.

In the 31 clinical pharmacology studies, 1169 subjects received vortioxetine: 1120 healthy subjects (of whom 48 were elderly aged 65 to 78 years), 16 subjects with hepatic impairment, and 33 subjects with renal impairment.

Three additional studies (Studies 14029A, CPH-004 and Study 14520A) had been completed as of 31 August 2013.

The pharmacokinetics of vortioxetine have been evaluated following oral administration of immediate release (IR) tablets in single doses of 2.5 to 75mg and multiple doses of 2.5 to 60mg/day. In addition, an intravenous formulation, an oral drops solution, oral solutions, and two alternative experimental enteric-coated tablet formulations have been administered in the clinical pharmacology studies. Pharmacokinetic data for the enteric-coated formulations are not presented in this Marketing Authorisation Application, since the sponsor is not seeking marketing authorisation for these formulations. However, the pharmacokinetic data for the IR tablet formulations collected in those studies are included in the population pharmacokinetic analysis, and in the pooled descriptive statistics of the non-compartmental pharmacokinetic parameters.

The effect of intrinsic factors (race, gender, age, hepatic and renal impairment, CYP450 genotype) has been investigated by the applicant.

Multiple pharmacokinetic and pharmacodynamic drug-drug interaction studies have been conducted to evaluate the effect of other compounds on vortioxetine as well as the effect of vortioxetine on other compounds.

Two population pharmacokinetic analyses have been performed for vortioxetine: one analysis used data from 26 clinical pharmacology studies and a second analysis was performed on the more sparse pharmacokinetic data that were obtained in patients with Major Depressive Disorder (MDD) or Generalised Anxiety Disorder (GAD) in 12 phase II/III clinical efficacy and safety studies. Subsequently, pharmacokinetic/pharmacodynamic (PK/PD) analyses were conducted to assess the relationships between exposure and efficacy/tolerability for vortioxetine in patients with MDD.

The analytical methods used to analyse vortioxetine and its major metabolites have been well described. Justification for the absence of ISR in pivotal Studies 10272 and 11492A has been provided based on the document ‘Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party’ (EMA/618604/2008 Rev. 7). It was concluded that all bioanalytical methods used were reliable for the detection of the compounds of interest.

Absorption

Vortioxetine is highly soluble in aqueous media. Taking into account the high intestinal permeability suggested by the mass balance study, vortioxetine could be categorized as a Class I (highly soluble, highly permeable) drug according to the BCS classification system.

Vortioxetine is slowly absorbed after oral administration of IR tablets or solution. Following single and multiple oral doses of 5, 10, or 20mg (IR tablets), median t_{max} values of 7 to 11 hours were observed. The reported absolute bioavailability (BA) was approximately 75%. The administration of 20 mg vortioxetine did not have a statistically significant effect on gastric emptying, but did have a statistically significant pro-kinetic effect on small intestinal transit and subsequent colon arrival (mean decrease of approximately 1 to 2 hours depending on the radioactive marker and time of measurement).

Differences in AUC and tmax across studies are still within the acceptable ranges and these differences have no implications on the conclusions of the individual studies.

Bioequivalence (BE) of the tablets used in early development stage as well as in the pivotal clinical studies and those intended for marketing could be considered demonstrated. In addition, no difference in absorption is expected for the different strengths of the to-be-marketed formulation. The food effect has been explored during two studies (of which two with the formulation intended to be marketed); results indicated that there is no effect of food on the pharmacokinetics of vortioxetine.

Distribution

Following single and multiple doses of vortioxetine, the estimated volume of distribution (Vz/F) is approximately 2500 to 3400 L, which indicates extensive extravascular distribution of vortioxetine. Vortioxetine binds extensively (>98%) to plasma proteins in vitro and appears to be independent from the plasma concentrations. In addition, ex vivo protein binding experiments using samples from subjects with hepatic or renal impairment showed that no difference could be observed in comparison with healthy subjects.

The in vitro plasma protein binding of Vortioxetine and Lu AA34443 in human plasma was investigated in Studies 12287 and 14179 and was found to be independent of concentration in the ranges of 10 to 12000ng free base/mL (Vortioxetine) and 5 to 4500ng free base/mL (Lu AA34443). At steady state, the Cmax in humans following 20mg Vortioxetine is approximately 33 ng/mL for both compounds. Therefore, it is not likely that the binding sites are saturated at these concentrations and, consequently, displacement of one of the compounds by the other, or by other drugs, is unlikely.

Elimination

The estimated total plasma clearance of vortioxetine was approximately 500 to 670 mL/min. The mean half-life was estimated to 60 to 70 hours following single and multiple doses of vortioxetine. Because of its long elimination half-life, the risk of PK interactions can persist for several days or even weeks after vortioxetine withdrawal. However, as vortioxetine did not show any relevant potential for inhibition or induction, this is not a concern.

The mass balance study indicated that the mean recovery of ^{14}C-radioactivity was 85% in 360 hours, with approximately 59% excreted in the urine and 26% in faeces. Vortioxetine and radioactivity levels declined with similar rates. The extent of systemic exposure to vortioxetine, based upon mean AUC_{0-t}, accounted for approximately 13% of the total exposure to radioactivity in plasma. Furthermore, the combined extent of systemic exposure to vortioxetine and Lu AA34443 accounted for approximately 27% of the total exposure to radioactivity in plasma. Vortioxetine is extensively metabolised and the major biotransformation pathway seem to be oxidation to the major metabolite, Lu AA34443 followed by glucuronic acid conjugation.

As approximately all radioactivity could be attributed to vortioxetine and the identified metabolites, there is no risk for unidentified metabolites potentially impairing the safety profile of vortioxetine.

From the results of the mass balance study it is clear that the pathway leading to Lu AA34443 and subsequently to its glucuronide is by far the major one. The three other pathways are minor ones, contributing to only 3% of the metabolism of vortioxetine.

A large number of enzymes (CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8, and CYP2B6) can catalyse the clearance of vortioxetine in CYP2D6 PMs.

In vitro experiments indicated that several CYP isoenzymes are involved in the metabolism of vortioxetine: CYP2D6, CYP2C9, CYP3A4/5, CYP2A6, CYP2C8, CYP2C19, CYP2B6. Also UGT is playing a role in the conjugation reactions of vortioxetine metabolites.

Genotyping for CYP2D6, CYP2C9, and CYP2C19 alleles was performed in most of the clinical pharmacology studies to evaluate the potential relationship between the inferred metabolic status and the pharmacokinetics of vortioxetine. In general, although not consistent, the poor metabolisers (PMs) for CYP2D6 showed the highest AUC values for vortioxetine and the lowest for Lu AA34443. In addition, a 47% lower CL/F in CYP2D6 PMs than in Ems (extensive metaboliser) has been observed. The approximately 2-fold higher vortioxetine exposure in CYP2D6 PMs does not translate into significant changes in the safety and tolerability profile of vortioxetine relative to that in CYP2D6 EMs according to the applicant. However, the frequency of some adverse effects is doubled in the PM group versus EM group, like for dizziness and pruritus and the DDI study with bupropion showed a higher incidence of adverse events due to the 2-fold higher vortioxetine exposure when bupropion was added to vortioxetine in steady state.

It is the Applicant's view that Vortioxetine is well tolerated. The majority of the adverse events were transient and *mild* or *moderate*. A subgroup analysis showed no clinically relevant differences in the tolerability profiles between the overall population and healthy subjects genotyped as CYP2D6 PMs or patients categorised as low-clearance patients (covering exposure in CYP2D6 PMs) based on their pharmacokinetic data. The incidences of nausea, vomiting, and insomnia were not higher in the subpopulations categorised as low clearance patients.

Hence, the overall dose recommendations in the product information seem adequate, that is, a recommended dose of 10mg with a possibility of a reduction to 5mg based on individual patient response. As a consequence, CYP2D6 genotyping/phenotyping, changes in titration, or therapeutic drug monitoring are not considered to be of clinical relevance. The currently recommended dose regimen is considered both appropriate and manageable for the prescriber.

In the population pharmacokinetic analysis in healthy subjects (*Population Pharmacokinetics of Vortioxetine in Healthy Subjects* [PopPK phase I]), the oral clearance for CYP2D6 ultra-rapid metabolizers (UMs) was estimated to 52.9L/h compared to 34.1L/h for CYP2D6 EMs, which gives a ratio of 1.55. Consequently, the CYP2D6 UMs will have a 36% lower Vortioxetine exposure than CYP2D6 EMs. For a starting dose of 10mg, CYP2D6 UMs will, in general, still have exposure levels above those expected in CYP2D6 EMs following the therapeutic dose of 5mg Vortioxetine. The CHMP agreed that in CYP2D6 UMs, the exposure levels are still sufficient for an adequate efficacy. Concerning safety, an analysis of tolerability *versus* exposure in the MDD Short-term studies was conducted dividing the patients into 3 groups based on their clearance of Vortioxetine. High-clearance patients were defined as the 10% of patients with the lowest exposure (covering exposure in UMs) and their overall tolerability was the same as the other groups of metabolisers.

No clinically significant changes in exposure are observed in relation with the CYP2C19 and CYP2C9 inferred metabolic status.

Dose and time dependency

There was an approximately dose-proportional increase in AUC and C_{max}, over the range of single dose 2.5 – 75 mg/day and multiple dose 2.5 – 60 mg/day both in single dose as in multiple dose settings. The accumulation index (AI) for vortioxetine (based on AUC_{0-24h}) was estimated to be 5 to 6 following multiple doses of 5 to 20 mg/day, which is consistent with its long half-life. Steady state is reached after approximately 12 days of once daily administration of vortioxetine. No time dependency has been observed for the other pharmacokinetic parameters of vortioxetine.

Variability

The pharmacokinetics of vortioxetine are characterised by a moderate inter-individual and a low intra-individual variability.

Pharmacokinetics in target population and population PK studies

Two population pharmacokinetic analyses have been performed using data from healthy subjects and from patients with MDD or GAD. The goal of the analysis was to develop a population pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) models (efficacy/safety) for vortioxetine following oral administration of 1- 20 mg doses of vortioxetine in patients with MDD and GAD.

In the PopPK/PD phase III, in patients, the final covariate model included height and creatinine clearance as significant covariates for the oral clearance. However, the effect on the pharmacokinetics of Vortioxetine was not considered clinically relevant. Region for study conduct (Europe, United States, or rest of the world [RoW]) was a significant covariate for the oral clearance. The oral clearance estimate, its inter-individual variability, and frequency of samples below the lower limit of quantification (LLOQ) were higher in the United States than in Europe and in the RoW (*Population Pharmacokinetic/Pharmacodynamic Analysis of Vortioxetine in Patients with Major Depressive Disorder or Generalized Anxiety Disorder).* In addition, the proportion of samples with non-quantifiable concentrations (below the LLOQ) were 3%, 15%, and 5% in Europe, the United States, and the RoW, respectively.

According to the applicant, these findings cannot be explained by differences in demographic factors (weight, BMI, or CrCL) and indicate a higher rate of non-compliance in studies conducted in the United States compared to those conducted in Europe or RoW. In contrast, in the phase I population pharmacokinetic analysis, region was not identified as a significant covariate, which further support that the regional difference found in patients is most likely due to the less controlled study conditions in the patient studies.

Based on the population pharmacokinetic analyses, the pharmacokinetics of vortioxetine was similar in healthy subjects and in patients with MDD or GAD.

Special populations

• Renal impairment

Vortioxetine is almost completely cleared by metabolism. According to the results from study 112, the effects of renal impairment (mild, moderate, severe, or ESRD) on the pharmacokinetics of vortioxetine after single dose are not considered clinically meaningful. The CHMP agrees that the observed effects of renal impairment on the pharmacokinetics of vortioxetine after single dose are not altered to such an extent that the dosage should be adjusted.

With regard to the significant accumulation of vortioxetine, the applicant has justified the choice of a single dose to study renal impairment and has discussed the potential consequences of a multiple dose vortioxetine administration in patients with renal impairment. The applicant's answer was endorsed. According to the EMA Guidelines on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic and renal functions, a single dose study is sufficient when the product exhibits linear and time-independent pharmacokinetics.

There is an accumulation ratio index of 5 to 6 following multiple doses of 5 to 20 mg/day for vortioxetine AUC0-24h but this does not lead to a time-dependent PK as the parameters *CL* and V_{ss} do not change with time. This accumulation ratio is added in section 5.2. The differences in exposure after single dose are low and no clinically relevant differences are expected after multiple dose administration.

• Hepatic impairment

Even though vortioxetine is extensively metabolised, no clinically meaningful effect of mild or moderate hepatic impairment was observed on the pharmacokinetics of Vortioxetine after single dose.

The applicant has correctly justified the choice of a single dose study and discussed the potential consequences of a multiple dose vortioxetine administration in patients with hepatic impairment.

The extent of effects of hepatic impairment on the main metabolites are, somewhat, lesser than expected. However, the effects of hepatic impairment on vortioxetine are not in line with the results of the other studies of the pharmacology program. The mass balance study implied elimination by almost complete hepatic metabolisation and renal excretion of the metabolites. Consequently an increase of the extent of exposure for vortioxetine would have been expected, but the AUC and Cmax remain unchanged or are slightly even lowered for both hepatic impairment groups. The Applicant acknowledges that the lack of influence of hepatic insufficiency on the pharmacokinetics of Vortioxetine and the metabolites Lu AA39835 and Lu AA34443 may appear unexpected. There is no obvious explanation for the lack of increase in Vortioxetine exposure in the hepatic impairment groups.

The severity of hepatic impairment has been adequately described by the applicant in the context of Child-Pugh score for subjects included in study 114**.** There was no obvious correlation between the pharmacokinetic parameters and the Child-Pugh score.

The patients with severe hepatic impairment were not studied. In these patients, a clinically significant increase of exposure to vortioxetine and/or their metabolites cannot be ruled out. Caution should be exercised when prescribing to patients with severe hepatic impairment. This is well mentioned in sections 4.2, 4.4, of the SmPC and section 5.2 of the SmPC.

● Gender

Gender differences exist in the PK of antidepressants in men and women. Reduced expression and inhibition of many of the phase I enzymes necessary for the metabolism of antidepressants has been shown to result in higher serum levels of antidepressants in women. In terms of physiological differences, women have a generally lower body weight and organ size and a higher percentage of fat, factors which are known to affect distribution.

In study n°10467, the exposure to vortioxetine seemed to be slightly higher in women than in men following multiple doses of 40mg/day but the results are inconclusive based on the limited data from this study. According to the applicant, the small differences in exposure to vortioxetine may be attributed to the difference in body weight between men and women (men weights ranged from 62 to 105 kg compared to 47 to 85 kg for women) and this gender-related difference was no longer significant after weight correction.

In study CPH-001, there were no consistent differences in the exposure or CLr between male and female subjects. In study n°111, following single doses, the AUC0-t and Cmax of Vortioxetine were 18% and 16% higher, respectively, in women than in men. Following multiple doses, the AUC0-24h and Cmax of Vortioxetine were 27% and 24% higher, respectively, in women than in men.

In the phase I population pharmacokinetic analysis, sex was not a significant covariate in the final model. The modest, sex-related increases in Vortioxetine exposure in Study 111 are not considered clinically meaningful by the applicant.

It can be concluded that no clinically relevant changes related to sex were observed for vortioxetine, neither in the non-compartmental studies, neither in the POP PK analysis. The modest, sex-related increases in Vortioxetine exposure in Study 111 are not considered clinically meaningful.

● Race

Since CYP2D6 is the main isoform responsible for the metabolism of vortioxetine and the prevalence of the various phenotypes and genotypes are different among different ethnic groups (African, Hispanic and Asian populations), the possible effects of race on the pharmacokinetics of vortioxetine were considered.

In study n°111, following multiple doses, the AUC0-24h and Cmax of Vortioxetine were 25% and 33% higher, respectively, in Black subjects than in White subjects.

In study n° 12260A, following multiple doses, AUC0-24h and Cmax of Vortioxetine were slightly higher (8% and 9%, respectively) in Japanese subjects than in Caucasian subjects.

The CHMP agrees that no clinically meaningful changes in Vortioxetine exposure related to race or ethnicity were observed in Study n°12260A (Asian population) and in study n°111 (black versus white).

However, when we compare the PK parameters across studies of the both phase I ascending dose studies CPH001 and 10272, carried out respectively in Japanese healthy subjects and in a majority of Caucasians (46 except 3 Asian and 5 Black men), a higher exposure (1.6 fold) is observed in Japanese subjects after 20 mg single dose. The applicant justifies this observation by the considerable differences in body weights among subjects (in Study 10272 body weights varied between 60 and 100 kg, in Study CPH-001 values ranged between 51 and 79 kg).

The phase I population pharmacokinetic analysis suggested that race or ethnicity (including Japanese versus non-Japanese, Black versus non-Black, and Hispanic versus non-Hispanic) did not have any significant impact on the pharmacokinetics of Vortioxetine (PopPK phase I). No clinically meaningful changes in Vortioxetine exposure related to race or ethnicity were observed.

● Body weight

According to the phase I population pharmacokinetic analysis, body size does not have any clinically meaningful effect on the exposure to Vortioxetine.

Since Vortioxetine is lipophilic and has a large volume of distribution, the applicant discussed the clinical relevance of the influence of body weight on vortioxetine clearance, exposure and volume of distribution.

In the population pharmacokinetic analysis in healthy subjects (*Population Pharmacokinetics of Vortioxetine in Healthy Subjects* [PopPK phase I]), central volume of distribution was significantly related with height, weight, and lean body mass (LBM), but not with BMI. Oral clearance was significantly related with height. In the final population pharmacokinetic model, only the relationship between height and volume of distribution remained in the model. Since weight, LBM, and height are all heavily correlated, especially for subjects participating in phase I studies with narrow inclusion ranges, the inclusion of the most significant of them in the model often leaves the other ones out. The central volume of distribution increased with 17L for every cm increase in height. For Subject A, with a height of 155cm, and Subject B, with a height of 187cm, the model predicted V2 values of 1760 and 2320L, respectively. In terms of exposure, Subject A will have a 5% higher Cmax and AUC0-24h at steady state than the population mean (the average subject). Subject B will have a 4% lower Cmax and AUC0-24h than the population mean. The impact of height, weight, and/or LBM on the central volume of distribution, and thereby on exposure, is not considered clinically relevant.

In the final population pharmacokinetic model for patients with MDD/GAD (*Population Pharmacokinetic/Pharmacodynamic Analysis of Vortioxetine in Patients with Major Depressive Disorder or Generalized Anxiety Disorder* [PopPK/PD phase III]), a significant relationship was found between height and oral clearance. Relative to a typical patient with a height of 166cm, patients are not expected to have greater than a ±17% difference in exposure to Vortioxetine at steady state over the range evaluated (153 to 184cm), based on a simulated dose of 10mg/day of Vortioxetine.

Hence, as assessed in the population pharmacokinetic analyses, both in healthy subjects and in patients with MDD/GAD, the impact of height, weight, and/or LBM on the central volume of distribution and oral clearance, and thereby on exposure, is not considered clinically relevant. Based on this, it can be concluded that the benefit/risk is unchanged in these groups.

In general, there was very good agreement between the pharmacokinetic parameter values estimated by population pharmacokinetic analysis and those estimated by non-compartmental analysis (NCA). Following single and multiple doses of Vortioxetine, the volume of distribution (Vz/F) was estimated to approximately 2500 to 3400L using NCA. The extensive distribution of Vortioxetine was confirmed in the phase I population pharmacokinetic analysis, in which the sum of the volumes of distribution in the central (V2/F) and peripheral (V3/F) compartments was approximately 2600L. Using NCA, the estimated CL/F of Vortioxetine was approximately 30 to 40L/h and the t½ was estimated to 60 to 70 hours following single or multiple doses of Vortioxetine. In the phase I population pharmacokinetic analysis, the overall population mean CL/F was estimated to 33L/h and the t½ was 66 hours. The applicant's argumentation is mainly based on the population PK model in volunteers and patients with MDD/GAD and can be considered as sufficient to conclude that the impact of height and weight on the central volume of distribution is not considered clinically relevant.

● Age

Antidepressants being among the most commonly prescribed medicinal products for older agents, age-related changes in drug PK parameters should be adequately investigated. In general, PK changes that accompany aging result in higher and more variable plasma drug concentrations.

For vortioxetine, Cmax was 23% higher and AUC0-24h was 27% higher in elderly than in young subjects on day 28 in study n°111. Based on the results of the non-compartmental studies and the phase I population PK analysis, the modest age-related increases in Vortioxetine exposure, are not considered clinically meaningful by the applicant.

However, the applicant was asked to provide a stratification based on age to evaluate the impact of age on PK parameters in the three ranges of age (65-74), (75-84) and 85+ and to provide the proportion of very elderly (> 85 –year old) subjects. As no data was available on this population, it was asked to add in the SmPC that caution should especially be done when vortioxetine is administered in patients of more than 85 years of age.

In the population pharmacokinetic analysis in healthy subjects (*Population Pharmacokinetics of Vortioxetine in Healthy Subjects* [PopPK phase I]), age was treated as a continuous covariate and a significant relation was found between CL/F and age. For every year increase in age, CL/F decreased by 0.28L/h. No healthy subjects >85 years were included in the clinical pharmacology studies.

Four patients >85 years (3 women, 1 man) received 5 or 10 mg/day Vortioxetine in the short-term placebo-controlled studies. In these patients, treatment was well tolerated and none of them prematurely discontinued treatment or reported serious adverse events during the study. Pharmacokinetic data are available for two of the patients, both receiving 5mg/day Vortioxetine. Due to the limited data available, the impact of age on the pharmacokinetics cannot be evaluated for patients >85 years. For information, the individual CL/F values in these 2 patients were 14 and 21L/h.

The Product information reflects in section 5.2 the following: In elderly healthy subjects (aged ≥65 years; n=20), the exposure to vortioxetine increased up to 27% (C_{max} and AUC) compared to young healthy control subjects (aged ≤45 years) after multiple doses of 10 mg/day. The lowest effective dose of 5 mg vortioxetine once daily should always be used as starting dose in patient's ≥ 65 years (see section 4.2). However, caution should be exercised when prescribing to elderly patients at doses higher than 10 mg vortioxetine once daily

Section 4.2 also reflects the following statement: *Caution is advised when treating patients' ≥ 65 years of age with doses higher than 10 mg vortioxetine once daily for which data are limited*

No pharmacokinetic studies in children have been carried out. BRINTELLIX is not recommended for the treatment of depression in patients under 18 years of age since safety and efficacy of BRINTELLIX have not been established in this age group.

An agreed-upon Paediatric Investigational Plan for vortioxetine is in place (PIP number: EMEA-000455-PIP02-10-M01).

● Metabolic status

Genotyping for CYP2D6, CYP2C9 and CYP2C19 alleles was performed in most of the clinical pharmacology studies to evaluate the potential relationship between the inferred metabolic status and the pharmacokinetics of vortioxetine, since these three CYP isozymes are involved in the metabolism of vortioxetine.

There is no specific PK study comparing the PK profiles in CYP2D6 poor and extensive metabolisers. A potential effect of inferred metabolic status for CYP2D6, CYP2C19, and CYP2C9 was assessed in the phase I population pharmacokinetic analysis. The approximately 2-fold higher Vortioxetine exposure in CYP2D6 PMs does not translate into clinically significant changes in the safety and tolerability profile of Vortioxetine relative to that in CYP2D6 EMs (see discussion above).

Drug-drug Interactions

Vortioxetine is metabolized by multiple cytochrome P-450s and has little inhibition or induction effect on the CYP system. Vortioxetine has therefore a low potential for clinically relevant interactions with other drugs.

Effect of other compounds on the Pharmacokinetics of Vortioxetine

For bupropion (Study 117), rifampicin (Study 115), ketoconazole, and fluconazole (for AUC only) (Study 103), the 90% CIs for Cmax and AUC were outside the limits of 80% to 125%.

The approximately 2-fold increase in Vortioxetine exposure following co-administration with a strong CYP2D6 inhibitor (bupropion) is comparable to the higher exposure in CYP2D6 PMs, relative to CYP2D6 Ems. These observations are reflected in the SmPC where it is mentioned that depending on individual patient response, a lower dose of vortioxetine may be considered if strong inhibitors are added to vortioxetine treatment.

According to the guideline on the Investigation of Drug Interactions, CPMP/EWP/560/95/Rev1 –Corr*, if the interaction study with the strong inhibitor results in a marked effect on the exposure of the investigational drug, potentially leading to dose adjustments, an additional study with a moderate inhibitor of the enzyme is recommended in order to support the evaluation of the need for specific treatment recommendations for other inhibitors of the enzyme. In this context, the applicant was asked to discuss the necessity to include the moderate CYP2D6 inhibitors in the recommendations in section 4.2. The CHMP agrees with the applicant's answer that the interaction study with the strongest CYP2D6 inhibitor bupropion does not result in a marked effect on the exposure of the investigational drug: AUC0-24h was 2.3-fold higher and Cmax was 2.1-fold higher following co-administration with bupropion. To be noted, according to the Guideline on the Investigation of Drug Interactions, CPMP/EWP/560/95/Rev. 1 Corr*, June 2012, Appendix VIII, a strong inhibitor causes a > 5 fold increase in the plasma AUC values or ≥ 80% decrease in oral clearance, a moderate inhibitor causes a > 2 fold increase in the plasma AUC or 50-≤80% inhibition of oral clearance, a mild inhibitor causes 1.25 to 2 fold increase in the plasma AUC or ≤ 50% inhibition of oral clearance. For information, the US FDA recommends dosage adjustments if there is a ≥ 2-fold increase in AUC.

The applicant mentioned adequately in the SmPC section 4.2 that depending on individual patient response, a lower dose of Brintellix may be considered if strong CYP2D6 inhibitors (e.g. bupropion, quinidine, fluoxetine, paroxetine) are added to Brintellix treatment.

Rifampicin induces CYP3A4, CYP2C19, and CYP2C9, which results in the formation of metabolites other than Lu AA39835 and Lu AA34443 and in a reduction of the Vortioxetine concentration. Lu AA39835 and Lu AA34443 are mainly formed by CYP2D6, which is a non-inducible enzyme. The decreasing exposure to these metabolites is caused by the reduced amount of Vortioxetine available for metabolism to Lu AA39835 and Lu AA34443.

An increase in Lu AA39835 concentration following fluconazole inhibition (CYP2C9, CYP2C19, and CYP3A4) is expected, since CYP2C9 only plays a minor role in the formation of Lu AA39835 and since the Vortioxetine concentration increases 30 to 40% due to inhibition of other metabolic pathways dependent on CYP3A4, CYP2C19, or CYP2C9. The higher concentrations of Vortioxetine are then metabolised by the major enzyme catalyzing the formation of Lu AA39835, that is, the uninhibited CYP2D6 enzyme, which results in higher concentrations of Lu AA39835.

In conclusion, the results of the CYP induction and inhibition studies are expected and the metabolism of Vortioxetine is considered to be well understood.

The combined treatment with antidepressant and antiepileptic drugs is frequently reported in both neurologic and psychiatric practice. Antiepileptics like carbamazepine and phenytoin are also inducers. Drug inducers such as carbamazepine may theoretically increase vortioxetine clearance, being metabolized by CYP3A4. Phenytoin being CYP2C9 inducer, it can also theoretically increase vortioxetine clearance, being partly metabolized by CYP2C9.
Even if not anticipated by the applicant, a DDI could not be excluded with these other antiepileptic inducers. Therefore, as required by the RAP, the applicant proposes adequately to add carbamazepine and phenytoin in section 4.5 and in section 4.2.

Co-administration of vortioxetine with multiple doses of a CYP3A4/5 and P-gp inhibitor (ketoconazole) or a CYP2C19, CYP2C9, and CYP3A4/5 inhibitor (fluconazole) led to increases of 30% and 46% for AUC0-t and 26% and 15% for Cmax of vortioxetine, respectively. Ketoconazole and fluconazole, two antifungal agents, are potent inhibitors of CYP3A and CYP2C9/C19 enzyme subtypes, respectively. Administration of ketoconazole results in significant interaction with drugs metabolized by CYP3A and is generally recommended as an inhibitory probe for that enzyme. Its investigation is therefore fully endorsed. In the same way, fluconazole is an adequate inhibitory probe for CYP2C9. The applicant mentions correctly in section 4.5. of the SmPC that when vortioxetine was co-administered following 6 days of ketoconazole 400 mg/day, a 1.3-fold increase in vortioxetine AUC was observed and that no dose adjustment is needed. The same statement is added for the co-administration of fluconazole 200mg/day with a 1.5-fold increase in AUC.

CYP2C19 is involved in the metabolism of several important groups of drugs including many proton pump inhibitors. The DDI study with omeprazole (CYP2C19 inhibitor and substrate) indicates adequately that its co-administration with vortioxetine does not affect the PK of vortioxetine.

No pharmacokinetic interaction was observed following co-administration of aspirin and vortioxetine. Co-administration of a single dose of ethanol had no effect on the pharmacokinetics of Vortioxetine.

In vivo results demonstrating an absence of interaction should only be mentioned in section 4.5 if this is of major importance to the prescriber. As required by RAP, the absence of effect of omeprazole (CYP2C19 inhibitor), aspirin and ethanol on the pharmacokinetics of vortioxetine has been added in section 4.5 (Potential for other medicinal products to affect vortioxetine).

Effect of Vortioxetine on the Pharmacokinetics of other Compounds

No substantial effect on the pharmacokinetics of the cocktail components (caffeine, tolbutamide, dextromethorphan, and midazolam) was observed following multiple doses of 10mg/day Vortioxetine. This indicates that Vortioxetine is not an inhibitor or inducer of CYP1A2, CYP2C9, CYP2D6, or CYP3A4/5. This simultaneous administration of a mixture of substrates of multiple CYP enzymes in one study (i.e. cocktail approach) to evaluate the drug's inhibition or induction potential is adequate. The negative results observed for this study eliminate the need for further evaluation of particular CYP enzymes. Moreover, co-administration of multiple doses of vortioxetine and warfarin confirms that Vortioxetine is not an inhibitor or inducer of CYP2C9, as already observed in the "cocktail approach" study.

The DDI study with diazepam (CYP2C19 substrate) indicates adequately that Vortioxetine is not an inhibitor or inducer of CYP2C19 either. Co-administration of multiple doses of Vortioxetine with omeprazole, CYP2C19 substrate and inhibitor, had no effect on the pharmacokinetics of omeprazole, confirming that Vortioxetine is not an inhibitor or inducer of CYP2C19.

Co-administration of Vortioxetine is not anticipated to have an impact on the efficacy of the COC.

The effects of vortioxetine on the pharmacokinetics of ethanol, aspirin, and lithium have also been evaluated. No pharmacokinetic interaction was observed following co-administration of these drugs and Vortioxetine.

The potential for drug interactions with metabolites of vortioxetine has been investigated. In vitro, the metabolites did not show any potential for clinically meaningful CYP inhibition for any of the CYP isozymes tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5). In addition, the major metabolite Lu AA34443 did not induce CYP enzyme activity in vitro for any of the CYP isozymes tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5).

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism of action of vortioxetine responsible for its antidepressant effect is based on preclinical studies. In vitro studies indicate that vortioxetine is a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist, and an inhibitor of the 5-HT transporter.

Thus, the mechanism of action of vortioxetine is thought to be a combination of 2 pharmacological modes of action: direct modulation of receptor activity and inhibition of the serotonin transporter.

In humans, two positron emission tomography (PET) studies have been conducted using 5-HT transporter ligands (11C-MADAM or 11C-DASB) to quantify the 5-HT transporter occupancy in the brain across different dose levels. The mean 5-HT transporter occupancy in the raphe nuclei was approximately 50% at 5 mg/day, 65% at 10 mg/day and increased to above 80% [lower limit 95% CI; upper limit 95% CI] at 20 mg/day.

Primary and Secondary pharmacology

• Primary pharmacodynamics

The primary pharmacodynamics of vortioxetine are poorly understood since the observations from *in vitro* and animal studies could not be replicated in humans.

Pharmacodynamic biomarkers such as serotonin in platelets, whole blood and CSF, serum cortisol, serum prolactin, body temperature, and pupil size were explored to investigate the effects of vortioxetine on the 5-HT_1A receptor and the serotonin transporter (5-HTT). Some inconclusive effects were observed, without a clear dose dependency.

In humans, two positron emission tomography (PET) studies have been conducted using 5-HT transporter ligands (^{11}C-MADAM or ^{11}C-DASB) to quantify the 5-HT transporter occupancy in the brain across different dose levels. The mean 5-HT transporter occupancy in the *raphe nucle*i was approximately 50% (40-70% range) at 5 mg/day, 65% (31-83% range) at 10 mg/day and increased to above 80% (71-97% range) at 20 mg/day.

• Secondary pharmacodynamics

In pharmacodynamic studies using healthy subjects, vortioxetine 10 and 40 mg did not have a clinically meaningful effect on cardiac repolarisation. Vortioxetine did not impair on-the-road driving

performance, nor impair the cognitive function or psychomotor skills in healthy subjects using a battery of pharmacodynamic tests assessing various cognitive domains.

2.4.4. Discussion on clinical pharmacology

The pharmacodynamic profile of vortioxetine has been thoroughly investigated, however the pharmacodynamics of antidepressants is not well established and validated biomarkers are lacking. Shortcomings in our basic knowledge of the mechanisms underlying changes in binding potential currently impede the application of PET scans to measure regional changes in endogenous neurotransmitters, evoked by challenges that could alter synaptic neurotransmitter concentration.

Hence, the mode of action of vortioxetine remains largely elusive.

Vortioxetine had no influence on driving performance in healthy young subjects. However, whether vortioxetine affects driving performance in depressed patients, in particular upon long-term treatment, is currently unknown.

The panel of clinical drug-drug interactions (DDI studies) investigating the potential effects of vortioxetine on the pharmacokinetics of other compounds and conversely the potential effects of other compounds on the pharmacokinetics of vortioxetine is detailed and adapted.

Because of its long elimination half-life, the risk of PK interactions can persist for several days or even weeks after vortioxetine withdrawal. However, as vortioxetine did not show any relevant potential for inhibition or induction, this is not a concern.

Investigation of transporters involved in drug elimination are indicated if available, and in vivo data shows that active renal, biliary or gut wall secretion of unchanged drug is involved in a main part of the drug elimination and thus modulation of the transporter involved may be of clinical relevance.

Hepatic or biliary secretions as well as the renal secretion are well below 25% of the total clearance for vortioxetine. In the mass balance study, unchanged vortioxetine represents a minor part of the total AUC of radioactivity. Vortioxetine is extensively metabolised and two metabolites are excreted in considerable amounts; Lu AA34443 which was excreted in both urine and faeces, and its glucuronide conjugate (M4(b)) which was excreted in urine. The identification of transporters is also not relevant for Lu AA34443 for which the contribution to the in vivo pharmacological effect is non-existent.

Since the conjugation reactions only involve the Vortioxetine metabolites, which are pharmacologically inactive, and not Vortioxetine itself, inhibition of UGT will have no effect on Vortioxetine exposure. Therefore, an investigation of a potential UGT-based interaction will have no clinical relevance.

Some antipsychotics/neuroleptics, particularly phenothiazines, may competitively inhibit the CYP2D6-mediated metabolism of vortioxetine, potentially raising its plasma concentrations. The potential for PK interactions with relevant antipsychotic drugs was asked to be discussed from a mechanistic perspective and the need not to conduct formal studies justified. The applciant's answer is endorsed: in CYP2D6 extensive metabolisers, the Vortioxetine exposure was moderately (2-fold) increased following inhibition by the strong CYP2D6 inhibitor bupropion (Study 117). The Vortioxetine exposure seen following co-administration with bupropion was similar to that observed in CYP2D6 poor metabolisers. Thus, administration of any CYP2D6 inhibitor can maximally result in a 2-fold increase in Vortioxetine exposure. Therefore, the Applicant does not consider it relevant to conduct formal studies with antipsychotic/neuroleptics that may inhibit the CYP2D6-mediated metabolism of Vortioxetine.

Patients with depression refractory to treatment with a single agent are sometimes tried on combination therapy. The potential for PK interactions with other relevant antidepressant drugs (i.e. paroxetine, fluoxetine and sertraline as potent/moderate CYP2D6 inhibitors…) was asked to be

discussed from a mechanistic perspective and clear recommendations have been provided in the SmPC with regard to combination therapy. The SmPC, section 4.2, also include the possibility of dose reduction with regards to combination therapy with potent CYP2D6 inhibitors. In addition to bupropion, the applicant has mentioned an exhaustive list of the potent CYP2D6 inhibitors in section 4.2 and 4.5. (quinidine, fluoxetine, paroxetine, terbinafine, ritonavir, cinacalcet…).
In addition to rifampicin, the other strong inducers of the CYPs involved in the vortioxetine metabolism were cited in section 4.5 of SmPC.

According to the guideline on SmPC*, in vivo* results demonstrating an absence of interaction should only be mentioned in section 4.5 if this is of major importance to the prescriber. The absence of effect of omeprazole (CYP2C19 inhibitor), aspirin and ethanol on the pharmacokinetics of vortioxetine were added in section 4.5 (Potential for other medicinal products to affect vortioxetine).

2.4.5. Conclusions on clinical pharmacology

The primary pharmacodynamic properties of vortioxetine have been investigated in two positron emission tomography (PET) studies investigating the occupancy of the 5-HT transporter and/or the 5-HT1A receptor (Studies 10985 and 12260A) and one study assessing neurotransmitter concentrations in the cerebrospinal fluid (CSF; Study 124).

The secondary pharmacodynamic properties of vortioxetine have been investigated in studies 10272, 10467, and 12260A.
Pharmacodynamic drug interactions have been studied in thirteen studies including a study on cardiac repolarisation (Study 104, with moxifloxacin) and driving performance (Study 12689A, with mirtazapine).
However, the pharmacodynamic studies performed with vortioxetine shed no light on its mechanism of action in humans *in vivo*.
Vortioxetine is thought to target serotonin, norepinephrine and dopamine but at present no biomarkers are validated to study the effect of antidepressants. Pharmacodynamic parameters were studied in small sample sets, the data of which are often statistically inconclusive due to very large variations. At this stage, it is not possible to use any of the known potential biomarkers to predict a potential therapeutic effect of vortioxetine in patients with depression.

For most of the other exploratory, pharmacodynamic biomarkers, some effects, without a clear dose dependency, were observed. The multimodal effects of vortioxetine acting at several receptor targets and at the 5-HTT may complicate the interpretation of the responses from individual biomarkers as a particular effect, or lack of effect, might be due to the sum of several simultaneous pharmacodynamic responses.

No clinically relevant pharmacokinetic or pharmacodynamic interactions were observed following co-administration of Vortioxetine with aspirin, warfarin, oral contraceptives, or the CNS-active compounds alcohol, diazepam, or lithium.

Vortioxetine did not have any clinically meaningful effect on cardiac repolarisation. Vortioxetine did not impair on-the-road driving performance, the cognitive function or psychomotor skills in healthy subjects.

2.5. Clinical efficacy

2.5.1. Dose response studies

No real dose finding study was conducted. A dose justification was acquired from the short-term clinical studies supported by toxicological and pharmacological data. This was considered acceptable.

2.5.2. Main studies

The main clinical documentation for vortioxetine consists of nine short-term studies (11492A, 11984A, 305, 13267A, 315, 316, 303, 304, 12541A) including a placebo- and active controlled study in the ≥65 years population (12541A).

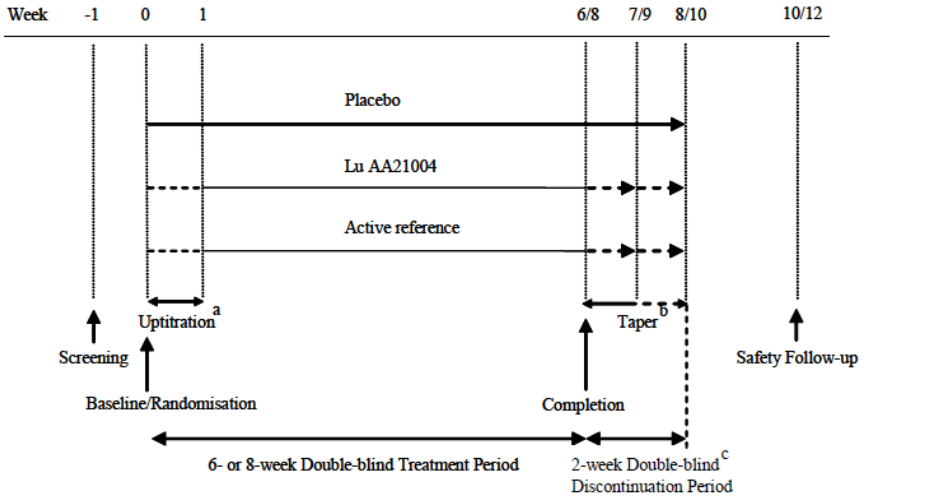
One relapse prevention study was performed for the evaluation of maintenance of effect (11985A). Long-term effect was also studied in open label extensions of the short-term studies 11492A, 11984A, 305, and 304.

Additional studies were completed between MAA submission and 31 August 2013.

Studies in children were not performed.

The study design was similar for the initially sumitted short-term studies.

Table 6: Overall study design of short-term studies



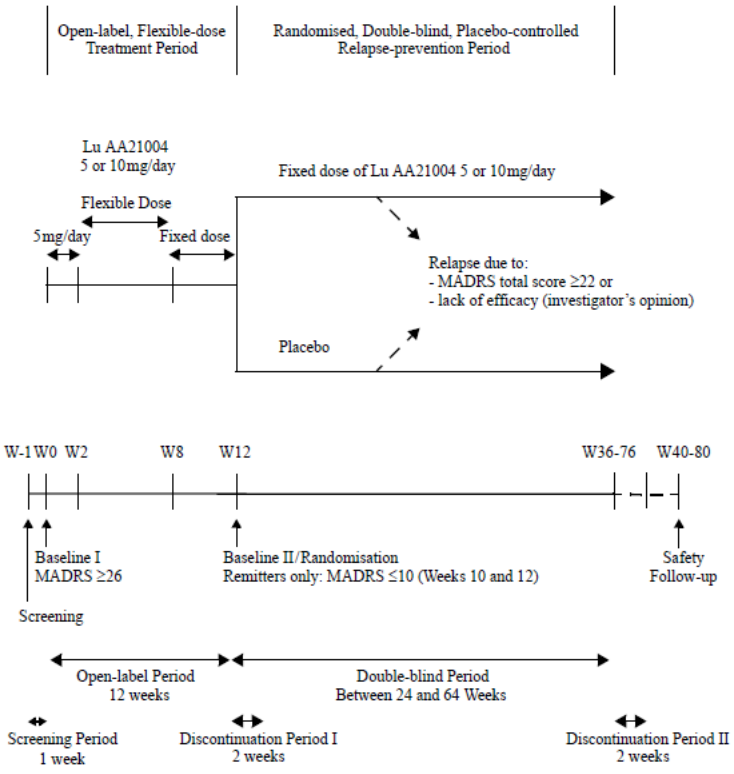
a Started at assigned doses, except in Studies 13267A, 315, and 316, where patients randomised to 15 or 20mg/day Lu AA21004 received 10mg/day the first week. The active reference was uptitrated according to the *SmPC* or *USPI*, not shown in figure.

b Abrupt discontinuation, except in Study 11492A, where 10 mg/day Lu AA21004 was down-tapered to 5mg/day in the first week. The active reference was down-tapered according to the *SmPC* or *USPI*.

c Discontinuation symptoms for Lu AA21004 were assessed in Studies 11492A, 13267A, 315, 316, and 303.

d Study 317 is ongoing and therefore not included in this *Summary of Efficacy*

Table 7: Study Design of Relapse-prevention Study 11985A



Methods

Description of methods is summarized below for all initially submitted short-term studies. The studies are submitted subsequentally are described in section 2.5.3.

- **Study participants**

The inclusion and exclusion criteria were similar for all studies with slight differences as mentioned below.

Diagnosis and main criteria of Inclusion
In all the studies, the study population consisted of in- or out patients from psychiatric settings with a primary diagnosis of MDE within MDD, according to the DSM-IV-TR™ criteria who:

- were aged ≥18 and ≤75 years (with the exception of Study 11492A, which included patients aged ≥18 and ≤65 years)

- had *mild* to *severe* MDD (Montgomery and Åsberg Depression Rating Scale [MADRS] total score:
  ≥22 [Study 304],
  ≥26 [Studies 11984A, 305, 13267A, 315, and 316], or
  ≥30 [Studies 11492A and 303]).

- In Studies 13267A, 315, and 316, there was an additional requirement for a Clinical Global Impression – Severity of Illness (CGI-S)score ≥4.

- The duration of the current MDE had to be ≥3 months (>3 months in Study 13267A), and, in Study 11492A, the current MDE had to have lasted <12 months.

- In Studies 13267A, 315, and 316, and 12541A the patients had to have had at least one MDE prior to the current episode.

- In the relapse-prevention study 11985A a patient had to have a baseline MADRS total score ≥26; the duration of the current MDE had to be ≥4 weeks and the patient had to have had at least one MDE prior to the current episode.

Main exclusion criteria
A patient was excluded from the studies if he/she (selected criteria):

• had any current psychiatric disorder other than MDD (the MINI or the SCID was used to assist in the exclusion of disallowed Axis I disorders); a history of manic or hypomanic episode; schizophrenia; any other psychotic disorder; a mental disorder due to a general medical condition; or any significant Axis II disorder
• was at significant risk of suicide, defined as:
– as judged by the investigator OR
– a MADRS item 10 [*suicidal thoughts*] score ≥5 at the Screening and Baseline Visits OR
– a suicide attempt during the last 6 months (not used in Study 11492A)
• had significant somatic co-morbidity
• had had any substance-related disorder (except nicotine or caffeine) within 6 months (2 years in Studies 13267A and 315) prior to the Screening Visit; no current diagnosis or history of substance abuse was allowed in Study 316

• had treatment-resistant depression (defined as resistant to two adequate antidepressant treatments of ≥6 weeks' duration, as judged by the investigator)
• was receiving formal cognitive or behavioural therapy
• had received electroconvulsive therapy (or vagal nerve stimulation, or repetitive transcranial magnetic stimulation [Studies 13267A, 315, and 316]) within 6 months prior to the Screening Visit

• had a history of lack of response to previous adequate treatment with duloxetine (Studies 11984A, 13267A, 315, 304, and 12541A) or venlafaxine (Study 11492A)
• had a history of severe drug allergy or hypersensitivity, or known hypersensitivity to duloxetine (Studies 11984A, 13267A, 304, and 12541A) or venlafaxine (Study 11492A)

- **Treatments**

In short-term clinical studies patients were treated with fixed doses of Vortioxetine encapsulated tablets: 1mg, 2.5mg, 5mg, 10 mg, 15mg and 20 mg (the doses varied across studies and can be found in table 1 above and in the detailed descriptions of the individual studies below), matching placebo, or, in six of the studies, a fixed dose of the active reference venlafaxine capsules 75mg and 150mg i.e. 225 mg/day (Study 11492A) or duloxetine capsules 60 mg/day (studies 11984A, 13267A, 315, 304 and 12541A).

The IMPs were encapsulated tablets (Vortioxetine) or overencapsulated capsules (venlafaxine; duloxetine; placebo). All IMPs were supplied as brownish red/orange capsules of identical appearance. The investigators were instructed to store the IMPs below 30°C.

The medication was administered once daily, preferably in the morning, with or without food. The dose was taken orally, with a glass of water.

- **Objectives**

The primary objective of the short-term studies was to evaluate the efficacy, safety and tolerability of fixed doses of LUAA21004 versus placebo in patients with Major Depressive Disorder (MDD).

Study 12541A was a dedicated study in the elderly to evaluate the efficacy, safety and tolerability of fixed doses of LUAA21004 versus placebo in elderly patients with Major Depressive Disorder (MDD).

Study 11985A had the objective to evaluate the efficacy of Vortioxetine (5 and 10 mg/day) in the prevention of relapse of major Depressive Episodes (MDE).

The long-term extension studies had the objectives to evaluate the long-term safety and tolerability of flexible doseses of Vortioxetine over a period of 52 weeks in patients with MDD who completed the respective short-term studies.

- **Outcomes/endpoints**

The primary efficacy endpoints in the short-term studies are summarized in the table below.

Table 8: Primary Efficacy Analyses in the short-term studies

Study	Endpoint	Comparison	Statistical Methodology
11492A	Δ MADRS total score at Week 6	10mg/day *versus* PBO	ANCOVA (LOCF)
11984A	Δ MADRS total score at Week 8	5mg/day *versus* PBO 10mg/day *versus* PBO	ANCOVA (LOCF)
305	Δ HAM-D_{24} total score at Week 8	10mg/day *versus* PBO	MMRM
13267A	Δ MADRS total score at Week 8	15mg/day *versus* PBO 20mg/day *versus* PBO	MMRM
315	Δ MADRS total score at Week 8	15mg/day *versus* PBO 20mg/day *versus* PBO	MMRM
316	Δ MADRS total score at Week 8	10mg/day *versus* PBO 20mg/day *versus* PBO	MMRM
303	Δ HAM-D_{24} total score at Week 6	5mg/day *versus* PBO	ANCOVA (LOCF)
304	Δ HAM-D_{24} total score at Week 8	5mg/day *versus* PBO	ANCOVA (LOCF)
12541A	Δ HAM-D_{24} total score at Week 8	5mg/day *versus* PBO	ANCOVA (LOCF)

Δ = change from baseline; all the analyses were performed on the FAS

Either the MADRS or Hamilton Depression Rating Scale (HAM-$D)_{24}$ was the primary efficacy assessment tool.

Table 9: Secondary endpoints used are summarized in the following table:

Assessment Tool Derived Variable(s)	Study								
	11492A	11984A	305	13267A	315	316	303	304	12541A
Efficacy									
MADRS									
MADRS total score	√	√	√	√	√	√	√	√	√
MADRS single-item scores	√	√	√	√	√	√			√
$MADRS_6$ subscale score	√	√	√	√		√	√	√	√
MADRS IVRS total score (PRO)	√								
MADRS-S total score (PRO)							√	√	
HAM-D									
HAM-D_{24} total and single-item scores	√	√	√				√	√	√
HAM-D_{17} total score	√	√	√				√	√	√
HAM-D_6 subscale score	√	√	√				√	√	√
HAM-D-MAIER subscale score		√	√				√	√	√
HAM-D-ANX subscale score	√	√	√				√	√	√
HAM-A									
HAM-A total score	√	√	√	√	√	√	√	√	√
HAM-A single-item scores	√	√	√				√	√	√
Clinical Global Impression									
CGI-S score	√	√	√	√	√	√	√	√	√
CGI-I score	√	√	√	√	√	√	√	√	√
Response									
≥50% reduction in MADRS total score	√	√	√	√	√	√	√	√	√
≥50% reduction in HAM-D_{24} total score	√	√	√				√	√	√
CGI-I score ≤2	√	√	√	√	√	√	√	√	√
Sustained response	√	√	√				√	√	
Remission									
MADRS total score ≤10	√	√	√	√	√	√	√	√	√
HAM-D_{17} total score ≤7	√	√	√				√	√	√
CGI-S score ≤2	√	√	√	√	√	√	√	√	√
Sustained remission		√	√				√	√	
Cognitive Dysfunction									
RAVLT									√
DSST									√
CPFQ (PRO)						√			

See *List of Abbreviations and Definitions of Terms* for scale names.

Assessment Tool Derived Variable(s)	Study								
	11492A	11984A	305	13267A	315	316	303	304	12541A
Health-related Quality of Life and Overall Functioning									
SF-36 (PRO) domain scores	√	√	√				√		
Q-LES-Q (SF) (PRO) total and single-item scores				√					
EuroQol (PRO) utility index (EQ-5D) and health state (EQ VAS) scores	√								
HSQ-12 (PRO) domain scores									√
SDS (PRO) total and single-item scores		√	√	√	√	√	√	√	
Other Patient-reported Outcomes (PROs) and Pharmacoeconomics									
HAD-D subscale score[36]		√	√						
HAD-A subscale score[36]		√	√						
FSS total score[37]		√							
SCL-90-R total and subscale scores[38]	√								
GDS total and single-item scores[39,40]									√
LSEQ total and single-item scores[41,42]							√	√	√
WPAI (PRO) subscale scores[43]				√					
HEA total score		√	√	√			√	√	√

See *List of Abbreviations and Definitions of Terms* for scale names.

They include the MADRS single-item scores, the Hamilton Anxiety Rating Scale (HAM-A) total score, which is used to assess anxiety symptoms, the proportions of responders and remitters, and the Clinical Global Impression –Global Improvement (CGI-I) score, which reflects the investigator's global clinical judgement of the outcome of treatment.

Additional variables were used to evaluate the effect of Vortioxetine on cognitive dysfunction, health-related quality of life (HRQoL), and overall functioning. Cognitive dysfunction was evaluated using the neuropsychological tests RAVLT (a verbal learning and memory task), DSST (a task reliant on speed of processing, executive function and attention), and CPFQ (a patient-reported outcome [PRO]) designed to assess clinically relevant cognitive and physical symptoms associated with depression); HRQoL and overall functioning was evaluated using SF-36 domain scores, the Q-LES-Q (SF) total and single-item scores, the EQ-5D score, the HSQ-12 score, and the SDS total and single-item scores.

- **Statistical methods**

For each pivotal study, a Statistical Analysis Plan (SAP) was prepared before the study was unblinded and before the data were analysed.

Short-term studies

All the analyses in adults and the elderly were performed on the full- analysis-set (FAS), which was defined as all randomised patients who took at least one dose of investigational medicinal product (IMP) and who had at least one valid post-baseline measurement of the primary efficacy variable.

The primary efficacy endpoint was the change from baseline to Week 6 or 8 in MADRS or HAM-D24 total score, and the statistical analysis was either a mixed model repeated measures (MMRM) analysis

using observed cases (OC) or an analysis of covariance (ANCOVA) using the last observation carried forward (LOCF) (see table Primary efficacy analysis in short-term studies above).

The MMRM analysis used OC and all the data from the Treatment Period. The model had a completely unstructured covariance matrix and included terms for site, baseline score-by-visit interaction, and treatment-by-visit interaction. The ANCOVA used the LOCF, with treatment and site as fixed factors and the baseline scale score as a covariate. The data for the patients treated with the active reference were kept in the models to improve the precision of the estimates.

In each study, a hierarchically-ordered testing strategy was defined a priori in the SAP and comprised the primary efficacy endpoint, as well as the key secondary efficacy endpoints (see Table below Testing Strategies in short-term studies). The testing strategy comprised either one sequence or two sequences tested in parallel. The testing stopped within a sequence as soon as a hypothesis in the hierarchy could not be rejected.

Hierarchical testing was used to control the 2-sided Type I error over the primary and key secondary endpoints. When the testing strategy comprised one sequence (Studies 11492A,305, 304, and 12541A), each step in the sequence was tested separately versus placebo at a significance level of 0.05; when the testing strategy comprised two parallel sequences (Studies 11984A, 13267A, 315, and 316), each step in each sequence was tested separately versus placebo at a Bonferroni-corrected significance level of 0.025. In Study 303, the testing strategy comprised two steps: the first step comprised one sequence, with a single endpoint that was tested versus placebo at a significance level of 0.05; the second step comprised two parallel sequences, and each step in each sequence was tested separately versus placebo at a Bonferroni-corrected significance level of 0.025.

In the studies that included an active reference, comparisons of the active reference versus placebo were performed outside the testing strategy, at a significance level of 0.05.

For endpoints outside the testing strategy, or endpoints within the testing strategy that were not tested because the procedure had stopped, nominal p-values are reported. For individual short-term studies, the phrase “separation from placebo” is used to describe findings with a nominal p-value <0.05. For simplicity, in the tabulations of the secondary efficacy results, the p-values are designated as nominal, regardless of the results in the testing strategy.

The endpoints (except for response and remission) in the testing strategy were all analysed using the same methodology as that used for the primary efficacy analysis. The results for response and remission were based on logistic regression (LREG), LOCF, adjusting for the baseline score and treatment, with p-values derived from odds ratios. For the CGI-I, the baseline CGI-S score was used as a covariate. In addition, Fisher’s exact test and $\chi 2$-tests were performed. Sustained response was analysed in the same way. Time to event (that is, time to response, remission, or sustained response) was analysed using both a log-rank test and the Cox proportional hazards model.

Endpoints outside the testing strategy were analysed using the same methods as for endpoints within the testing strategy.

Table 10: Testing Strategies in the Short-term studies

Study	Testing Strategy
11492A (ANCOVA, LOCF)	Hierarchical testing in one sequence; $\alpha = 0.05$: • Δ MADRS total score at Week 6 – 10 mg/day • Δ MADRS total score at Week 6 – 5 mg/day • Δ MADRS total score at Week 1 – 10 mg/day • Δ MADRS total score at Week 1 – 5 mg/day
11984A (ANCOVA, LOCF)	Hierarchical testing in two parallel sequences (5 and 10mg/day); each at $\alpha = 0.025$ – at Week 8: • Δ MADRS total score • Δ HAM-D_{24} total score • Response – defined as a ≥50% reduction in MADRS total score • CGI-I score • Δ HAM-D_{24} total score in patients with a HAM-A total score ≥20 at baseline • Δ SDS total score • Remission – defined as a MADRS total score ≤10
Study	**Testing Strategy**
305 (MMRM)	Hierarchical testing in one sequence; $\alpha = 0.05$ – at Week 8: • Δ HAM-D_{24} total score – 10mg/day • Δ SDS total score – 10mg/day • CGI-I score – 10mg/day • Response – defined as a ≥50% reduction in HAM-D_{24} total score – 10mg/day • Δ HAM-D_{24} total score in patients with a HAM-A total score ≥20 at baseline – 10mg/day • Remission – defined as a MADRS total score ≤10 – 10mg/day • Δ HAM-D_{24} total score – 5mg/day • Δ SDS total score – 5mg/day • CGI-I score – 5mg/day • Response – defined as a ≥50% reduction in HAM-D_{24} total score – 5mg/day • Δ HAM-D_{24} total score in patients with a HAM-A total score ≥20 at baseline – 5mg/day • Remission – defined as a MADRS total score ≤10 – 5mg/day
13267A (MMRM)	Hierarchical testing in two parallel sequences (15 and 20mg/day); each at $\alpha = 0.025$ – at Week 8: • Δ MADRS total score • Response – defined as a ≥50% reduction in MADRS total score • CGI-I score • Δ MADRS total score in patients with a HAM-A total score ≥20 at baseline • Remission – defined as a MADRS total score ≤10 • Δ SDS total score
315 (MMRM)	Hierarchical testing in two parallel sequences (15 and 20mg/day); each at $\alpha = 0.025$ – at Week 8: • Δ MADRS total score • Response – defined as a ≥50% reduction in MADRS total score • CGI-I score • Δ MADRS total score in patients with a HAM-A total score ≥20 at baseline • Remission – defined as a MADRS total score ≤10 • Δ SDS total score
316 (MMRM)	Hierarchical testing in two parallel sequences (10 and 20mg/day); each at $\alpha = 0.025$ – at Week 8: • Δ MADRS total score • Response – defined as a ≥50% reduction in MADRS total score • CGI-I score • Δ MADRS total score in patients with a HAM-A total score ≥20 at baseline • Remission – defined as a MADRS total score ≤10 • Δ SDS total score

Study	Testing Strategy	
303 (ANCOVA, LOCF)	Hierarchical testing in two steps: Step 1: 5mg/day; $\alpha = 0.05$: • Δ HAM-D_{24} total score at Week 6	
	Step 2 (if significance at Step 1): Hierarchical testing in two parallel sequences; each at $\alpha = 0.025$:	
	Sequence 1: 5mg/day: • Δ HAM-D_{24} total score at Week 5 • Δ HAM-D_{24} total score at Week 4 • Δ HAM-D_{24} total score at Week 3 • Δ HAM-D_{24} total score at Week 2 • Δ HAM-D_{24} total score at Week 1	Sequence 2: 5mg/day: • Response – defined as a ≥50% reduction in HAM-D_{24} total score at Week 6 • Remission – defined as a MADRS total score ≤10 at Week 6 • CGI-I score at Week 6 • Δ HAM-D_{24} total score at Week 6 in patients with a HAM-A total score ≥20 at baseline • Δ MADRS-S score at Week 6 • Δ SDS total score at Week 6 • Δ MADRS-S score at Week 4 • Δ MADRS-S score at Week 1
304 (ANCOVA, LOCF)	Hierarchical testing in one sequence; $\alpha = 0.05$ – at Week 8: • Δ HAM-D_{24} total score – 5mg/day • Response – defined as a ≥50% reduction in HAM-D_{24} total score – 5mg/day • CGI-I score – 5mg/day • Δ HAM-D_{24} total score in patients with a HAM-A total score ≥20 at baseline – 5mg/day • Δ SDS total score – 5mg/day • Remission – defined as a MADRS total score ≤10 – 5mg/day • Δ HAM-D_{24} total score – 2.5mg/day	
12541A (ANCOVA, LOCF)	Hierarchical testing in one sequence (5mg/day); $\alpha = 0.05$: • Δ HAM-D_{24} total score at Weeks 8, 6, 4, 2, and 1	

Δ = change from baseline; α = level of statistical significance
The analysis used for the primary endpoint was used for all the endpoints within a testing strategy, with the exception that response and remission were analysed using logistic regression. All the analyses were *versus* placebo and were done in descending order.

As sensitivity analysis, ANCOVA (LOCF) and MMRM were performed, applying the method that had not been used for primary analysis (i.e. ANCOVA (LOCF) primary analysis -> MMRM sensitivity analysis, and vice versa). Furthermore, post-hoc sensitivity analyses were performed to further confirm the robustness of the results; these included a placebo-mean imputation (PMI) analysis of the change from baseline in MADRS total score and LREG, observed cases (OC) and non-response-imputation (NRI) analyses of response and remission.

For comparisons across studies and to support findings from the individual studies, side-by-side results from each study together with results from a meta-analysis are presented (Forest plots). To provide consistent input for the meta-analyses, a similar analysis approach was applied to all the studies. The MMRM was chosen as the main analysis, however, analyses based on ANCOVA, LOCF were also performed. The PMI results were also used as input for meta-analyses.

Since not all doses of Vortioxetine were included in all the studies, the meta- analysis approach (rather than a pooled analysis of individual patient data) was considered the statistical methodology that would provide the most reliable estimates of overall treatment effect. The meta-analyses were performed applying standard methodology including tests for heterogeneity and estimation under random effects assumptions. Heterogeneous treatment effects were also assessed by evaluating I^2. The meta-analysis is a transparent analysis as it is possible to determine which studies drive the observed effect.

Meta-analyses including all the short-term studies (except the dedicated study in the elderly, as it only included patients aged ≥65 years) were performed on the MADRS (total score and single items), CGI-I score, HAM-A (total score and item 5), SF-36 MCS and Physical Component Summary scores, SF-36 domain scores, and SDS total scores. Meta-analyses were also performed for the subset of studies conducted outside the United States. Pooled analyses (based on the MADRS total score) were only performed on small subpopulations for which there were too few patients in the individual studies for analysis.

The effect of treatment with Vortioxetine on cognitive dysfunction is presented from three different perspectives: the effect in neuropsychological tests (DSST and RAVLT) as objective measures of cognitive performance (study 12541A in the elderly only); the effect on the single items of the MADRS and HAM-A that address the aspect of cognitive symptoms as assessed by the clinician (MADRS item 6 and HAM-A item 5, respectively); and the effect on subjective self-ratings of cognitive symptoms associated with depression using a patient-reported outcome (CPFQ) (study 316 only).
To evaluate the clinical relevance of the results on the DSST and RAVLT, the standardised effect sizes were calculated based on an ANCOVA, LOCF. To evaluate the effect in patients with significant symptoms, a baseline CPFQ total score >25 was used as a cut-off in the analyses. The CPFQ data were analysed using an ANCOVA, LOCF supplemented with an ANCOVA, OC. A path analysis was performed for the cognitive assessment tools (DSST, RAVLT, and CPFQ) to assess the direct and indirect effects of Vortioxetine on cognitive dysfunction.

To evaluate the clinical relevance of the HRQoL data, in line with the EMA Reflection Paper, the standardised effect size was calculated, and the standard 0.2 threshold was used to interpret the clinical relevance of the results.

Relapse-prevention study

The efficacy analysis was performed on the FAS, defined as all randomised patients who took at least one dose of IMP in the Double-blind Period. The primary analysis of time to relapse considered data up to Week 24 in the double-blind period. The treatment groups were compared using a Cox model with an exact method to handle ties; this analysis was supplemented by Kaplan-Meier plots. Withdrawals that occurred before Week 24 in the Double-blind Period due to reasons other than lack of efficacy (relapse) were censored at dropout time, i.e. considered non-relapses.
A secondary analysis of time to relapse considered all data in the double-blind period.
As a sensitivity analyses, the Cox analysis was repeated excluding all relapses that occurred within 1,2, and 4 weeks after randomization, in order to separate the possible effects of rebound and discontinuation symptoms from relapses in the placebo group. Another analysis excluded all relapses that occurred >5 days after the date of last dose of double-blind study medication. Sensitivity analyses using a standard log-rank test and accelerated failure time models, taking the interval-censored nature of the data into account, were also performed. Various distributions were studied in these models including Weibull and log-normal.
The secondary variables were evaluated using descriptive statistics, ANCOVA, using both the OC and LOCF, and χ^2 tests for response and remission.
Time to event analyses including log-rank tests and Kaplan-Meier estimates were provided to compare treatment arms with respect to all reasons leading to withdrawal, adverse events leading to withdrawal, and lack of efficacy leading to withdrawal.

Results

Summary of main study(ies)

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 11: Summary of efficacy for the main 8 Phase III clinical trials

Title: Double-blind, randomised, placebo-controlled study comparing the efficacy and safety of two fixed dosages of a novel antidepressant compound to that of placebo in patients with Major Depressive Disorder	
Study identifier	**11492A**

Design	Randomized, double-blind, parallel-group, placebo-controlled, active-referenced		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Treatment Period: 6 weeks not applicable Taper Period: 2 weeks Safety Follow-up Period: 4 weeks
Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	VOR_5		Vortioxetine 5 mg/day, 6 weeks, n=109
	VOR_10		Vortioxetine 10 mg/day, 6 weeks, n=101
	VLF		Venlafaxine 225 mg/day, 6 weeks, n=114
	PBO		Placebo, 6 weeks, n=105
Endpoints and definitions	Primary endpoint	MADRS	Change from baseline in MADRS total score at week 6
	Secondary endpoints	MADRS Response	Response defined as ≥50% decrease from baseline in MADRS total score
		MADRS Remission	Remission defined as MADRS total score of 10 or less
		SF-36	Medical Outcomes Study (MOS) 36-item Short-form Health Survey
		CGI-I	
Notes	SDS was not assessed in this study		
Database lock	Not reported in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Full Analysis Set (FAS): All randomized patients who took at least one dose of IMP and who had at least one valid post-baseline assessment of the MADRS total score Week 6				
Descriptive statistics and estimate variability	Treatment group	VOR_5	VOR_10	VLF	PBO
	Number of subject	108	100	112	105
	LS Mean change from baseline in MADRS total score	-20.40	-20.20	-20.92	-14.50
	Standard Error	1.01	1.04	0.99	1.03

Effect estimate per comparison	Primary endpoint: change from baseline in MADRS total score	Comparison groups	VOR_5, PBO	VOR_10, PBO	VLF, PBO
		Mean differerence	-5.90	-5.70	-6.42
		Standard Error	1.39	1.42	1.38
		P-value	<.0001	<.0001	<.0001
Notes	ANCOVA adjusting for centre and baseline MADRS, LOCF imputation Both doses of vortioxetine were statistically significantly superior to placebo in mean change from baseline in MADRS total score at Week 6				
Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 6				

Secondary endpoint: MADRS Response Rate	Comparison groups	VOR_5	VOR_10	VLF	PBO
	Number of subject	108	100	112	105
	MADRS Response Rate (%)	66.7	68.0	72.3	44.8

Effect estimate per comparison	MADRS Response Rate	Comparison groups	VOR_5, PBO	VOR_10, PBO	VLF, PBO
		Difference %	21.9	23.2	27.6
		95% CI	8.9, 34.9	10.1, 36.4	15.0, 40.2
		P-value	0.002	0.001	0.000

Notes	Fisher's exact test, LOCF imputation
Analysis description	**Secondary analysis**
Analysis population and time point description	FAS Week 6

Secondary endpoint: MADRS Remission Rate	Comparison groups	VOR_5	VOR_10	VLF	PBO
	Number of subject	108	100	112	105
	MADRS Remission Rate (%)	49.1	49.0	55.4	26.7

Effect estimate per comparison	MADRS Remission Rate	Comparison groups	VOR_5, PBO	VOR_10, PBO	VLF, PBO
		Difference %	22.4	22.3	28.7
		95% CI	9.4, 35.3	9.7, 35.1	16.2, 41.2
		P-value	0.001	0.001	0.000

Notes	Fisher's exact test, LOCF imputation
Analysis description	**Secondary Analysis**
Analysis population and time point description	FAS Week 6

Descriptive statistics and estimate variability	Treatment group	VOR_5	VOR_10	VLF	PBO
	Number of subject	108	98	111	104
	LS Mean change from baseline in SF-36 total score	7.97	8.89	9.10	6.53
	Standard Error	1.58	1.64	1.55	1.60

Effect estimate per comparison	Primary endpoint: change from baseline in SF-36 total score	Comparison groups	VOR_5, PBO	VOR_10, PBO	VLF, PBO
		Mean difference	1.44	2.35	2.57
		Standard Error	2.16	2.23	2.15
		P-value	0.5070	0.2922	0.2332

Notes	ANCOVA adjusting for centre and baseline, LOCF imputation
Analysis description	**Secondary Analysis**

Analysis population and time point description	FAS Week 6				
Descriptive statistics and estimate variability	Treatment group	VOR_5	VOR_10	VLF	PBO
	Number of subject	108	100	111	105
	LS Mean change from baseline in CGI-I score	2.05	2.04	1.96	2.64
	Standard Error	0.12	0.12	0.12	0.12

Effect estimate per comparison	change from baseline in CGI-I score	Comparison groups	VOR_5, PBO	VOR_10, PBO	VLF, PBO
		Mean difference	-0.58	-0.60	-0.67
		Standard Error	0.16	0.16	0.16
		P-value	0.0003	0.0003	<.0001

Notes	ANCOVA adjusting for centre and baseline, LOCF imputation

Title: A randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating the efficacy and safety of three dosages of Vortioxetine, in acute treatment of Major Depressive Disorder

Study identifier	**11984A**		
Design	Randomized, double-blind, parallel-group, placebo-controlled, active-referenced		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment Period: 8 weeks not applicable Taper Period: 1 week (only active reference) Safety Follow-up Period: 4 weeks	
Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	VOR_2.5	Vortioxetine 2.5 mg/day, 8 weeks, n=155	
	VOR_5	Vortioxetine 5 mg/day. 8 weeks, n=159	
	VOR_10	Vortioxetine 10 mg/day, 8 weeks n=153	
	DUL	Duloxetine 60 mg/day, 8 weeks, n=157	
	PBO	Placebo. 8 weeks, n=152	
Endpoints and definitions	Primary endpoint	MADRS	Change from baseline in the MADRS total score at Week 8
	Secondary endpoints	MADRS Response	Response defined as 50% decrease from baseline in MADRS total score at Week 8
		MADRS Remission	Remission defined as MADRS total score of 10 or less at Week 8
		SDS	Sheehan Disability Scale (SDS) total score
		CGI-I	
Database lock	Not reported in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	FAS Week 8

Descriptive statistics and estimate variability	Treatment group	VOR_2.5	VOR_5	VOR_10	DUL	PBO
	Number of subject	155	155	151	149	145
	LS Mean change from baseline in MADRS total score	-16.2	-16.5	-16.3	-16.8	-14.8
	Standard Error	0.79	0.80	0.80	0.81	0.82

Effect estimate per comparison	Change from baseline in MADRS total score at week 8	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	VOR_10, PBO	DUL, PBO
		Mean difference	-1.38	-1.70	-1.50	-2.04
		Standard Error	1.12	1.13	1.13	1.14
		P-value	0.2187	0.1321	0.1847	0.0741

Notes	ANCOVA adjusting for centre and baseline, LOCF imputation The comparisons of 5 and 10 mg were considered primary. The comparisons of 5 and 10 mg were considered primary and, in order to control for multiplicity, each was tested at a Bonferonni corrected significance level of 2.5%.
Analysis description	**Secondary analysis**
Analysis population and time point description	FAS Week 8

Secondary endpoint: MADRS Response rate	Comparison groups	VOR_2.5	VOR_5	VOR_10	DUL	PBO
	Number of subject	155	155	151	149	145
	MADRS Response Rate (%)	54.2	56.1	57.6	57.1	46.9

Effect estimate per comparison	MADRS Response Rate	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	VOR_10, PBO	DUL, PBO
		Odds ratio	1.34	1.41	1.54	1.52
		95% CI	0.85, 2.12	0.90, 2.23	0.97, 2.43	0.96, 2.40
		P-value	0.2023	0.1370	0.0664	0.0765

Notes	Logistic regression adjusting for baseline, LOCF imputation
Analysis description	**Secondary analysis**
Analysis population and time point description	FAS Week 6

Secondary endpoint: MADRS Remission rate	Comparison groups	VOR_2.5	VOR_5	VOR_10	DUL	PBO
	Number of subject	155	155	151	149	145
	MADRS Remission Rate (%)	32.9	36.1	35.8	34.9	33.8

Effect estimate per comparison	MADRS Remission Rate	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	VOR_10, PBO	DUL, PBO
		Odds ratio	0.96	1.13	1.09	1.05

		95% CI	0.59, 1.55	0.70, 1.81	0.68, 1.76	0.65, 1.69
		P-value	0.8651	0.6258	0.7178	0.8563
Notes	Logistic regression adjusting for baseline, LOCF imputation					
Analysis description	**Secondary Analysis**					
Analysis population and time point description	FAS Week 8					
Descriptive statistics and estimate variability	Treatment group	VOR_2.5	VOR_5	VOR_10	DUL	PBO
	Number of subject	115	119	115	108	116
	LS Mean change from baseline in SDS total score	-7.10	-6.52	-7.81	-7.91	-6.11
	Standard Error	0.74	0.73	0.74	0.76	0.72
Effect estimate per comparison	Change from baseline in SDS total score	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	VOR_10, PBO	DUL, PBO
		Mean difference	-0.99	-0.41	-1.70	-1.80
		Standard Error	0.99	0.98	0.99	1.01
		P-value	0.3186	0.6748	0.0871	0.0768
Notes	ANCOVA adjusting for centre and baseline, LOCF imputation					
Analysis description	**Secondary Analysis**					
Analysis population and time point description	FAS Week 8					
Descriptive statistics and estimate variability	Treatment group	VOR_2.5	VOR_5	VOR_10	DUL	PBO
	Number of subject	155	154	155	149	145
	LS Mean change from baseline in CGI-I score	2.32	2.32	2.35	2.31	2.52
	Standard Error	0.10	0.10	0.10	0.10	0.10
Effect estimate per comparison	Change from baseline in CGI-I score	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	VOR_10, PBO	DUL, PBO
		Mean difference	-0.20	-0.20	-0.20	-0.21
		Standard Error	0.14	0.14	0.14	0.14
		P-value	0.1389	0.1436	0.2114	0.1271
Notes	ANCOVA adjusting for centre and baseline, LOCF imputation					
Title: A randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study comparing the efficacy and safety of 3 doses of vortioxetine in acute treatment of adults with Major Depressive Disorder						
Study identifier	**305**					
Design	Randomized, Double-Blind, Parallel-Group, Placebo-Controlled					
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment Period: 8 weeks not applicable Safety Follow-up Period: 4 weeks				

Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	VOR_1		Vortioxetine 1 mg/day, 8 weeks, n=140
	VOR_5		Vortioxetine 5 mg/day, 8 weeks, n=140
	VOR_10		Vortioxetine 10 mg day, 8 weeks, n=140
	PBO		Placebo. 8 weeks, n=140
Endpoints and definitions	Primary endpoint	HAM-D24	Mean change from baseline in HAM-D24 total at Week 8
	Secondary endpoints	MADRS	Mean change from baseline in MADRS total at Week 8
		HAM-D24 Response	Response defined as ≥50% decrease in the HAM-D24 total score from Baseline
		MADRS Remission	Remission defined as a MADRS total score ≤10
		SDS	Sheehan Disability Scale (SDS) total score
		CGI-I	
Database lock	Not reported in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Full Analysis Set Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_1	VOR_5	VOR_10	PBO
	Number of subject (at baseline)	139	139	139	139
	Number of subject (at Week 8)	124	129	122	128
	Mean change from baseline in HAM-D24 total score	-14.82	-15.42	-16.23	-11.30
	Standard Error	0.745	0.743	0.755	0.738
Effect estimate per comparison	Primary endpoint: change from baseline in HAM-D24 total score	Comparison groups	VOR_1, PBO	VOR_5, PBO	VOR_10, PBO
		Mean difference	-3.52	-4.12	-4.93
		Standard error	1.043	1.042	1.050
		P-value	<.001	<.001	<.001
Notes	Mixed model for repeated measurements (MMRM) with centre, week, baseline*week, and week*treatment as factors, unstructured covariance matrix. The comparisons of 10 mg were considered primary. The efficacy endpoints were tested in a pre-defined sequential order at significance level 0.05; as soon as an endpoint was non-significant at 0.05, the testing procedure stopped for all subsequent endpoints. The Vortioxetine 10 mg group was statistically significantly different from placebo. Since the formal testing was stopped at the second variable in the pre-specified order, none of the subsequent endpoints in the testing hierarchy were considered statistically significantly different from placebo. This includes the change from Baseline in HAM-D24 total score after 8 weeks of treatment for the 5 mg.				

Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_1	VOR_5	VOR_10	PBO
	Number of subject (at baseline)	139	139	139	139
	Number of subject (at Week 8)	124	129	122	128
	Mean change from baseline in MADRS total score	-14.9	-15.1	-15.7	-10.9
	Standard Error	0.7	0.7	0.7	0.7
Effect estimate per comparison	Change from baseline in MADRS total score	Comparison groups	VOR_1, PBO	VOR_5, PBO	VOR_10, PBO
		Mean difference	-4.0	-4.2	-4.8
		Standard Error	1.0	1.0	1.0
		P-value	<0.001	<0.001	<0.001
Notes	MMRM with centre, week, baseline*week, and week*treatment as factors, unstructured covariance matrix				
Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Secondary endpoint: HAM-D24 Response rate	Comparison groups	VOR_1	VOR_5	VOR_10	PBO
	Number of subject	139	139	139	139
	HAM-D24 Response Rate (%)	47.5	45.3	49.6	23.0
Effect estimate per comparison	HAM-D24 Response Rate	Comparison groups	VOR_1, PBO	VOR_5, PBO	VOR_10, PBO
		Odds ratio	3.02	2.74	3.35
		95% CI	1.80, 5.06	1.63, 4.60	1.99, 5.62
		P-value	<0.001	<0.001	<0.001
Notes	Logistic regression adjusting for baseline, LOCF imputation				
Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Secondary endpoint: MADRS Remission rate	Comparison groups	VOR_1	VOR_5	VOR_10	PBO
	Number of subject	139	139	139	139
	MADRS Remission Rate (%)	25.9	28.8	26.6	16.5

Effect estimate per comparison	MADRS Remission Rate	Comparison groups	VOR_1, PBO	VOR_5, PBO	VOR_10, PBO
		Odds ratio	1.75	2.06	1.95
		95% CI	0.97, 3.16	1.15, 3.67	1.08, 3.52
		P-value	0.062	0.015	0.026
Notes	Logistic regression adjusting for baseline, LOCF imputation				
Analysis description	**Secondary Analysis**				
Analysis population and time point description	Full Analysis Set Week 8				

Descriptive statistics and estimate variability	Treatment group	VOR_1	VOR_5	VOR_10	PBO
	Number of subject	139	139	139	139
	LS Mean change from baseline in SDS total score	-6.58	-7.65	-8.08	-6.54
	Standard Error	0.729	0.713	0.756	0.716

Effect estimate per comparison	Change from baseline in SDS total score	Comparison groups	VOR_1, PBO	VOR_5, PBO	VOR_10, PBO
		Mean difference	-0.05	-1.11	-1.54
		Standard error	1.009	0.994	1.029
		P-value	0.963	0.263	0.135
Notes	MRM with centre, week, baseline*week, and week*treatment as factors				
Analysis description	**Secondary Analysis**				
Analysis population and time point description	Full Analysis Set Week 8				

Descriptive statistics and estimate variability	Treatment group	VOR_1	VOR_5	VOR_10	PBO
	Number of subject	124	129	122	128
	LS Mean change from baseline in CGI-I score	2.37	2.37	2.29	2.84
	Standard Error	0.090	0.089	0.091	0.089

Effect estimate per comparison	Change from baseline in CGI-I score	Comparison groups	VOR_1, PBO	VOR_5, PBO	VOR_10, PBO
		Mean difference	-0.47	-0.47	-0.55
		Standard error	0.125	0.125	0.126
		P-value	<0.001	<0.001	<0.001
Notes	MRM with centre, week, baseline*week, and week*treatment as factors				

Title: A randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating the efficacy and safety of vortioxetine (15 and 20mg/day) in the acute treatment of adult patients with Major Depressive Disorder

Study identifier	**13267A**	
Design	Randomized, double-blind, parallel-group, placebo-controlled, active-referenced	
	Duration of main phase:	Treatment Period: 8 weeks

	Duration of Run-in phase: Duration of Extension phase:		not applicable Discontinuation Period: 2 weeks Safety Follow-up Period: 4 weeks
Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	VOR_15		Vortioxetine 15 mg/day, 8 weeks, n=152
	VOR_20		Vortioxetine 20 mg day, 8 weeks, n=151
	DUL		Duloxetine 60 mg/day, 8 weeks, n=147
	PBO		Placebo. 8 weeks, n=158
Endpoints and definitions	Primary endpoint	MADRS	Mean change from baseline in MADRS total at Week 8
	Secondary endpoints	MADR Response rate	Response defined as ≥50% decrease in the MADRS total score from Baseline
		MADRS Remission rate	Remission defined as a MADRS total score ≤10
		SDS	Sheehan Disability Scale (SDS) total score
		CGI-I	
Database lock	Not reported in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_15	VOR_20	DUL	PBO
	Number of subject (at baseline)	149	151	146	158
	Number of subject (at 8 weeks)	118	125	131	130
	LS Mean change from baseline in MADRS total score	-17.23	-18.79	-21.15	-11.70
	Standard Error	0.79	0.78	0.77	0.76

Effect estimate per comparison	Primary endpoint: change from baseline in MADRS total score	Comparison groups	VOR_15, PBO	VOR_20PBO	DUL, PBO
		Mean difference	-5.53	-7.09	-9.45
		Standard error	1.09	1.08	1.07
		P-value	<.0001	<.0001	<.0001

Notes	MMRM with treatment, centre, week, baseline*week, and week*treatment as factors, unstructured covariance matrix. To adjust for multiplicity, the 15 and 20mg doses of vortioxetine were tested separately *versus* placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025. A predefined sequence of hierarchically ordered primary and key secondary endpoints was fixed in the SAP. Both doses of Vortioxetine were statistically significantly superior to placebo in mean change from baseline in MADRS total score at Week 8. In addition, both doses of vortioxetine were statistically significantly superior to placebo in all the key secondary efficacy analyses (MADRS response, CGI-I score, Δ MADRS total score [baseline HAM-A≥20], MADRS remission, and Δ SDS total score).				
Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Secondary endpoint: MADRS Response rate	Comparison groups	VOR_15	VOR_20	DUL	PBO
	Number of subject	149	151	146	158
	MADRS Response Rate (%)	57.0	61.6	74.0	32.3
Effect estimate per comparison	MADRS Response Rate	Comparison groups	VOR_15, PBO	VOR_20PBO	DUL, PBO
		Odds ratio	2.80	3.36	5.94
		95% CI	1.76, 4.47	2.10, 5.36	3.61, 9.78
		P-value	<.0001	<.0001	<.0001
Notes	Logistic regression adjusting for baseline, LOCF imputation				
Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Secondary endpoint: MADRS Remission rate	Comparison groups	VOR_15	VOR_20	DUL	PBO
	Number of subject	149	151	146	158
	MADRS Remission Rate (%)	34.9	38.4	54.1	19.0
Effect estimate per comparison	MADRS Remission Rate	Comparison groups	VOR_15, PBO	VOR_20PBO	DUL, PBO
		Odds ratio	2.32	2.65	5.01
		95% CI	1.37, 3.91	1.58, 4.44	2.99, 8.37
		P-value	0.0016	0.0002	<.0001
Notes	Logistic regression adjusting for baseline, LOCF imputation				
Analysis description	**Secondary Analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate	Treatment group	VOR_15	VOR_20	DUL	PBO

variability	Number of subject (at baseline)	97	107	99	115
	Number of subject (at Week 8)	65	80	79	81
	LS Mean change from baseline in SDS total score	-7.70	-8.38	-11.39	-4.46
	Standard Error	0.89	0.85	0.85	0.82

Effect estimate per comparison	Change from baseline in SDS total score	Comparison groups	VOR_15, PBO	VOR_20PBO	DUL, PBO
		Mean difference	-3.24	-3.92	-6.93
		Standard error	1.16	1.11	1.13
		P-value	0.0054	0.0005	<.0001

Notes	MMRM with treatment, centre, week, baseline*week, and week*treatment as factors
Analysis description	**Secondary Analysis**
Analysis population and time point description	FAS Week 8

Descriptive statistics and estimate variability	Treatment group	VOR_15	VOR_20	DUL	PBO
	Number of subject (at baseline)	151	151	147	158
	Number of subject (at Week 8)	118	125	131	130
	LS Mean change from baseline in CGI-I score	2.18	1.92	1.75	2.86
	Standard Error	0.09	0.09	0.09	0.09

Effect estimate per comparison	Change from baseline in CGI-I score	Comparison groups	VOR_15, PBO	VOR_20PBO	DUL, PBO
		Mean difference	-0.69	-0.95	-1.12
		Standard error	0.13	0.13	0.13
		P-value	<.0001	<.0001	<.0001

Notes	MMRM with treatment, centre, week, baseline*week, and week*treatment as factors

Title: A phase 3, randomized, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of 2 doses (15 and 20 mg) of vortioxetine in acute treatment of adults with Major Depressive Disorder

Study identifier	**315**	
Design	Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Active-Referenced	
	Duration of main phase:	Treatment Period: 8 weeks
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		Discontinuation Period: 2 weeks Safety Follow-up Period: 4 weeks
Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	VOR_15		Vortioxetine 15 mg/day. 8 weeks, n=147
	VOR_20		Vortioxetine 20 mg day. 8 weeks, n=154
	DUL		Duloxetine 60 mg/day. 8 weeks, n=152
	PBO		Placebo. 8 weeks, n=161
Endpoints and definitions	Primary endpoint	MADRS	Mean change from baseline in MADRS total at Week 8
	Secondary endpoints	MADR Response	Response defined as ≥50% decrease in the MADRS total score from Baseline
		MADRS Remission	Remission defined as a MADRS total score ≤10
		SDS	Sheehan Disability Scale (SDS) total score
		CGI-I	
Database lock	Not reported in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_15	VOR_20	DUL	PBO
	Number of subject (at baseline)	145	147	146	153
	Number of subject (at Week 8)	113	112	115	129
	LS Mean change from baseline in MADRS total score	-14.30	-15.57	-16.90	-12.83
	Standard Error	0.890	0.880	0.884	0.834

Effect estimate per comparison	Change from baseline in MADRS total score	Comparison groups	VOR_15, PBO	VOR_20, PBO	DUL, PBO
		Mean difference	-1.48	-2.75	-4.07
		Standard error	1.214	1.206	1.214
		P-value	0.224	0.023	<.001

Notes	MMRM with treatment centre, week, baseline*week, and week*treatment as factors, unstructured covariance matrix. For the two Vortioxetine doses 15 mg and 20 mg the efficacy endpoints will be tested for each dose in a sequential order, predefined in the SAP, at significance level 0.025. Vortioxetine 20 mg was statistically significantly better than placebo in reducing the MADRS total score at Week 8.
Analysis description	**Secondary analysis**

Analysis population and time point description	FAS Week 8				
Secondary endpoint: MADRS Response rate	Comparison groups	VOR_15	VOR_20	DUL	PBO
	Number of subject	145	147	146	153
	MADRS Response Rate (%)	44.1	44.2	54.8	39.2
Effect estimate per comparison	MADRS Response Rate	Comparison groups	VOR_15, PBO	VOR_20, PBO	DUL, PBO
		Odds ratio	1.25	1.26	1.99
		95% CI	0.79, 1.98	0.79, 1.99	1.25, 3.17
		P-value	0.348	0.332	0.004
Notes	Logistic regression adjusting for baseline, LOCF imputation				
Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Secondary endpoint: MADRS Remission rate	Comparison groups	VOR_15	VOR_20	DUL	PBO
	Number of subject	145	147	146	153
	MADRS Remission Rate (%)	26.9	29.3	26.0	26.8
Effect estimate per comparison	MADRS Remission Rate	Comparison groups	VOR_15, PBO	VOR_20, PBO	DUL, PBO
		Odds ratio	1.05	1.19	1.10
		95% CI	0.63, 1.78	0.71, 1.99	0.65, 1.86
		P-value	0.845	0.503	0.728
Notes	Logistic regression adjusting for baseline, LOCF imputation				
Analysis description	**Secondary Analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_15	VOR_20	DUL	PBO
	Number of subject (at baseline)	145	147	146	153
	Number of subject (at Week 8)	77	77	73	85
	LS Mean change from baseline in SDS total score	-7.73	-8.55	-9.66	-7.68
	Standard Error	0.821	0.810	0.834	0.776
Effect estimate per comparison	Change from baseline in	Comparison groups	VOR_15, PBO	VOR_20, PBO	DUL, PBO
		Mean difference	-0.05	-0.88	-1.99

	SDS total score	Standard error	1.111	1.103	1.123
		P-value	0.962	0.427	0.078
Notes	MMRM with treatment centre, week, baseline*week, and week*treatment as factors				
Analysis description	**Secondary Analysis**				
Analysis population and time point description	FAS Week 8				

Descriptive statistics and estimate variability	Treatment group	VOR_15	VOR_20	DUL	PBO
	Number of subject (at baseline)	145	147	146	153
	Number of subject (at Week 8)	112	111	115	129
	LS Mean change from baseline in CGI-I score	2.54	2.47	2.31	2.65
	Standard Error	0.102	0.101	0.101	0.096

Effect estimate per comparison	Change from baseline in CGI-I score	Comparison groups	VOR_15, PBO	VOR_20, PBO	DUL, PBO
		Mean difference	-0.12	-0.19	-0.34
		Standard error	0.140	0.139	0.139
		P-value	0.400	0.177	0.014
Notes	MMRM with treatment centre, week, baseline*week, and week*treatment as factors				

Title: A phase 3, randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study comparing the efficacy and safety of 2 doses (10 and 20 mg) of vortioxetine in acute treatment of adults with Major Depressive Disorder

Study identifier	**316**		
Design	Randomized, Double-Blind, Parallel-Group, Placebo-Controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Treatment Period: 8 weeks not applicable Discontinuation Period: 2 weeks Safety Follow-up Period: 4 weeks
Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	VOR_10		Vortioxetine 10 mg/day, 8 weeks, n=155
	VOR_20		Vortioxetine 20 mg day, 8 weeks, n=150
	PBO		Placebo. 8 weeks, n=157
Endpoints and definitions	Primary endpoint	MADRS	Mean change from baseline in MADRS total at Week 8
	Secondary endpoints	MADR Response	Response defined as ≥50% decrease in the MADRS total score from Baseline
		MADRS Remission	Remission defined as a MADRS total score ≤10
		SDS	Sheehan Disability Scale (SDS) total score
		CGI-I	

Database lock	Not reported in the CSR
Results and Analysis	
Analysis description	**Primary Analysis**
Analysis population and time point description	FAS Week 8

Descriptive statistics and estimate variability	Treatment group	VOR_10	VOR_20	PBO
	Number of subject (at baseline)	154	148	155
	Number of subject (at Week 8)	124	122	139
	LS Mean change from baseline in MADRS total score	-12.96	-14.41	-10.77
	Standard Error	0.832	0.845	0.807

Effect estimate per comparison	Change from baseline in MADRS total score	Comparison groups	VOR_10, PBO	VOR_20, PBO
		Mean difference	-2.19	-3.64
		Standard error	1.151	1.161
		P-value	0.058	0.002

Notes	MMRM with treatment, centre, week, baseline*week, and treatment*week as factors, unstructured covariance matrix. To control the two-sided type I error over all the efficacy endpoints that are intended to support potential claims among the two Vortioxetine doses 10 mg and 20 mg, the efficacy endpoints were tested for each dose in a predefined sequential order at significance level 0.025. Vortioxetine 20 mg was statistically significantly better than placebo in mean change from Baseline in MADRS total score at Week 8. The parallel sequence testing strategy stopped for the 20-mg dose at the MADRS responders step which was not significantly different from placebo. Vortioxetine 10 mg was not significantly different from placebo at Week.
Analysis description	**Secondary analysis**
Analysis population and time point description	FAS Week 8

Secondary endpoint: MADRS Response rate	Comparison groups	VOR_10	VOR_20	PBO
	Number of subject	154	148	155
	MADRS Response Rate (%)	33.8	39.2	28.4

Effect estimate per comparison	MADRS Response Rate	Comparison groups	VOR_10, PBO	VOR_20, PBO
		Odds ratio	1.29	1.64
		95% CI	0.80, 2.09	1.01, 2.65
		P-value	0.301	0.044

Notes	Logistic regression adjusting for baseline, LOCF imputation
Analysis description	**Secondary analysis**
Analysis population and time point description	FAS Week 8

Secondary endpoint: MADRS Remission rate	Comparison groups	VOR_10	VOR_20	PBO
	Number of subject	154	148	155
	MADRS Remission Rate (%)	21.4	22.3	14.2

Effect estimate per comparison	MADRS Remission Rate	Comparison groups	VOR_10, PBO	VOR_20, PBO
		Odds ratio	1.67	1.78
		95% CI	0.92, 3.02	0.98, 3.23
		P-value	0.093	0.059

Notes	Logistic regression adjusting for baseline, LOCF imputation
Analysis description	Primary Analysis
Analysis population and time point description	FAS Week 8

Descriptive statistics and estimate variability	Treatment group	VOR_10	VOR_20	PBO
	Number of subject (at baseline)	154	148	155
	Number of subject (at Week 8)	89	77	86
	LS Mean change from baseline in SDS total score	-7.25	-8.26	-5.86
	Standard Error	0.747	0.794	0.771

Effect estimate per comparison	Change from baseline in SDS total score	Comparison groups	VOR_10, PBO	VOR_20, PBO
		Mean difference	-1.39	-2.40
		Standard error	1.042	1.066
		P-value	0.183	0.025

Notes	MMRM with treatment, centre, week, baseline*week, and treatment*week as factors.
Analysis description	**Secondary Analysis**
Analysis population and time point description	FAS Week 8

Descriptive statistics and estimate variability	Treatment group	VOR_10	VOR_20	PBO
	Number of subject (at baseline)	154	148	155
	Number of subject (at Week 8)	124	122	139
	LS Mean change from baseline in CGI-I score	2.69	2.59	2.89
	Standard Error	0.093	0.094	0.090

Effect estimate per comparison	Change from baseline in CGI-I score	Comparison groups	VOR_10, PBO	VOR_20, PBO
		Mean difference	-0.20	-0.29
		Standard error	0.129	0.129
		P-value		

Notes	MMRM with treatment, centre, week, baseline CGI-S*week, and treatment*week as factors

Title: A randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study comparing the efficacy and safety of vortioxetine versus placebo in acute treatment of adults with Major Depressive Disorder			
Study identifier	**303**		
Design	Randomized, Double-Blind, Parallel-Group, Placebo-Controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment Period: 6 weeks not applicable Discontinuation Period: 2 weeks Safety follow-up Period: 4 weeks	
Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	VOR_5		Vortioxetine 5 mg/day, 6 weeks, n=300
	PBO		Placebo. 6 weeks, n=300
	Secondary endpoints	HAM-D24 Response	Response defined as ≥50% decrease in the HAM-D24 total score from Baseline
		MADRS Remission	Remission defined as a MADRS total score ≤10
		MADRS	Change from baseline in MADRS total at Week 6
		SDS	Sheehan Disability Scale (SDS) total score
		CGI-I	
Database lock	Not reported in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	FAS Week 6		
Descriptive statistics and estimate variability	Treatment group	VOR_5	PBO
	Number of subject	292	286
	LS Mean change from baseline in HAM-D24 total score	-14.61	-13.87
	Standard Error	0.650	0.662

Effect estimate per comparison	Primary endpoint: change from baseline in HAM-D24 total score	Comparison groups	VOR_5, PBO
		Mean difference	-0.74
		Standard error	0.887
		P-value	0.407
Notes	ANCOVA adjusting for centre and baseline HAM-D24, LOCF imputation. To control the 2-sided type I error across all the efficacy endpoints that are intended to support potential claims, the efficacy endpoints were analyzed using pre-specified sequential testing procedures.		

Analysis description	**Secondary analysis**		
Analysis population and time point description	FAS Week 6		
Descriptive statistics and estimate	Treatment group	VOR_5	PBO
	Number of subject	292	286

variability	LS Mean change from baseline in MADRS total score	-15.80	-15.48
	Standard Error	0.698	0.708

Effect estimate per comparison	Change from baseline in MADRS total	Comparison groups	VOR_5, PBO
		Mean difference	-0.32
		Standard error	0.950
		P-value	0.736

Notes	ANCOVA adjusting for centre and baseline MADRS, LOCF imputation
Analysis description	**Secondary analysis**
Analysis population and time point description	FAS Week 6

Descriptive statistics and estimate variability	Treatment group	VOR_5	PBO
	Number of subject	292	286
	HAM-D24 Response rate (%)	46.2	46.2

Effect estimate per comparison	HAM-D24 Response Rate	Comparison groups	VOR_5, PBO
		Odds ratio	1.01
		95% CI	0.73, 1.41
		p-value	0.927

Notes	Logistic regression adjusting for baseline, LOCF imputation
Analysis description	**Secondary analysis**
Analysis population and time point description	**FAS** **Week 6**

Descriptive statistics and estimate variability	Treatment group	VOR_5	PBO
	Number of subject	292	286
	MADRS Remission rate (%)	29.1	32.2

Effect estimate per comparison	MADRS Remission rate	Comparison groups	VOR_5, PBO
		Odds ratio	0.87
		95% CI	0.61, 1.2
		p-value	0.443

Notes	Logistic regression adjusting for baseline, LOCF imputation
Analysis description	**Secondary analysis**
Analysis population and time point description	FAS Week 6

Descriptive statistics and estimate variability	Treatment group	VOR_5	PBO
	Number of subject	292	286
	LS Mean change from baseline in SDS total score	-6.69	-6.61
	Standard Error	0.557	0.548

Effect estimate per comparison	Change from baseline in SDS total	Comparison groups	VOR_5, PBO
		Mean difference	-0.09
		Standard error	0.753
		P-value	0.908
Notes	ANCOVA adjusting for centre and baseline SDS, LOCF imputation		
Analysis description	**Secondary analysis**		
Analysis population and time point description	FAS Week 6		
Descriptive statistics and estimate variability	Treatment group	VOR_5	PBO
	Number of subject	292	286
	LS Mean change from baseline in CGI-I Score	2.57	2.61
	Standard Error	0.075	0.076
Effect estimate per comparison	Change from baseline in CGI-I score	Comparison groups	VOR_5, PBO
		Mean difference	-0.04
		Standard error	0.103
		P-value	0.688
Notes	ANCOVA adjusting for centre and baseline CGI-S, LOCF imputation		

Title: A randomized, double-blind, parallel-group, placebo-controlled, active-referenced, fixed-dose study comparing the efficacy and safety of 2 doses of vortioxetine in acute treatment of adults with Major Depressive Disorder

Study identifier	**304**		
Design	Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Active-Referenced		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment Period: 8 weeks not applicable Discontinuation (Taper-down) Period: 1 week (active reference only) Safety Follow-up Period: 4 weeks after completion of the Treatment Period	
Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	VOR_2.5	Vortioxetine 2.5 mg/day, 8 weeks, n=153	
	VOR_5	Vortioxetine 5 mg day, 8 weeks, n=153	
	DUL	Duloxetine 60 mg/day, 8 weeks, n=152	
	PBO	Placebo. 8 weeks, n=153	
Endpoints and definitions	Primary endpoint	HAM-D24	Change from baseline in HAM-D24 total at Week 8
	Secondary endpoints	HAM-D24 Response	Response defined as ≥50% decrease in the HAM-D24 total score from Baseline at Week 8
		MADRS Remission	Remission defined as a MADRS total score ≤10
		MADRS	Change from baseline in MADRS total at Week 8
		SDS	Sheehan Disability Scale (SDS) total score
		CGI-I	
Database lock	Not reported in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_2.5	VOR_5	DUL	PBO
	Number of subject	146	153	149	149
	LS Mean change from baseline in HAM-D24 total score	-12.04	-11.08	-13.47	-10.50
	Standard Error	0.744	0.737	0.750	0.757

Effect estimate per comparison	Primary endpoint: change from baseline in HAM-D24 total score at week 8	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	DUL, PBO
		Mean difference	-1.54	-0.58	-2.96
		Standard error	1.038	1.036	1.047
		P-value	0.138	0.577	0.005
Notes	ANCOVA adjusting for centre and baseline HAM-D24, LOCF imputation. To control the type I error over all the efficacy endpoints that were intended to support potential claims, the efficacy endpoints were tested in a pre-defined sequential order at significance level 0.05.				

Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_2.5	VOR_5	DUL	PBO
	Number of subject	146	153	149	149
	HAM-D24 Responder rate (%)	41.1	37.9	51.0	32.2

Effect estimate per comparison	HAM-D24 Responder rate	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	DUL, PBO
		Odds ratio	1.47	1.29	2.18
		95% CI	0.91, 2.37	0.80, 2.07	1.36, 3.49
		p-value	0.111	0.296	0.001
Notes	Logistic regression analysis adjusting for baseline, LOCF imputation				

Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_2.5	VOR_5	DUL	PBO
	Number of subject	100	120	110	119
	MADRS Remission Rate (%)	33.0	26.7	46.4	27.7

Effect estimate per comparison	MADRS Remission rate	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	DUL, PBO
		Odds ratio	1.25	0.92	2.16
		95% CI	0.70, 2.25	0.52, 1.64	1.24, 3.77
		p-value	0.453	0.777	0.007
Notes	Logistic regression analysis adjusting for baseline Reported as LOCF in the core report but as Observed Cases (OC) in the source table				

Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_2.5	VOR_5	DUL	PBO
	Number of subject	146	153	149	149
	LS Mean change from baseline in MADRS total score	-11.61	-11.30	-14.10	-11.22
	Standard Error	0.805	0.797	0.811	0.819

Effect estimate per comparison	Primary endpoint: change from baseline in MADRS total score	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	DUL, PBO
		Mean difference	-0.39	-0.08	-2.87
		Standard error	1.121	1.121	1.132
		p-value	0.730	0.943	0.011
Notes	ANCOVA adjusting for centre and baseline MADRS, LOCF imputation				

Analysis description	**Secondary analysis**				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_2.5	VOR_5	DUL	PBO
	Number of subject	122	123	114	130
	LS Mean change from baseline in SDS total score	-6.46	-6.59	-8.91	-6.83
	Standard Error	0.640	0.641	0.672	0.638

Effect estimate per comparison	Primary endpoint: change from baseline in SDS total score	Comparison groups	VOR_2.5, PBO	VOR_5, PBO	DUL, PBO
		Mean difference	0.37	0.23	-2.09
		Standard error	0.876	0.874	0.900
		p-value	0.672	0.790	0.021

Notes	ANCOVA adjusting for centre and baseline SDS, LOCF imputation				
Analysis description	Secondary analysis				
Analysis population and time point description	FAS Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_2.5	VOR_5	DUL	PBO
	Number of subject	146	153	149	149
	LS Mean change from baseline in CGI-I score	2.73	2.63	2.39	2.79
	Standard Error	0.096	0.095	0.097	0.098

Effect estimate per comparison	Primary endpoint: change from baseline in CGI-I score	Comparison groups	VOR_2.5, placebo	VOR_5, placebo	DUL, placebo
		Mean difference	-0.06	-0.16	-0.40
		Standard error	0.134	0.134	0.135
		p-value	0.680	0.230	0.003
Notes	ANCOVA adjusting for centre and baseline CGI-S, LOCF imputation				

Table 12: Summary of efficacy for the four Phase III clinical trials completed between MAA submission and 31.August 2013

Title: A Phase 3, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Fixed-Dose Study Comparing the Efficacy and Safety of 2 Doses (10 and 15 mg) of Vortioxetine in Acute Treatment of Adults With Major Depressive Disorder			
Study identifier	**317**		
Design	Randomized, double-blind, parallel-group, placebo-controlled		
	Duration of main phase: Duration of Extension phase:	Treatment Period: 8 weeks Safety Follow-up Period: 4 weeks	
Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	PBO	Placebo, 8 weeks, n=160	
	VOR_10	Vortioxetine 10 mg/day, 8 weeks, n=157	
	VOR_15	Vortioxetine 10 mg/day, 1 week + Vortioxetine 15 mg/day, 7 weeks, n=152	
Endpoints and definitions	Primary endpoint	MADRS	Change from baseline in MADRS total score at week 8
	Secondary endpoints	MADRS Response	Response defined as ≥50% decrease from baseline in MADRS total score

		MADRS Remission	Remission defined as MADRS total score ≤ 10
		CGI-I	Mean CGI-I score at Week 8
		SDS	Change from Baseline in SDS total score at Week 8

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS): All randomized patients who took at least 1 dose of IMP and who had at least 1 valid post-baseline assessment of primary efficacy Week 8			
Descriptive statistics and estimate variability	Treatment group	VOR_10	VOR_15	PBO
	Number of subject	126	123	113
	LS Mean change from baseline in MADRS total score	-12.87	-13.66	-13.36
	Standard Error	1.043	1.064	1.087

Effect estimate per comparison	Primary endpoint: change from baseline in MADRS total score	Comparison groups	VOR_10, PBO	VOR_15, PBO
		Mean difference	-0.79	-0.49
		Standard Error	1.488	1.501
		P-value	0.597	0.745
Notes	MMRM model with baseline*week, center, week, treatment, and week*treatment as factors and unstructured covariance matrix.			

Analysis description	**Secondary analyses**			
Secondary analysis of primary endpoint				
Descriptive statistics and estimate variability	Treatment group	VOR_10	VOR_15	PBO
	Number of subject	143	142	149
	LS Mean change from baseline in MADRS total score	-13.17	-12.63	-12.13
	Standard Error	1.037	1.038	1.013

Effect estimate per comparison	Primary endpoint: change from baseline in MADRS total score	Comparison groups	VOR_10, PBO	VOR_15, PBO
		Mean difference	-1.04	-0.50
		Standard Error	1.432	1.429
		P-value	0.469	0.725
Notes	ANCOVA – LOCF			
Analyses of secondary endpoints				
Secondary endpoint: MADRS Response Rate	Comparison groups	VOR_10	VOR_15	PBO
	Number of subjects	143	142	149
	MADRS Response Rate (%)	37.8	37.3	32.9
Effect estimate per comparison	Secondary endpoint: MADRS Response Rate	Comparison groups	VOR_10, PBO	VOR_15, PBO
		Difference %	4.9%	4.4%
		Odds ratio	1.232	1.212
		95% Confidence interval	0.761, 1.995	0.748, 1.963
		P-value	0.396	0.435
Secondary endpoint: MADRS Remission Rate	Comparison groups	VOR_10	VOR_15	PBO
	Number of subjects	143	142	149
	MADRS Remission Rate (%)	26.6	23.9	22.1
Effect estimate per comparison	Secondary endpoint: MADRS Remission Rate	Comparison groups	VOR_10, PBO	VOR_15, PBO
		Difference %	4.5%	1.8%
		Odds ratio	1.291	1.116
		95% Confidence interval	0.754, 2.211	0.646, 1.928

		P-value	0.352	0.694
Notes	Logistic regression (LOCF) for response and remission.			
Descriptive statistics and estimate variability	Treatment group	VOR_10	VOR_15	PBO
	Number of subject	123	114	127
	LS Mean CGI-I	2.56	2.60	2.65
	Standard Error	0.107	0.110	0.105
Effect estimate per comparison	Secondary endpoint: CGI-I	Comparison groups	VOR_10, PBO	VOR_15, PBO
		Mean difference	-0.09	-0.05
		Standard Error	0.149	0.151
		P-value	0.554	0.739
Descriptive statistics and estimate variability	Treatment group	VOR_10	VOR_15	PBO
	Number of subject	74	62	77
	LS Mean change from baseline in SDS total score	-10.30	-8.69	-9.38
	Standard Error	0.959	0.990	0.877
Effect estimate per comparison	Secondary endpoint: change form baseline in SDS score	Comparison groups	VOR_5, PBO	VOR_10, PBO
		Mean difference	-0.92	0.69
		Standard Error	1.250	1.322
		P-value	0.464	0.600
Notes	MMRM model for continuous variables.			

Title: A Multinational, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study to Assess the Efficacy and Safety of Vortioxetine in Patients with Major Depressive Disorder			
Study identifier	**CCT-002**		
Design	Randomized, double-blind, parallel-group, placebo-controlled		
	Duration of main phase: Duration of Extension phase:	Treatment Period: 8 weeks Discontinuation Period: 2 weeks Safety Follow-up Period: 4 weeks	
Hypothesis	Superiority (vortioxetine vs placebo)		
Treatments groups	PBO	Placebo, 8 weeks, n=152	
	VOR_5	Vortioxetine 5 mg/day, 8 weeks, n=144	
	VOR_10	Vortioxetine 10 mg/day, 8 weeks, n=150	
	VOR_20	Vortioxetine 10 mg/day, 1 week + Vortioxetine 20 mg/day, 7 weeks, n=154	
Endpoints and definitions	Primary endpoint	MADRS	Change from baseline in MADRS total score at week 8
	Secondary endpoints	MADRS Response	Response defined as ≥50% decrease from baseline in MADRS total score
		MADRS Remission	Remission defined as MADRS total score ≤ 10
		CGI-I	Mean CGI-I score at Week 8
		SDS	Change from Baseline in SDS total score at Week 8

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Full Analysis Set (FAS): All randomized patients who took at least 1 dose of study drug Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_5	VOR_10	VOR_20	PBO
	Number of subject	142	147	149	150
	LS Mean change from baseline in MADRS total score	-14.69	-15.54	-15.52	-13.46
	Standard Error	0.85	0.83	0.82	0.83
Effect estimate per comparison	Primary endpoint: change from baseline in	Comparison groups	VOR_5, PBO	VOR_10, PBO	VOR_20, PBO
		Mean difference	-1.23	-2.08	-2.07

	MADRS total score	Standard Error	1.08	1.06	1.06
		P-value*	0.2521	0.0503	0.0522
Notes	ANCOVA adjusting for centre and baseline, LOCF imputation				
Analysis description	**Secondary analyses**				
Secondary analysis of primary endpoint					
Descriptive statistics and estimate variability	Treatment group	VOR_5	VOR_10	VOR_20	PBO
	Number of subject	126	132	131	135
	LS Mean change from baseline in MADRS total score	-15.73	-17.30	-17.28	-14.89
	Standard Error	0.77	0.76	0.75	0.75
Effect estimate per comparison	Primary endpoint: change from baseline in MADRS total score	Comparison groups	VOR_5, PBO	VOR_10, PBO	VOR_20, PBO
		Mean difference	-0.84	-2.42	-2.40
		Standard Error	1.05	1.05	1.04
		P-value	0.4250	0.0211	0.0220
Notes	MMRM with treatment, centre, week, baseline*week, and week*treatment as factors, unstructured covariance matrix.				
Analyses of secondary endpoints					
Secondary endpoint: MADRS Response Rate	Comparison groups	VOR_5	VOR_10	VOR_20	PBO
	Number of subjects	142	147	149	150
	MADRS Response Rate (%)	49.3	54.4	51.0	39.3
Effect estimate per comparison	Secondary endpoint: MADRS Response Rate	Comparison groups	VOR_5, PBO	VOR_10, PBO	VOR_20, PBO
		Difference %	10	15.1	11.7
		Odds ratio	1.501	1.837	1.604

		95% Confidence interval	0.943, 2.388	1.158, 2.914	1.013, 2.538
		P-value	0.0866	0.0098	0.0437
Secondary endpoint: MADRS Response Rate	Comparison groups	VOR_5	VOR_10	VOR_20	PBO
	Number of subjects	142	147	149	150
	MADRS Remission Rate (%)	24.6	29.3	30.9	26.7
Effect estimate per comparison	Secondary endpoint: MADRS Remission Rate	Comparison groups	VOR_5, PBO	VOR_10, PBO	VOR_20, PBO
		Difference %	-2.1	2.6	4.2
		Odds ratio	0.899	1.142	1.231
		95% Confidence interval	0.531, 1.521	0.687, 1.897	0.745, 2.034
		P-value	0.6908	0.6084	0.4170
Notes	Logistic regression (LOCF) for response and remission.				
Descriptive statistics and estimate variability	Treatment group	VOR_5	VOR_10	VOR_20	PBO
	Number of subject	142	147	149	150
	LS Mean CGI-I	2.39	2.32	2.41	2.62
	Standard Error	0.10	0.09	0.09	0.09
Effect estimate per comparison	Secondary endpoint: CGI-I	Comparison groups	VOR_5, PBO	VOR_10, PBO	VOR_20, PBO
		Mean difference	-0.22	-0.30	-0.21
		Standard Error	0.12	0.12	0.12
		P-value	0.0663	0.0136	0.0874

Descriptive statistics and estimate variability	Treatment group	VOR_5	VOR_10	VOR_20	PBO
	Number of subject	109	114	118	126
	LS Mean change from baseline in SDS total score	-6.22	-7.96	-6.97	-6.02
	Standard Error	0.68	0.67	0.65	0.64
Effect estimate per comparison	Secondary endpoint: change form baseline in SDS total score	Comparison groups	VOR_5, PBO	VOR_10, PBO	VOR_20, PBO
		Mean difference	-0.20	-1.94	-0.95
		Standard Error	0.86	0.84	0.83
		P-value	0.8144	0.0219	0.2553
Notes	ANCOVA – LOCF for continuous variables.				

Title: Randomised, double-blind, parallel-group, active-controlled, flexible-dose study evaluating the effects of Vortioxetine *versus* agomelatine in adult patients suffering from Major Depressive Disorder with inadequate response to antidepressant treatment			
Study identifier	**14178A**		
Design	Randomized, double-blind, parallel-group, active-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Treatment Period: 12 weeks not applicable Safety Follow-up Period: 4 weeks
Hypothesis	Non-inferiority		
Treatments groups	VOR 10 to 20 mg/day		Vortioxetine 10 to 20 mg/day, 12 weeks, n=255 randomised
	Agomelatine 25 to 50 mg/day		Agomelatine 25 to 50 mg/day, 12 weeks, n=246 randomised
Endpoints and definitions	Primary endpoint	ΔMADRS	Change from baseline in MADRS total score at week 8
	Secondary endpoints	ΔMADRS	Change from baseline in MADRS total score at week 12
		ΔHAM-A	Change from baseline at week 12
		ΔCGI-S and ΔCGI-I	Change from baseline at week 12
		MADRS Response	MADRS change from baseline ≥ 50%
		MADRS Remission	Remission defined as MADRS total score of 10 or less

		CGI-I Response	CGI-I Score ≤2
		CGI-S Remission	CGI-S score ≤2
		ΔSDS	Change from baseline at week 12
		ΔEQ-5D	Change from baseline at week 12
Notes	MMRM analysis was used for all continuous endpoints, ANCOVA, LOCF was used as additional analysis		
Database lock	Not reported in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Change from baseline in MADRS total score at week 8 based on FAS. A non-inferiority comparison of vortioxetine versus agomelatine was made using estimates from a mixed model for repeated measurements (MMRM, using all available data),		
Primary endpoint: ΔMADRS	Treatment group	VOR	AGO
	Number of subject	220	190
	LS Mean change from baseline in MADRS total score	-16.5	-14.4
	Standard Error	0.48	0.51
Effect estimate per comparison	Primary endpoint: change from baseline in MADRS total score	Comparison groups	VOR, AGO
		Mean difference	-2.16
		95% CI	-3.51 to -0.81
		P-value	0.002
Notes	Non-inferiority was established, as the upper bound of the 95% CI for the vortioxetine and agomelatine comparison was -0.81 MADRS points, and therefore clearly below the non-inferiority margin of +2 MADRS points versus agomelatine. The positive results were confirmed by the sensitivity analyses (PPS, MMRM; ANCOVA, FAS, LOCF).		
Analysis description	**Secondary analysis**		
Analysis population and time point description	FAS Week 12		
Secondary endpoint ΔMADRS total score	Treatment group	VOR	AGO
	Number of subjects	200	178
	Mean change from baseline in total score	-16.92	-18.95
	Standard error	0.50	0.53
Effect estimate per comparison	MADRS total score	Comparison groups	VOR,AGO
		Mean difference to AGO	-2.03
		95% CI	-3.45;-0.60
		p-value	0.0054
Notes	FAS, MMRM supported by LOCF, ANCOVA		
Analysis description	**Secondary analysis**		
Analysis population and time point description	FAS Week 12		

Secondary endpoint: ΔHAM-A TOTAL SCORE	Treatment group	VOR	AGO
	Number of subject	200	178
	Mean change from baseline in total score	-13.52	-11.59
	Standard Error	0.40	0.42
Effect estimate per comparison	HAM-A Rating Scale	Comparison groups	VOR, AGO
		Mean Difference to AGO	-1.93
		95% CI	-3.04; -0.81
		P-value	0.0007
Notes	FAS , MMRM, supported by LOCF, ANCOVA		
Analysis description	**Secondary analysis**		
Analysis population and time point description	FAS Week 12		
Secondary endpoint: ΔCGI-S Score	Treatment group	VOR	AGO
	Number of subject	200	178
	Mean change from baseline in total score	-2.20	-1.93
	Standard Error	0.07	0.07
Effect estimate per comparison	CGI-S Score	Comparison groups	VOR, AGO
		Mean Difference to AGO	-0.27
		95% CI	-0.47; -0.07
		P-value	0.0075
Notes	FAS , MMRM, supported by LOCF, ANCOVA		
Analysis description	**Secondary analysis**		
Analysis population and time point description	FAS Week 12		
Secondary endpoint: ΔCGI-I Score	Treatment group	VOR	AGO
	Number of subject	200	178
	Mean change from baseline in total score	1.74	1.99
	Standard Error	0.06	0.07
Effect estimate per comparison	CGI-I Score	Comparison groups	VOR, AGO
		Mean Difference to AGO	-0.25
		95% CI	-0.42; -0.07
		P-value	0.0055
Notes	FAS , MMRM, supported by LOCF, ANCOVA		
Analysis description	**Secondary analysis**		

Analysis population and time point description	FAS Week 12		
Secondary endpoint: MADRS Response Rate	Treatment group	VOR	AGO
	Number of subject	252	241
	MADRS Response Rate (%)	69.8%	56%
Effect estimate per comparison	MADRS Response Rate	Comparison groups	VOR, AGO
		Odds Ratio	1.83%
		95% CI	1.26;2.65
		P-value	0.0014
Notes	FAS , LOCF, LREG; Response defined as at least 50% reduction from baseline in MADRS total score		
Analysis description	**Secondary analysis**		
Analysis population and time point description	FAS Week 12		
Secondary endpoint: MADRS Remission Rate	Treatment group	VOR	AGO
	Number of subject	139	95
	MADRS Remission Rate (%)	55.2%	39.4%
Effect estimate per comparison	MADRS Remission Rate	Comparison groups	VOR, AGO
		Odds Ratio	2.01
		95% CI	1.39;2.90
		P-value	0.0002
Notes	FAS, LOCF, LREG, Remission defined as a MADRS Total Score less than or equal to 10		
Analysis description	**Secondary Analysis**		
Analysis population and time point description	FAS Week 12		
Secondary endpoint: CGI-I Response Rate	Treatment group	VOR	AGO
	Number of subjects	187	154
	CGI Response Rate (%)	74.2%	63.9%
Effect estimate per comparison	CGI-I response rate	Comparison groups	VOR,AGO
		Odds ratio	1.62%
		95% CI	1.10;2.39
		p-Value	0.0142
Notes	FAS, LOCF, LREG; Response defined as a CGI-I score less than or equal to 2		
Analysis description	**Secondary Analysis**		
Analysis population and time point description	FAS Week 12		
Secondary endpoint: CGI-S Remission Rate	Treatment group	VOR	AGO
	Number of subjects	140	106
	CGI Response Rate (%)	55.6%	44%

Effect estimate per comparison	CGI-S remission rate	Comparison groups	VOR,AGO
		Odds ratio	1.63
		95% CI	1.14;2.33
		p-Value	0.0077
Notes	FAS, LOCF, LREG; Remission is defined as a CGI-S score less than or equal to 2		
Analysis description	**Secondary Analysis**		
Analysis population and time point description	FAS Week 12		
ΔSDS total score	Treatment group	VOR	AGO
	Number of subject	148	132
	LS Mean change from baseline in SDS total score	-10.99	-9.24
	Standard Error	0.55	0.58
Effect estimate per comparison	SDS total score	Comparison groups	VOR, AGO
		Mean difference	-1.75
		Standard Error	0.75
		P-value	0.0209
Notes	FAS, MMRM		
Analysis description	**Secondary Analysis**		
Analysis population and time point description	FAS Week 12		
ΔEQ-5D	Treatment group	VOR	AGO
	Number of subject	200	178
	LS Mean change from baseline in EQ-5D	0.25	0.20
	Standard Error	0.01	0.02
Effect estimate per comparison	EQ-5D score	Comparison groups	VOR,AGO
		Mean difference	0.05
		Standard Error	0.02
		P-value	0.0127
Notes	FAS,MMRM		

Title: A randomized, double-blind, parallel-group, placebo-controlled, fixed dose study on the efficacy of Vortioxetine on cognitive dysfunction in adult patients with Major Depressive Disorder (MDD)			
Study identifier	**14122A**		
Design	Randomized, double-blind, parallel-group, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of uptitration: Duration of Extension phase:		Treatment Period: 8 weeks not applicable Only in the Vor 20 mg group Vor 10mg/day for 1 week Safety Follow-up Period: 4 weeks
Hypothesis	Superiority (vortioxetine versus placebo)		
Treatments groups	VOR 10 mg/day		Vortioxetine 10 mg/day, 8 weeks, n= 197 randomised
	VOR 20 mg/day		Vortioxetine 20mg/day, 8 weeks , n=207 randomised
	Placebo (PBO)		Placebo for 8 weeks, n= 198 randomised
Endpoints and definitions	Primary endpoint cognition	Composite z-score	Change from baseline to week 8 in Composite z-score of DSST and RAVLT
	Key secondary endpoint	ΔDSST	Change from baseline to week 8
		ΔRAVLT acquisition score (learning)	Change from baseline to week 8
		ΔRAVLT delayed recall score (memory)	Change from baseline to week 8
	Secondary endpoints Depressive symptoms	ΔMADRS	Change from baseline in MADRS total score at week 8
		ΔCGI-S	Change from baseline in CGI-S score at week 8
		ΔCGI-I	Change from baseline in CGI-I score at week 8
Notes	MMRM analysis, ANCOVA,OC and LOCF was used as additional analysis		
Database lock	Not reported in the CSR		
Results and Analysis			

Analysis description	**Primary Analysis (FAS,MMRM)**			
Analysis population and time point description	Change from baseline to Week 8 in DSST (number of correct symbols), RAVLT (learning) and RAVLT(memory) using the composite z-score defined as the weighted sum of the individual patient z-scores			
Primary endpoint: z-score	Treatment group	VOR 10 mg	VOR 20 mg	PBO
	Number of subject	180	187	178
	LS Mean change from baseline in z- score	0.128	0.095	-0.235
	Standard Error	0.052	0.051	0.053
Effect estimate per comparison	Primary endpoint: change from baseline z-score	Comparison groups	VOR 10mg, PBO	VOR 20 mg, PBO
		Mean difference	0.36	0.33
		95% CI	0.22 to 0.50	0.19 to 0.47
		p-value	<0.0001	<0.0001
Notes	The positive results were confirmed by the sensitivity analyses (FAS, OC, LOCF, ANCOVA).			
Analysis description	**Key Secondary analysis**			
Analysis population and time point description	FAS, MMRM Week 8			
Secondary endpoint: ΔDSST score	Treatment groups	VOR 10 mg	VOR 20 mg	PBO
	Number of subject	180	187	179
	Mean change from baseline in total score	9.03	9.09	4.83
	Standard Error	0.63	0.61	0.63
	ΔDSST score	Comparison groups	VOR 10mg, PBO	VOR 20 mg, PBO
		Mean Difference to PBO	4.20	4.26
		95% CI	2.5; 5.9	2.57;5.94
		P-value	<0.001	<0.001
Notes	FAS , MMRM, supported by LOCF,OC, ANCOVA			

Analysis description	**Key Secondary analysis**			
Analysis population and time point description	FAS, MMRM Week 8			
Secondary endpoint: ΔRAVLT acquisition score (learning)	Treatment groups	VOR 10 mg	VOR 20mg	PBO
	Number of subject	180	187	179
	Mean change from baseline in total score	4.08	3.65	3.06
	Standard Error	0.34	0.33	0.34
Effect estimate per comparison	ΔRAVLT acquisition score (learning)	Comparison groups	VOR 10mg, PBO	VOR20mg, PBO
		Mean Difference to PBO	1.02	0.59
		95% CI	(0.11;1.93)	(-0.31,1.5)
		P-value	0.029	0.199
Notes	FAS , MMRM, supported by LOCF,OC, ANCOVA As the p-values were >0.025, the testing strategy was stopped.			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS, MMRM Week 8			
Secondary endpoint: ΔRAVLT delayed recall store (memory)	Treatment groups	VOR 10 mg	VOR 20 mg	PBO
	Number of subject	180	187	178
	Mean change from baseline in total score	1.63	1.56	0.91
	Standard Error	0.18	0.17	0.18
Effect estimate per comparison	ΔRAVLT delayed recall store (memory)	Comparison groups	VOR 10mg, PBO	VOR 20mg, PBO
		Mean Difference to PBO	0.71	0.65
		95% CI	0.24; 1.19	0.17; 1.12
		P-value	0.0033	0.0073
Notes	FAS , MMRM, supported ANCOVA, OC and LOCF			

Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS, MMRM Week 8			
Secondary endpoint: ΔMADRS	Treatment groups	VOR 10 mg	VOR 20mg	PBO
	Number of subject	174	181	165
	Mean change from baseline in total score	-15.56	-17.55	-10.85
	Standard error	0.63	0.62	0.64
Effect estimate per comparison	ΔMADRS	Comparison groups	VOR 10mg, PB0,	VOR 20 mg, PBO
		Mean difference to PBO	-4.70	-6.70
		95% CI	-6.45; -2.96	-8.43;-4.98
		P-value	<0.0001	<0.0001
Notes	FAS, MMRM supported by ANCOVA, OC and LOCF			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS, MMRM Week 8			
Secondary endpoint:ΔCGI-S	Comparison groups	VOR 10 mg	VOR 20mg	PBO
	Number of subject	174	181	165
	Mean change from baseline in total score	-1.80	-2.00	-1.15
	Standard error	0.08	0.08	0.08
Effect estimate per comparison	ΔCGI-S	Comparison groups	VOR 10mg, PBO	VOR 20mg, PBO
		Mean difference to PBO	-0.65	-0.85
		95% CI	-0.88; -0.42	-1.08; -0.62
		P-value	<0.0001	<0.0001

Notes	FAS, MMRM supported by ANCOVA, OC and LOCF			
Analysis description	**Secondary Analysis**			
Analysis population and time point description	FAS Week 8			
Secondary endpoint: ΔCGI-I	Comparison groups	VOR 10 mg	VOR 20 mg	PBO
	Number of subjects	174	181	165
	Mean change from baseline in total score	2.24	1.99	2.85
	Standard error	0.08	0.07	0.08
Effect estimate per comparison	ΔCGI-I	Comparison groups	VOR10 mg, PBO	VOR 20 mg, PBO
		Mean difference to PBO	-0.61	-0.86
		95% CI	-0.81; -0.40	-1.06,-0.65
		p-Value	<0.0001	<0.0001
Notes	FAS, MMRM supported by ANCOVA, OC and LOCF			

Table 13: Summary of efficacy for the Phase III clinical trial in elderly patients

Title: Randomised, double-blind, parallel-group, placebo controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of vortioxetine in acute treatment of Major Depressive Disorder in elderly patients					
Study identifier	**12541A**				
Design	Randomized, double-blind, parallel-group, placebo controlled, active-referenced				
	Duration of main phase:		Treatment Period: 8 weeks		
	Duration of Run-in phase:		not applicable		
	Duration of Extension phase:		Taper Period: 1 week Safety follow-up Period: 4 weeks after completion/withdrawal		
Hypothesis	Superiority (vortioxetine vs placebo)				
Treatments groups	VOR_5		Vortioxetine 5 mg/day, 8 weeks, n=157		
	DUL		Duloxetine 60 mg/day, 8 weeks, n=151		
	PBO		Placebo. 8 weeks, n=145		
Endpoints and definitions	Primary endpoint	HAM-D24	Change from baseline in HAM-D24 total score at Week 8		
	Secondary endpoints	HAM-D24 Response	Response defined as ≥50% decrease in the HAM-D24 total score from Baseline at Week 8		
		MADRS Remission	Remission defined as a MADRS total score ≤10 at Week 8		
		MADRS	Change from baseline in MADRS total score at Week 8		
		CGI-I	CGI-I at Week 8		
	SDS was not assessed in this study				
Database lock	Not reported in the CSR				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Full Analysis Set Week 8				
Descriptive statistics and estimate variability	Treatment group	VOR_5	DUL	PBO	
	Number of subject	155	148	145	
	LS Mean change from baseline in HAM-D24 total score	-13.7	-15.8	-10.3	
	Standard Error	0.74	0.75	0.76	
Effect estimate per comparison	Primary endpoint: change from baseline in HAM-D24 total score	Comparison groups	VOR_5, PBO	DUL, PBO	
		Mean difference	-3.32	-5.48	
		Standard error	1.01	1.03	
		P-value	0.0011	<.0001	
Notes	ANCOVA adjusting for centre and baseline HAM-D24, LOCF imputation A statistical testing strategy, based on a pre-defined hierarchy of ordered hypotheses was defined a priori in the SAP VOR_5 was statistically significantly superior to placebo on the mean change from baseline in HAM-D24 total score at Week 8 and at Week 6, but not at Week 4; the testing strategy was therefore stopped at Week 4				
Analysis description	**Secondary analysis**				

Analysis population and time point description	FAS Week 8			
Descriptive statistics and estimate variability	Treatment group	VOR_5	DUL	PBO
	Number of subject	155	148	145
	HAM-D24 Response Rate (%)	53	63	35

Effect estimate per comparison	HAM-D24 Response Rate	Comparison groups	VOR_5, PBO	DUL, PBO
		Odds ratio	0.43	0.27
		95% CI	0.26, 0.70	0.16, 0.45
		p-value	0.0008	<.0001
Notes	Logistic regression analysis adjusting for baseline, LOCF imputation			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS Week 8			

Descriptive statistics and estimate variability	Treatment group	VOR_5	DUL	PBO
	Number of subject	155	148	145
	MADRS Remission Rate (%)	34	47	21

Effect estimate per comparison	MADRS Remission Rate	Comparison groups	VOR_5, PBO	DUL, PBO
		Odds ratio	0.47	0.24
		95% CI	0.27; 0.83	0.13; 0.42
		p-value	0.0090	<.0001
Notes	Logistic regression analysis adjusting for baseline, LOCF imputation			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS Week 8			

Descriptive statistics and estimate variability	Treatment group	VOR_5	DUL	PBO
	Number of subject	155	148	145
	LS Mean change from baseline in MADRS total score	-15.5	-18.0	-11.2
	Standard Error	0.75	0.76	0.77

Effect estimate per comparison	Change from baseline in MADRS total score	Comparison groups	VOR_5, PBO	DUL, PBO
		Mean difference	-4.29	-6.83
		Standard error	1.03	1.05
		p-value	<.0001	<.0001
Notes	ANCOVA adjusting for centre and baseline MADRS, LOCF imputation			
Analysis description	**Secondary analysis**			

Analysis population and time point description	FAS Week 8			
Descriptive statistics and estimate variability	Treatment group	VOR_5	DUL	PBO
	Number of subject	155	148	145
	MADRS Response Rate (%)	60	71	36
Effect estimate per comparison	MADRS Response Rate	Comparison groups	VOR_5, PBO	DUL, PBO
		Odds ratio	0.33	0.19
		95% CI	0.20, 0.55	0.11, 0.32
		p-value	<.0001	<.0001
Notes	Logistic regression analysis adjusting for baseline, LOCF imputation			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS Week 8			
Descriptive statistics and estimate variability	Treatment group	VOR_5	DUL	PBO
	Number of subject	155	148	145
	LS for CGI-I score	2.35	2.07	2.91
	Standard Error	0.09	0.10	0.10
Effect estimate per comparison	CGI-I score	Comparison groups	VOR_5, PBO	DUL, PBO
		Mean difference	-0.56	-0.84
		Standard error	0.13	0.13
		p-value	<.0001	<.0001
Notes	ANCOVA adjusting for centre and baseline, LOCF imputation			

Table 14: Summary of efficacy for the Phase III relapse prevention trial

Title: A double-blind, randomised, placebo-controlled, multicentre, relapse-prevention study with two doses of vortioxetine in patients with Major Depressive Disorder		
Study identifier	**11985A**	
Design	Randomized, double-blind, placebo-controlled	
	Duration of main phase:	Open-label, flexible-dose Period: 12 weeks Double-blind, fixed-dose Period: 24 to 64 weeks
	Duration of Run-in phase:	not applicable
	Duration of Extension phase	Discontinuation Period I: 2 weeks after Baseline II / Randomisation Discontinuation Period II: 2 weeks after completion of the Double-blind Period Safety Follow-up Period: 4-week period after the last dose of investigational medicinal product
Hypothesis	Superiority (vortioxetine vs placebo)	
Treatments groups	VOR	Vortioxetine 5 or 10 mg/day, n=206

	PBO		Placebo, n=194
Endpoints and definitions	Primary endpoint Secondary endpoints	Time to relapse	Time to relapse within the first 24 weeks of the Double-blind Period based on: a MADRS total score ≥22 or an unsatisfactory treatment effect lack of efficacy) as judged by the investigator
		MADRS	Change from Baseline II in MADRS total score at Week 24
		Time to relapse 2	Time to relapse within the entire Double-blind Period
		MADRS Response	Response defined as a ≥50% decrease from Baseline I in MADRS total score
		MADRS Remission	Remission defined as a MADRS total score ≤10
		SDS	Change from Baseline II in Sheehan Disability Scale total score
		CGI-I	CGI-I at Week 24
Notes	Baseline I: beginning of the Open-label Period (that is, Visit 2 at Week 0) Baseline II: beginning of the Double-blind Period (defined as the last visit [that is, Visit 8 at Week 12] in the Open-label Period) when patients were randomised to double-blind treatment.		
Database lock	Not reported in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set : all patients who completed the open-label treatment period, were randomized to the double-blind treatment period and who took at least one dose of double-blind IMP Time to relapse within 24 weeks in the Double-blind Period		
Descriptive statistics	Treatment group	VOR	PBO
	Number of subject	204	192
	Number of event	27	50
Effect estimate per comparison	Primary endpoint: Time to relapse within the entire double-bling period	Comparison groups	VOR, PBO
		Hazard ratio	2.01
		95% CI	1.26, 3.21
		P-value	0.0035
Notes	Cox model; exact method for handle ties		
Analysis description	**Secondary analysis**		
Analysis population and time point description	FAS Time to relapse within the entire Double-blind Period		
Descriptive statistics	Treatment group	VOR	PBO
	Number of subject	204	192
	Number of event	31	58
Effect estimate per comparison	Primary endpoint: Time to relapse within 24 weeks	Comparison groups	VOR, PBO
		Hazard ratio	2.09
		95% CI	1.35, 3.23
		P-value	0.0010
Notes	Cox model, exact method for handle ties		
Analysis description	**Secondary analysis**		

Analysis population and time point description	FAS Double-blind Period Week 24			
Descriptive statistics and estimate variability	Treatment group		VOR	PBO
	Number of subject		151	132
	LS Mean change from Baseline II in MADRS total score		-0.62	1.45
	Standard Error		0.51	0.55
Effect estimate per comparison	Change from Baseline II in MADRS total	Comparison groups	VOR, PBO	
		Mean difference	-2.06	
		Standard error	0.66	
		p-value	0.0020	
Notes	ANCOVA adjusting for centre and baseline MADRS, OC The mean values per visit during the Double-blind Period are quite different, depending on whether OC or the LOCF is used. This difference occurs since a considerably larger proportion of patients in the placebo group withdrew from the study. The mean treatment differences to placebo in the Double-blind Period were generally larger for the VOR group in the LOCF analyses than in the OC analyses, however, primarily OC data are presented in the body of this report as they best reflect the patients who responded to treatment.			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS Double-blind Period Week 24 of the Double-blind Period			
Descriptive statistics and estimate variability	Treatment group		VOR	PBO
	Number of subject		151	132
	MADRS Response Rate (%)		98.01	91.67
Effect estimate per comparison	MADRS Response Rate	Comparison groups	VOR, PBO	
		Difference (%)	6.35	
		95% CI	1.13, 11.56	
		P-value	0.025	
Notes	Fisher's exact test, Observed Cases (OC)			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS Double-blind Period Week 24 of the Double-blind Period			
Descriptive statistics and estimate variability	Treatment group		VOR	PBO
	Number of subject		151	132
	MADRS Remission Rate (%)		94.70	82.58
Effect estimate per comparison	MADRS Remission Rate	Comparison groups	VOR, PBO	
		Difference (%)	12.13	
		95% CI	4.73, 19.52	
		P-value	0.002	
Notes	Fisher's exact test, OC			
Analysis description	**Secondary analysis**			

Analysis population and time point description	FAS Double-blind Period Week 24			
Descriptive statistics and estimate variability	Treatment group		VOR	PBO
	Number of subject		135	118
	LS Mean change from Baseline II in SDS total score		-0.53	0.14
	Standard Error		0.57	0.58
Effect estimate per comparison	Change from Baseline II in CGI-I score	Comparison groups	VOR, PBO	
		Mean difference	-0.67	
		Standard error	0.73	
		p-value	0.3642	
Notes	ANCOVA adjusting for centre and baseline value, OC			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS Double-blind Period Week 24			
Descriptive statistics and estimate variability	Treatment group		VOR	PBO
	Number of subject		32	32
	LS Mean change from Baseline II in SDS total score		4.02	4.33
	Standard Error		0.21	0.19
Effect estimate per comparison	Change from Baseline II in SDS total	Comparison groups	VOR, PBO	
		Mean difference	-0.32	
		Standard error	0.28	
		p-value	0.2569	
Notes	ANCOVA adjusting for centre and baseline CGI-S, OC			

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

Meta-analyses including all the short-term studies (except the dedicated study in the elderly, as it only included patients aged ≥65 years) were performed on the MADRS (total score, total score with baseline MADRS greater than or equal to 30, total score with baseline HAM-A greater than or equal to 20, and single items), CGI-I score, HAM-A (total score and item 5), SF-36 MCS and Physical Component Summary scores, SF-36 domain scores, and SDS total scores. Meta-analyses were also performed for the subset of studies conducted outside the United States.

All meta-analyses on the **MADRS** score showed a statistically significant improvement observed with the 5 mg, 10 mg and 20 mg dose, but not with the 15 mg dose. The 15 mg dose was included in two studies, one performed in Europe and South Africa (13267A) in which it turned out positive and one performed in the US (315) in which it turned out negative. The meta-analysis restricted to the four non-US studies (11492A, 11984A, 305, 13267A) showed that all doses were better than placebo as to the MADRS score. Stepwise updated meta-analyses (MMRM) of the mean change from baseline in MADRS total score at week 6/8 were conducted to illustrate the effect of the addition of each of short-term, placebo-controlled Studies 317, 14122 A and CCT-002 that were completed between MAA submission and 31 August 2013.

The effect in the individual studies was supported by the meta-analysis (MMRM) of the mean change from baseline in MADRS total score at Week 6/8 in the short-term, placebo-controlled studies in adults. In the meta-analysis, the overall mean difference to placebo across the studies was statistically significant: -2.3 points (p = 0.007), -3.6 points (p <0.001), and -4.6 points (p <0.001) for the 5, 10, and 20mg/day doses, respectively; the 15mg/day dose did not separate from placebo in the meta-analysis, but the mean difference to placebo was -2.6 points (Panel 9).

In the meta-analysis of all the short-term, placebo-controlled non-US studies in adults, the effect sizes and the increased effect with increasing dose were more pronounced (-3.2, -4.2, -5.5, and -5.4 points at Week 6/8 for the 5, 10, 15, and 20mg/day doses, respectively [Panel 9]) as expected when excluding negative or weak studies *in casu* the US studies 303, 304, 315, 316 and 303

In the meta-analysis of the initially submitted short-term studies, the oOverall mean difference to placebo in the change from Baseline in MADRS total score (FAS, MMRM) was of -2.57 [-0.67;-4.48] for the 5 mg/day dose, -4.11 [-2.06;-6.17] for the 10 mg/day dose, -3.54 [+0.43; -7.51] for the 15 mg/day dose, and –4.53 [-1.88;-7.19] for the 20 mg/day doseThree additional short-term studies completed between MAA submission and 31 August 2013 have subsequentially been included in the meta-analysis, of which two do not separate statistically from placebo in the primary efficacy endpoint (Study 317 and CCT-002), and one is a cognition study with efficacy on the MADRS scale as secondary endpoint (Study 14122A).

The inclusion of these additional studies in the meta-analysis results in lower effect sizes. The effect size in adults (Overall mean difference to placebo in the change from Baseline in MADRS total score (FAS, MMRM)) was **-2.27** [**-0.63**;**-3.92**] for the 5 mg/day dose, **-3.57** [-2.17;**-4.97**] for the 10 mg/day dose, **-2.60** [**+0.54**; **-5.75**] for the 15 mg/day dose, and –4.57 [-2.57;**-6.57**] for the 20 mg/day dose). The values presented in bold are decreased compared to the initial meta-analysis. Hence, the effect size of vortioxetine was moderate.

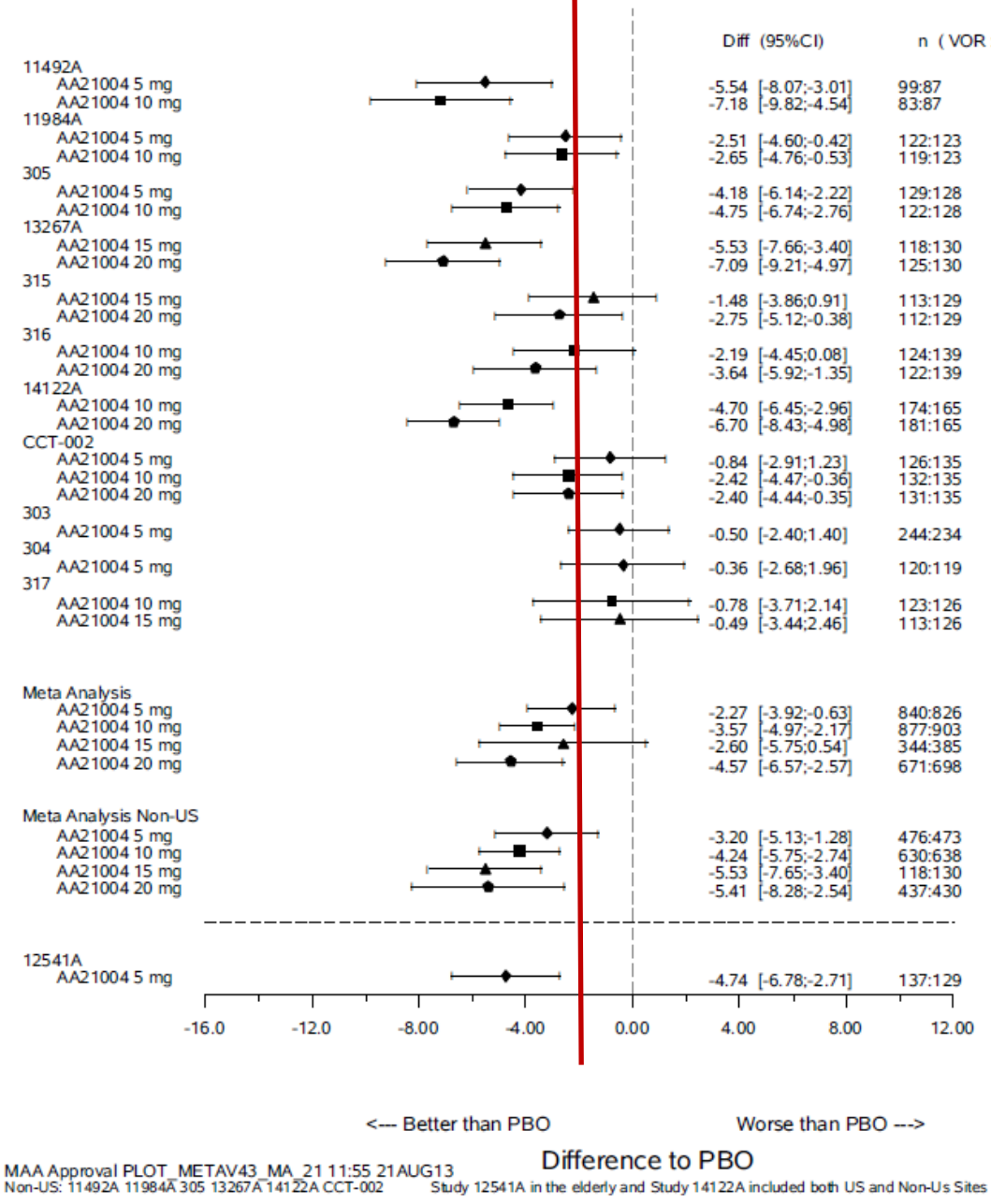
The inclusion of two additional studies (317, CCT-002) and one cognition study (14122A) reduced the overall effect size, which however remained clinically relevant.

Based on the overall data, a dose-response pattern has reasonably been established.

The lower efficacy showed in the US studies remains difficult to explain.

As a whole, the results suggested that the efficacy of vortioxetine compared to placebo is of moderate clinical relevance.

Panel 9 Change from Baseline in MADRS Total Score at Week 6/8 (FAS, MMRM)
All Short-term Studies - Original Adding Studies 317 14122A and CCT-002



The red line indicates the target of clinical relevance (2 point difference to placebo in the change from Baseline in MADRS total score used in antidepressant research).

With a stepwise addition of the recently completed short-term, placebo-controlled studies, the results of the meta-analyses did not change the overall dose-response pattern. However, the effect size was lower due to the addition of two failed/negative studies.

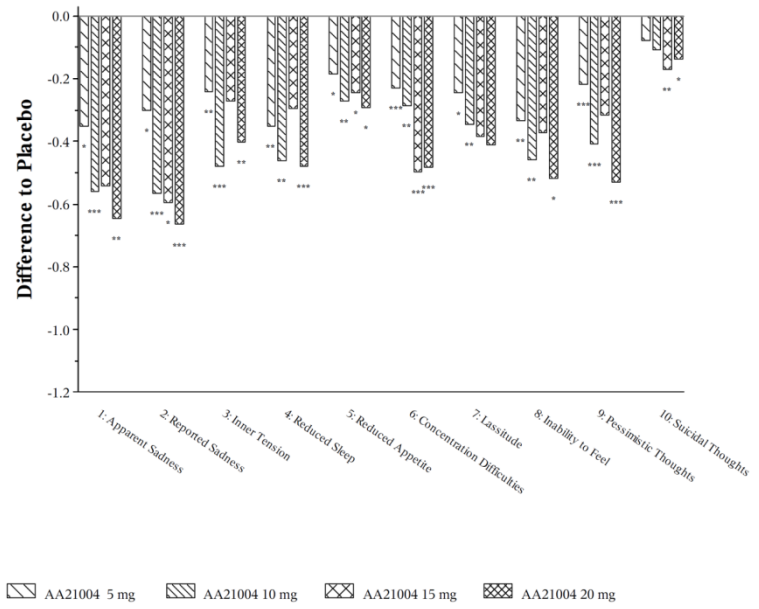
A similar tendency was observed in the meta-analyses on the **MADRS 50% response rate** at Week 6/8, the **MADRS≤10 remission rate** at Week 6/8, and the **HAM-A** total score at Week 6/8.

The meta-analyses on the **MADRS 50% response** at Week 6/8 showed that vortioxetine treatment separated from placebo in fourof the 8 studies in adults. In the meta-analysis, all doses except the 15 mg dose gave a statistically significant odds ratio of 1.6 to 2.

No meta-analysis was performed on the **MADRS≤10 remission** rate at Week 6/8 but data from the individual studies showed that a significant remission was obtained in 3 out of 8 studies in adults with the 5 mg and 10 mg dose in two studies (11492A, 305) and with the 15 mg and 20 mg dose in one study (13267A). Remission rates after vortioxetine treatment did not separate from placebo for the 5 mg, 10 mg, 15 mg, and 20 mg in the failed study (11984A) and the US studies (315, 316, 303, 304).

The 6-item version of the MADRS (**$MADRS_6$**) contains a subset of MADRS items that are regarded as core symptoms of depression: *apparent sadness, reported sadness, inner tension, lassitude, inability to feel*, and *pessimistic thoughts*. The meta-analysis on the MADRS single item score showed small effect sizes ranging between 0.22 and 0.66 point difference from placebo on the 6 core depression symptoms. The 15 mg dose did not separate from placebo except on the reported sadness itemon any of the 6 core items. Vortioxetine scored below 0.4 points and/or without statistical significance on *inner tension*, *lassitude* and *inability to feel*. A somewhat better score above 0.4 points and more statistical significance across the different doses was obtained on *apparent sadness*, *reported sadness*, and *pessimistic thoughts*.

Panel 82 Meta Analysis of Change from Baseline in MADRS Single Items at Week 6 (FAS, MMRM) - All Short-term Studies in Adults



*: p<0.05 **: p<0.01 ***: p<0.001

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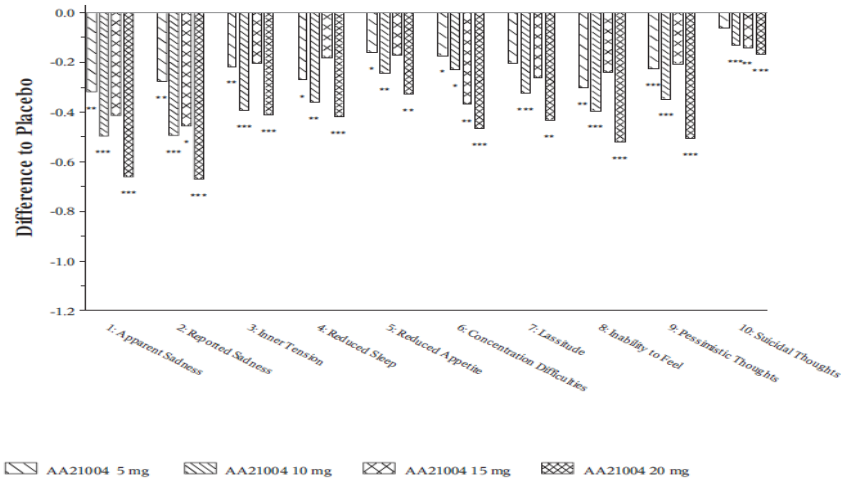
The meta-analyses of the MADRS single item scores at Week 6/8 in the short term, placebo-controlled studies in adults have been updated with Studies 317, 14122A, and CCT-002.

Panel 43 Meta Analysis of Change from Baseline in MADRS Single Items at Week 6/8 (FAS, MMRM) - All Short-term Studies in Adults



*: p<0.05 **: p<0.01 ***: p<0.001

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The results of the updated meta-analyses did not change the overall dose-response pattern of the MADRS single items score

The effects on the MADRS single items compared to placebo are modest and the overall data being lower in the second meta-analysis including all short-term studies than in the first meta-analysis. However, the differences compared to placebo were demonstrated to be statistically significant.

Table 10 Meta Analysis of Change from Baseline in MADRS Single Items at Week 6/8 (FAS, MMRM) All Short-term Studies in Adults

Item	Treatment	Week	N	Diff. to PBO	SE	Lower 95% CI	Upper 95% CI	p-value	Hetero. p-value
1: Apparent Sadness	PBO	8	1515	.	.	.	.	.	.
	AA21004 5 mg	8	840	-0.32	0.12	-0.56	-0.08	0.009	0.002
	AA21004 10 mg	8	877	-0.50	0.09	-0.67	-0.32	<.001	0.048
	AA21004 15 mg	8	344	-0.41	0.25	-0.91	0.08	0.100	0.003
	AA21004 20 mg	8	671	-0.66	0.16	-0.98	-0.34	<.001	<.001
2: Reported Sadness	PBO	8	1515	.	.	.	.	.	.
	AA21004 5 mg	8	840	-0.28	0.10	-0.48	-0.07	0.008	0.031
	AA21004 10 mg	8	877	-0.50	0.09	-0.68	-0.31	<.001	0.041
	AA21004 15 mg	8	344	-0.46	0.23	-0.91	-0.01	0.047	0.010
	AA21004 20 mg	8	671	-0.67	0.14	-0.95	-0.39	<.001	0.005
3: Inner Tension	PBO	8	1515	.	.	.	.	.	.
	AA21004 5 mg	8	840	-0.22	0.08	-0.37	-0.07	0.004	0.120
	AA21004 10 mg	8	877	-0.39	0.05	-0.50	-0.29	<.001	0.434
	AA21004 15 mg	8	344	-0.21	0.25	-0.69	0.28	0.406	<.001
	AA21004 20 mg	8	671	-0.41	0.09	-0.58	-0.24	<.001	0.106
4: Reduced Sleep	PBO	8	1515	.	.	.	.	.	.
	AA21004 5 mg	8	840	-0.27	0.13	-0.53	-0.01	0.040	0.002
	AA21004 10 mg	8	877	-0.36	0.11	-0.58	-0.14	0.001	0.007
	AA21004 15 mg	8	344	-0.18	0.21	-0.60	0.23	0.386	0.025
	AA21004 20 mg	8	671	-0.42	0.12	-0.65	-0.19	<.001	0.049
5: Reduced Appetite	PBO	8	1515	.	.	.	.	.	.
	AA21004 5 mg	8	840	-0.16	0.07	-0.30	-0.03	0.020	0.110
	AA21004 10 mg	8	877	-0.24	0.08	-0.40	-0.09	0.002	0.034
	AA21004 15 mg	8	344	-0.17	0.11	-0.39	0.05	0.122	0.230
	AA21004 20 mg	8	671	-0.33	0.11	-0.55	-0.11	0.004	0.010
6: Concentration Difficulties	PBO	8	1515	.	.	.	.	.	.
	AA21004 5 mg	8	840	-0.17	0.08	-0.32	-0.02	0.026	0.150
	AA21004 10 mg	8	877	-0.23	0.09	-0.41	-0.05	0.014	0.026
	AA21004 15 mg	8	344	-0.37	0.14	-0.65	-0.09	0.009	0.163
	AA21004 20 mg	8	671	-0.47	0.11	-0.68	-0.26	<.001	0.068
7:Lassitude	PBO	8	1515	.	.	.	.	.	.
	AA21004 5 mg	8	840	-0.20	0.11	-0.41	0.01	0.058	0.014
	AA21004 10 mg	8	877	-0.32	0.09	-0.49	-0.15	<.001	0.055
	AA21004 15 mg	8	344	-0.26	0.23	-0.72	0.19	0.256	0.007
	AA21004 20 mg	8	671	-0.43	0.15	-0.73	-0.14	0.004	<.001
8: Inability to Feel	PBO	8	1515	.	.	.	.	.	.
	AA21004 5 mg	8	840	-0.30	0.10	-0.50	-0.11	0.002	0.033
	AA21004 10 mg	8	877	-0.40	0.09	-0.58	-0.21	<.001	0.027
	AA21004 15 mg	8	344	-0.24	0.23	-0.70	0.21	0.296	0.007
	AA21004 20 mg	8	671	-0.52	0.14	-0.80	-0.24	<.001	0.002
9: Pessimistic Thoughts	PBO	8	1515	.	.	.	.	.	.
	AA21004 5 mg	8	840	-0.23	0.05	-0.33	-0.12	<.001	0.592
	AA21004 10 mg	8	877	-0.35	0.07	-0.49	-0.21	<.001	0.108
	AA21004 15 mg	8	344	-0.21	0.18	-0.56	0.15	0.258	0.022
	AA21004 20 mg	8	671	-0.51	0.08	-0.66	-0.35	<.001	0.178
10: Suicidal Thoughts	PBO	8	1515	.	.	.	.	.	.

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Item	Treatment	Week	N	Diff. to PBO	SE	Lower 95% CI	Upper 95% CI	p-value	Hetero. p-value
	AA21004 5 mg	8	840	-0.06	0.05	-0.15	0.03	0.168	0.039
	AA21004 10 mg	8	877	-0.13	0.03	-0.20	-0.07	<.001	0.257
	AA21004 15 mg	8	344	-0.14	0.05	-0.24	-0.05	0.003	0.424
	AA21004 20 mg	8	671	-0.17	0.03	-0.23	-0.10	<.001	0.447

MAA-Approval FINAL PLOT_META1_MA_SI_21 19AUG2013:11:33:05 SADs Build Number: IDB Efficacy v3.0

The meta-analyses of the initially submitted 9 short term studies on the **HAM-A** total score, which reflects the **anxiety level in depressed patients**, showed that the observed effect size obtained with the 15 mg dose was -1.30 points and did not reach clinical significance (p=0.296). In 4 placebo-controlled short-term studies in adults in which efficacy was established, vortioxetine separated from placebo (p <0.05) in the analysis (MMRM) of the mean change from baseline in HAM-A total score at

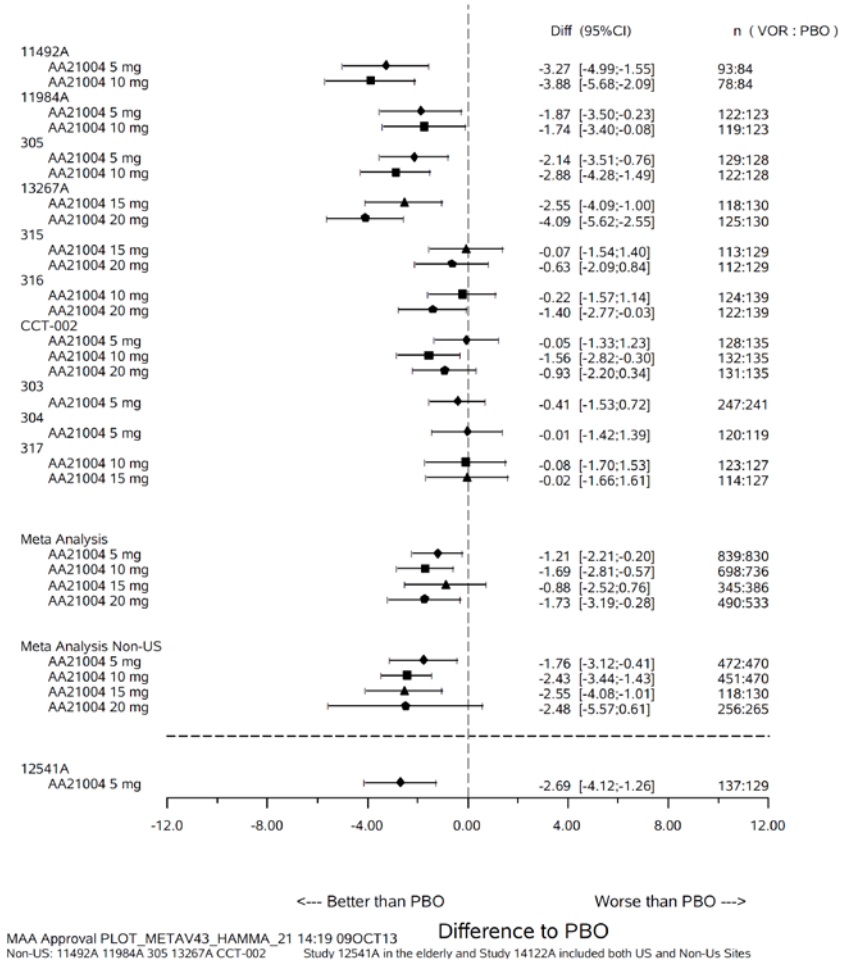
Week 6/8. The effect in the individual studies was supported by the meta-analysis (MMRM) of the mean change from baseline in HAM-A total score at Week 6/8 in the short-term studies in adults. In the meta-analysis, the overall mean difference to placebo across the studies was statistically significant: -1.5 points (p = 0.012), -2.1 points (p = 0.008), and -2.0 points (p = 0.046) for the 5, 10, and 20 mg/day doses, respectively.

The results of the updated meta-analysis including Studies 317 and CCT-002 confirm the less favourable outcome observed when all studies are included in the meta-analysis. The overall dose-response pattern did not change. However, the effect of vortioxetine on lowering anxiety levels in depressed patients is lower than previously estimated in the first meta-analysis. Inclusion of the additional studies results in overall lower HAM-A effect sizes for all doses, as indicated by the bold values:

-1.21 points (p =0.019), **-1.69** points (p =0.003), and **-1.73** points (p =0.020) for the 5, 10, and 20 mg/day doses, respectively; the 15mg/day dose did not separate from placebo in the meta-analysis with an effect size of -0.88 points (p=0.291).

Of note, in the four short-term GAD studies including doses of 2.5 to 10 mg (studies 308, 309, 310, 311) vortioxetine (5 mg) separated from placebo only in 1 of the 4 studies (European study 311) in the primary endpoint mean change from baseline in HAM-A total score after 8 weeks of treatment.

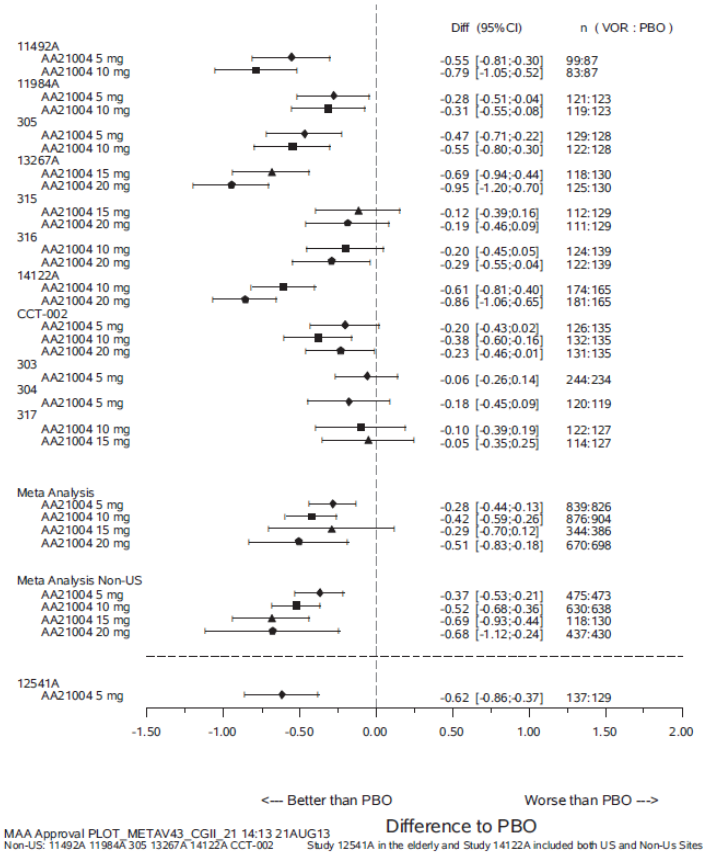
Panel 8 Change from Baseline in HAM-A Total Score at Week 6/8 (FAS, MMR
All Short-term Studies - Original Adding Studies 317 and CCT-002



In meta-analyses of the initially submitted short term studies of the **mean CGI-I score** at Week 6/8, the overall mean difference to placebo across the studies was statistically significant: -0.3 points (p =0.001), -0.5 points (p <0.001), and -0.5 points (p = 0.047) for the 5, 10, and 20mg/day doses, respectively; the 15mg/day dose did not separate from placebo in the meta-analysis (the difference to placebo was -0.4 points). The CGI-I scores of the active comparator, venlafaxine or duloxetine, were in general numerically superior to those of vortioxetine. The meta-analysis restricted to the four non-US studies (11492A, 11984A, 305, 13267A) showed that all doses were clinically relevant as to the CGI-I score.

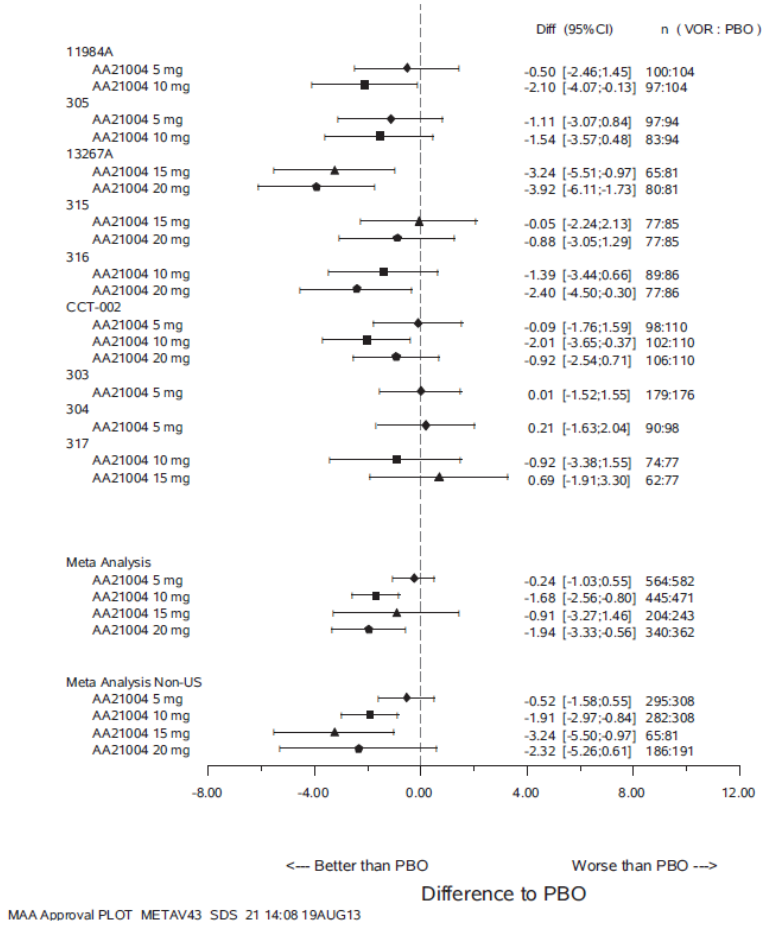
The results of the updated meta-analyses including studies 317, 14122 A, and CCT-002 did not change the overall dose-response pattern. However, the clinical relevance of the effect size was improved (Panel 45). The results are summarised below.
The overall mean difference to placebo across the studies was statistically significant: -0.3 points (p <0.001), -0.4 points (p <0.001), and -0.5 points (p = 0.002) for the 5, 10, and 20mg/day doses, respectively; the 15mg/day dose did not separate from placebo in the meta-analysis (the difference to placebo was -0.29 points). Therefore the overall effect on the CGI-score was modest. When the meta-analysis (MMRM) of the mean CGI-I score at Week 6/8 was repeated for the short-term, placebo-controlled studies in adults conducted outside the United States, the results were similar but more pronounced; the overall mean difference to placebo across the studies was statistically significant: -0.4 points (p <0.001), -0.5 points (p <0.001), -0.7 points (p <0.001), and -0.7 points (p = 0.002) for the 5, 10, 15, and 20mg/day doses, respectively.

Panel 45 CGI-I Score at Week 6/8 (FAS, MMRM)
All Short-term Studies - Original Adding Studies 317 14122A and CCT-002



The meta-analyses on the **SDS** total score, which provides a patient-rated assessment of impaired functioning in the areas of work, social life, and family life, showed clinical improvement for the 10 and 20 mg doses but not for the 5 mg and 15 mg dose. The 5 mg dose was also not clinically relevant in the meta-analysis restricted to the four non-US studies. (Panel 93).

Panel 46 Change from Baseline in SDS Total Score at Week 6/8 (FAS, MMRM)
All Short-term Studies - Original Adding Studies 317 and CCT-002



In the meta-analysis including studies 317 and CCT-002, the overall mean difference to placebo across the studies was statistically significant: -1.7 points ($p < 0.001$) for the 10mg/day dose and -1.9 points ($p = 0.006$) for the 20mg/day dose; the 5 and 15mg/day doses were not statistically significantly different from placebo. No consistent dose-effect could be shown.

The applicant presented an extensive analysis regarding HRQoL and overall functioning. Although it is agreed that all HRQoL and overall functioning instruments used in the clinical development programme are validated assessment tools with sufficient reliability their homogeneous use through all dosages has not been shown. The only scale that was used in most (9) of the short term-studies was the SDS scale. Results separated nominally from placebo ($p<0.05$) in four of the studies (studies 11984A for the 10 mg dose only, study 13267A for 15 and 20 mg, study 316 for 20 mg dose only, and study CCT-002 for 10 mg only but not for 5 and 20 mg) but not for all dosages in all domains; furthermore, as SDS endpoint in these studies was lower in the hierarchy of the testing strategies than endpoints which did not separate from placebo, superiority over placebo was not statistically significant according to the strategy for multiple testing. Analyses of clinical relevance were conducted post-hoc and were not pre-defined as requested in the “Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products” (EMEA/CHMP/EWP/ 139391/ 2004). Neither a strategy to control for multiplicity nor the effect size that can be considered as clinically relevant were pre-specified.

The Applicant agreed that the drug effect of Vortioxetine on HRQoL is expected to be mediated through an improvement in depressive symptoms. In this regard HRQoL assessments provide insight in the interpretation of the observed effect on the primary endpoint in terms of consequences for the patient.

It is acknowledged that a multidimensional approach (SDS, SF-36 Mental Component Summary (MCS), EQ-5D, Q-LES-Q) was chosen for demonstration of an effect on overall functioning observed in the Vortioxetine development programme.

Effect on cognitive dysfunction

Cognition parameters were evaluated in two studies, study 316 and in the dedicated study in the elderly 12541A. In both studies different assessment tools were used: study 316 included the patient reported outcome CPFQ as additional endpoint, study 12541A included two neuropsychological tests DSST and RAVLT.

In addition, a meta-analysis was conducted in the clinician-rated cognitive symptoms MADRS Item 6 – Concentration difficulties and HAM-A item 5 Difficulties in concentration and memory through 8 short-term studies was performed.

For MADRS Item 6 the overall mean difference to placebo across the studies was statistically significant: -0.2 points ($p < 0.001$), -0.3 points ($p = 0.007$), -0.5 points ($p < 0.001$), and -0.5 points ($p < 0.001$) for the 5, 10, 15, and 20mg/day doses, respectively. Overall, the results indicate that, although there were variations across the studies, the effect of Vortioxetine increased with increasing dose. In the dedicated study in the elderly (study 12541A) the difference of Vortioxetine 5mg/ day versus placebo was -0.4 points ($p<0.05$).

For HAM-A item 5 the overall mean difference to placebo across the studies was statistically significant: -0.1 points ($p = 0.006$), -0.2 points ($p = 0.001$), -0.35 points ($p = 0.002$), and -0.4 points ($p < 0.001$) for the 5, 10, 15, and 20mg/day doses, respectively. Overall, the results indicate that, although there were variations across the studies, the effect of Vortioxetine increased with increasing dose. In the dedicated study in the elderly (study 12541A) the difference of Vortioxetine 5mg/ day versus placebo was -0.25 points ($p<0.05$).

This meta-analysis according to the applicant supports the favourable effects of vortioxetine on cognitive dysfunction and is seen complementary to the results of the two neuropsychological tests RAVLT and DSST in study 12541A and the CPFQ Scores in study 316.

However, analyses were not pre-specified and may have been data-driven. A convincing independent effect on cognition through all studies has not been shown and the results of the meta-analysis are seen rather as an effect on the broad range of depressive symptoms than a specific effect on cognition since only some aspect of cognition are captured by these subscales. **Pooled analyses** (based on the MADRS total score) were only performed on small subpopulations for which there were too few patients in the individual studies for analysis.

Since submission of the MAA, additional nonclinical data have been generated that strengthen that Vortioxetine has the potential to enhance cognitive function. However, convincing clinical data to support this assumption are still lacking.

Pooled efficacy analysis in the elderly

A pooled efficacy analysis based on the short-term studies in adults was provided of **elderly** patients (aged ≥65 years). In these studies about 13% of the patients were aged ≥65 years. In the pooled analysis of patients aged ≥65 years from the short-term studies in adults, the effect sizes at Week 8 were -4.0 (p 0.07), -5.5 (p 0.04), 0.01 (p 0.99), and -3.2 (p 0.23) points on the MADRS total score for

5, 10, 15, and 20 mg/day, respectively. The data thus indicate that vortioxetine is effective in the dose range of 5 and 10 mg/day. Overall, in patients aged ≥65 years, the 15 mg dose had no effect whereas the effect of the 20 mg dose was not statistically different from placebo. However, the number of patients with the higher doses (15/20mg) is too small to draw clear conclusions.

Supportive studies

Persistence of efficacy was investigated as a secondary endpoint in three completed 52-week, open-label extension studies (Studies 11492C, 11984B, and 301) and two ongoing 52-week, open-label extension studies (Studies 13267B and 314). (see section 2.5.3 Discussion on supportive studies)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on a development program of 9 short-term studies including a dedicated study in the elderly and 1 long-term placebo-controlled relapse-prevention study.

The nine short-term studies were randomized, double-blind, parallel-group, placebo-controlled, fixed-dose studies of 6 or 8 weeks' duration. In six of the studies (including the dedicated study in the elderly), a fixed dose of an active reference was included solely for internal validation. The active reference included was either venlafaxine 225 mg/day (Study 11492A) or duloxetine 60 mg/day (studies 11984A, 13267A, 315, 304 and 12541A). The choice of the active comparators is acceptable since venlafaxine and duloxetine are widely approved and used in the treatment of MDD.

The relapse-prevention study (study 11985A) had a 12-week open-label, flexible dose period (Vortioxetine 5mg or 10mg) followed by a randomised, double-blind, placebo-controlled, fixed-dose period of at least 24 weeks (Vortioxetine 5mg or 10mg).

The studies were designed and conducted in accordance with the principles of the *Declaration of Helsinki* and in compliance with the principles of *Good Clinical Practice*. The study designs are generally in accordance with recommendations made in the EMA "Depression guideline" (CPMP/EWP/518/97, Rev 1, April 2002).

Three completed and two ongoing open-label, long-term extension studies provide supportive efficacy data. One of these two ongoing studies (study 13267B) was completed between MAA submission and 31 August 2013.
The study designs varied in terms of primary endpoints (MADRS or HAM-D scales), secondary endpoints, choice of active comparator, and statistical analysis strategy. The nine pivotal studies included a total of about 5700 patients of whom about 2700 were treated with vortioxetine in the short-term studies.

The relapse prevention study with 5 mg and 10 mg doses of vortioxetine included a total of 400 patients in a 24-week double-blind period following a 12-week open label period with 639 patients.

Three open-label extension studies included a total of 1443 patients and provided supportive efficacy data.

The patients included in the short-term studies had mainly moderate to severe MDD and a moderate level of anxiety symptoms as indicated by baseline scores on the MADRS, the Clinical Global Impression – Severity of Illness (CGI-S), and the HAM-A. Overall the patient population is considered

to be a rather homogen sub-population of the general MDD population since frequently occurring comorbidities and suicidal thoughts/suicidality, amongst others, were excluded. This is considered acceptable to to reduce confounders and facilitation of evaluation of the pure antidepressant effect. Approximately one-half to two-thirds of the patients in each of the short-term studies in adults had severe MDD (baseline MADRS total score ≥30). In addition, studies 11492A and 303 only recruited severely depressed patients with a baseline MADRS total score of 34. The exclusion and withdrawal criteria were considered adequate.

An additional 4 short-term clinical studies were completed between MAA submission and 31 August 2013. All studies were randomized, double-blind, parallel-group studies. Study 317 was of 8 weeks duration and compared fixed-doses of Vortioxetine 10 and 15 mg versus placebo, study 14178A was of 12 weeks duration and compared flexible doses of 10 and 20 mg of Vortioxetine versus flexible doses of agomelatine (25 or 50 mg/day) in MDD patients, study CCT-002 was an 8-week study in about 70 % Caucasian and 30% Asian (mainly Japanese) patients and compared fixed doses of Vortioxetine (5,10 or 20 mg/day) versus placebo. These three studies had the MADRS as primary endpoint whereas the primary objective of study 14122A was to evaluate the efficacy of treatment with Vortioxetine 10 or 20 mg/day versus placebo on cognitive dysfunction. No active comparator was included in this latter study.

Demographic characteristics across the studies in adults were similar, with approximately twice as many women as men and a mean age of 44 years (mean range: 42 to 47 years across studies). Differences in the racial distribution across the studies were observed, reflecting the fact that the studies were conducted in different geographical regions. The majority (overall, 81%) of the patients were Caucasian; the remaining patients were mainly Asians (mean: 6%; range: 7% to 21% across the studies that included Asians) or Blacks (mean: 12%; range: 21% to 28% across the studies that included Blacks).
The mean BMI differed somewhat between the studies conducted in the United States (approximately 31kg/m2) and those conducted outside the United States (approximately 26kg/m2). In the dedicated study in the elderly, the mean age of the patients was 71 years and the majority (>90%) of the patients were Caucasians. Otherwise, the baseline patient characteristics of this population were similar to that of the adult population.

The primary efficacy endpoint(s) in the short-term studies (including the dedicated study in the elderly) were either the MADRS or Hamilton Depression Rating Scale (HAM-D) 24. Both assessment tools are well established scales for assessing a change in depressive symptom severity and the use is in accordance with the guideline. In the long-term relapse-prevention study, the primary efficacy endpoint was the time to relapse of MDD within the first 24 weeks of the Double-blind Period.

The inter-rater reliability scores (kappa) were provided showing the raters were trained in using the efficacy rating scale used to assess the primary variable. The inter-rater variability was determined to be fair.

The efficacy of Vortioxetine was further assessed based on the MADRS single-item scores, the Hamilton Anxiety Rating Scale (HAM-A) total score, the proportions of responders and remitters, and the Clinical Global Impression – Global Improvement (CGI-I) score, which reflects the investigator's global clinical judgement of the outcome of treatment.

A ≥50% decrease from baseline in MADRS or HAM-D24 total score was defined in the protocols as a response criterion and a MADRS or HAM-D24 total score ≤10 was defined as a remission criterion which is in line with literature data. However, in the elderly study (12541A), response was defined as a

≥50% decrease from baseline in HAM-D24, MADRS, or HAM-D17 total score or a CGI-I score ≤2 and remission was defined as a MADRS total score ≤10, or a HAM-D17 total score ≤7, or a CGI-S score ≤2.

In addition, the effect of Vortioxetine was assessed in patients with severe MDD (baseline MADRS total score ≥30) or a high level of anxiety (defined as a baseline HAM-A total score ≥20), as these patients are difficult to treat and the treatment outcome is typically poorer.

Specific cognitive symptoms were evaluated in four studies. The neuropsychological tests Rey Auditory Verbal learning Test [RAVLT] (learning and memory) and the Digit Symbol Substitution Test [DSST] (speed of processing, executive function, and attention) were secondary endpoints in the dedicated study in the elderly. The Cognitive and Physical Functioning Questionnaire [CPFQ] which is a patient-reported outcome parameter designed to assess clinically relevant cognitive and physical symptoms associated with depression was an additional endpoint in studies 316 and 317. Cognitive impairment is recognised as an important characteristic during the acute phase of MDD. The applicant´s rationale to conduct neuropsychological tests primarily in the elderly was that cognitive dysfunction in MDD is known to be even more pronounced in the elderly than in adults and is therefore considered more sensitive to change. This is acknowledged, however for an assumed independent effect on cognition it would have been expected to show this effect in the overall population and not only in the elderly population. The Applicant provided study 14122A which was completed between MAA submission and 31 August 2013. The study was conducted in adult patients (aged 18 to 65 years) with MDD and the primary endpoint was a composite score of the DSST (executive function, speed of processing, and attention) and the RAVLT (learning and memory). Although it is acknowledged that with this study an effort was undertaken to study cognitive dysfunction in patients with MDD the results of this study still are not sufficient to support the claim of an independent effect on cognition as outlined above. The main caveat is the lack of an active comparator e.g. duloxetine to provide internal validity (assay sensitivity) of the study.
The following patient-reported health-related quality of life (HRQoL) assessment tools were included in the evaluation of Vortioxetine: The Study short Form 36 version 2.0 [SF-36 v2] was used as a cornerstone in the evaluation of the effect of Vortioxetine on the patients' HRQoL (5 studies), complemented with the Qualitiy of Life enjoyment and Satisfaction Questionnaire Short Form [Q-LES-Q SF] (1 study), the EuroQoL [EQ-5D] (1 study) and the Twelve item Health Status Questionnaire [HSQ-12] (in the elderly population study).

The patients' overall functioning was assessed by using the Sheehan Disability Scale [SDS] (9 studies), which provides an assessment of the impact of clinical conditions on the functional domains of work, social and family life. Inclusion of HRQoL assessment tools is in line with the "Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products"(EMEA/CHMP/EWP/139391/2004). However, analyses of clinical relevance were conducted post hoc and were not pre-defined as requested in the Reflection paper. The justification of clinical relevance for the SDS and SF-36 MCS based on the application of general 'standard' thresholds such as Cohen's rule that an SMD of 0.2 is a small effect size, 0.5 medium and 0.8 is not appropriate, as the relevance of a standardized effect size cannot be evaluated based on a general rule but has to be interpreted in dependence on the context.

Efficacy data and additional analyses

The first study (**11492A**) compared the efficacy of vortioxetine 5 mg and 10 mg vs. placebo with venlafaxine 225 mg as active comparator to check assay sensitivity. The primary efficacy analyses showed that both doses of vortioxetine were statistically superior to placebo in mean change from baseline in MADRS total score at Week 6, with a mean treatment difference to placebo of 5.9 (5 mg) and 5.7 points (10 mg). Venlafaxine was also statistically significantly superior to placebo at Week 6,

with a mean treatment difference to placebo of 6.4 points. Response and remission rates were about 22-percentage points% higher in the vortioxetine group compared to the placebo group. The rates were 28 percentage points higher in the venlafaxine group compared to placebo. Patients on 10 mg vortioxetine treatment improved somewhat better on the patient-rated quality of life scale, SF-36, than those on the 5 mg dose. The improvement of the patients' HRQoL was more pronounced in the venlafaxine group.

The second study (**11984A**) compared the efficacy of vortioxetine 2.5 mg, 5 mg and 10 mg vs. placebo with duloxetine 60 mg as active comparator. In the primary efficacy analysis, there was no statistically significant difference between vortioxetine 5 or 10 mg/day and placebo in the change from baseline in MADRS total score at Week 8. Hence, the pre-defined, sequential testing procedure was stopped at the first step. Also, there was no statistically significant difference between duloxetine 60mg/day and placebo in the primary efficacy analysis. Hence, this study is considered failed. In addition, vortioxetine 2.5 mg/day did not separate from placebo. The lack of efficacy of vortioxetine and duloxetine was believed mainly to be due to the early timing of withdrawals, resulting in missing data which affected the LOCF analysis. An MMRM analysis which is more robust towards missing data showed a separation from placebo in favour of vortioxetine 5 mg and 10 mg ($p < 0.05$) and duloxetine ($p < 0.01$) at Week 8, but not for vortioxetine 2.5 mg. The mean treatment differences to placebo were of about 2.5 points for vortioxetine (2.5 and 2.6 points for 5 and 10mg /day respectively) and 3 points for duloxetine.

The third study (**305**) compared the efficacy of vortioxetine 1 mg, 5 mg and 10 mg vs. placebo. Since the 1 mg dose was expected to be *not* efficacious, it was not included in the pre-specified statistical testing procedure. The vortioxetine 10 mg group was statistically different for the primary endpoint, i.e. change from Baseline in HAM-D24 total score at Week 8. However, the 10 mg dose was not statistically significantly different from placebo in the second variable in the testing hierarchy, i.e. change from Baseline in the SDS total score at Week 8, which is a patient-rated quality of life scale. Since the formal statistical testing was stopped at the second variable in the pre-specified order, none of the subsequent endpoints in the pre-specified testing hierarchy were considered statistically different from placebo. This includes the change from Baseline in HAM-D24 total score after 8 weeks of treatment for the 1 mg and the 5 mg dose even though nominal $P<0.001$ (MMRM). However, with the effect size shown and the nominal P-value <0.05 in the comparison of vortioxetine 5 mg versus placebo, it indicated clinical relevance of the 5 mg dose. Thus, only the outcome of the 10 mg dose versus placebo was statistically significant for the LS mean change from Baseline in HAM-D24 total score at Week 8 (primary endpoint, the first parameter in the pre-specified testing order that was statistically significant). However, the outcome of the 1 mg, 5 mg and 10 mg doses were clinically significant for the primary endpoint and several secondary endpoints including change from Baseline in MADRS total score at Week 8 ($P<0.001$), HAM-D24 response rate at Week 8 ($P<0.001$), and MADRS remission rate.

However, the vortioxetine treatments could not be distinguished from placebo, in the area of quality of life improvement, as self-rated by the patients.

The fourth study (**13267A**) compared the efficacy of vortioxetine 15 mg and 20 mg vs. placebo with duloxetine 60 mg as active comparator. Effect sizes were generally high in this study.The primary efficacy analyses showed that both doses of vortioxetine were statistically superior to placebo in mean change from baseline in MADRS total score at Week 8, with a mean treatment difference to placebo of 5.5 (15 mg) and 7.1 points (20 mg). Duloxetine was also statistically significantly superior to placebo at Week 8, with a mean treatment difference to placebo of 9.5 points. The odds ratios for response and remission were about 3 and 2.5, resp., in the vortioxetine group compared to the placebo group. The

active comparator showed odds ratios of 6 and 5, for response and remission, resp. Patients on 20 mg vortioxetine treatment improved somewhat better on the primary and secondary endpoints, including the patient-rated quality of life scale, SF-36, than those on the 15 mg dose. The improvement was again more pronounced in the duloxetine group. Thus, although a direct comparison between vortioxetine and duloxetine was not the objective of this study, the data show a greater numerical effect size with duloxetine than with vortioxetine

The fifth study (**315**) was performed in the US only and compared the efficacy of vortioxetine 15 mg and 20 mg vs. placebo with duloxetine 60 mg as active comparator. The primary efficacy analyses showed that only the 20 mg dose of vortioxetine was statistically superior to placebo in mean change from baseline in MADRS total score at Week 8, with a mean treatment difference to placebo of 2.75 (P=0.023). The 15 mg dose showed a minor improvement of 1.5 points over placebo in MADRS total scores, which was neither statistically nor clinically significant. Duloxetine was statistically significantly superior to placebo at Week 8, with a mean treatment difference to placebo of 4 points, which was less than half the value obtained in the previous study (13267A). The odds ratios for response and remission were about 1.3 and 1, resp., in the vortioxetine group compared to the placebo group. Duloxetine performed better with an odds ratio of 2 for response rate. The odds ratio for remission rates of duloxetine, however, was about 1 and hence not superior over vortioxetine or over placebo. None of the key secondary efficacy endpoints separated from placebo (nominal p<0.050) with either vortioxetine dose. The odds ratios for response indicate that response was twice as likely in the placebo group than in the vortioxetine treatment groups. The proportions of subjects in remission as defined by MADRS total score or CGI-S were generally similar across treatment groups. In the patient-rated SDS total score, the 15 mg dose was about equal to placebo with a mean difference of 0.05 points (P = 1). The 20 mg dose showed a 0.9 point improvement compared with placebo (P = 0.4).

The sixth study (**316**) was performed in the US only and compared the efficacy of vortioxetine 10 mg and 20 mg vs. placebo. The primary efficacy analyses showed that only the 20 mg dose of vortioxetine was statistically superior to placebo with a treatment difference of 3.64 points in mean change from baseline in MADRS total score at Week 8 (P=0.002). The 10 mg dose showed slight improvements in primary (2.19 points in mean change from baseline in MADRS total score) and secondary endpoints, including response and remission rate and the patient-rated SDS total score, but these did not reach statistical significance (P>0.05). The 20 mg dose also showed slight improvements in the secondary endpoints response and remission rate and SDS total score, with varying statistical significance (0.025<P<0.059).

The seventh study (**303**) was performed in the US only and compared the efficacy of vortioxetine 5 mg vs. placebo. The primary efficacy analyses showed that the 5 mg dose of vortioxetine was statistically not superior to placebo in mean change from baseline in HAM-D24 total score at Week 6. Values for the secondary efficacy variables from the sequential testing as well as the other secondary efficacy variables for 5 mg vortioxetine were similar to placebo.

The eighth study (**304**) was performed in the US only and compared the efficacy of vortioxetine 2.5 mg and 5 mg vs. placebo with duloxetine 60 mg as active comparator. The primary efficacy analyses showed that the 2.5 mg and 5 mg dose of vortioxetine did not separate from placebo in any of the primary or secondary efficacy endpoints, and did not provide evidence of a clinical benefit. However, duloxetine separated from placebo on the primary and all key secondary endpoints (P <0.05).

Additional pivotal studies completed between MAA submission and 31 August 2013:

Study **14178A** was conducted in Europe and included men or women, aged ≥ 18 and ≤ 75 years, who had depressive symptoms considered as non or partially responsive to no more than one adequate course (licensed doses for ≥6 weeks prior to the Screening Visit) of SSRI/SNRI monotherapy (SSRIs: citalopram, escitalopram, paroxetine, sertraline, and SNRIs: duloxetine, venlafaxine) for a single episode of MDD (diagnostic code 296.2x) or recurrent MDD (diagnostic code 296.3x), according to DSM-IV-TR™ criteria, and who were candidates for a switch in the investigator's opinion and wished to change antidepressant treatment to either vortioxetine or agomelatine. Treatment resistant patients (defined as inadequate response to two prior courses of at least 6 weeks of conventional antidepressant drugs in adequate dosages) were excluded from this trial. The rationale for choosing agomelatine as the active comparator was that it has a mechanism of action that is different from that of SSRIs/SNRIs, in that it is a norepinephrine dopamine inhibitor (NDDI), whereas Vortioxetine might represents a new pharmacological class of antidepressants, which might have a different mechanism of action, in that it could be a multimodal antidepressant. A total of 501 patients were randomized equally (1:1) to flexible doses of either Vortioxetine (VOR) 10 or 20mg/day or agomelatine 25 or 50mg/day for 12 weeks of double-blind treatment. The applied statistical methods were the same as utilized in the previous studies, which is considered appropriate (primary endpoint difference from baseline in MADRS total score at Week 8 was evaluated using a MMRM approach).

The CHMP did not agree with the definition of the patient population "patients with MDD who have responded inadequately to SRI antidepressant monotherapy", for the following reasons:

Inadequate response to previous SRI monotherapy is assumed based on the mean MADTRS total score at baseline/randomisation whereas documented evidence of the severity of depression at the onset of the first SRI monotherapy are not available and data on response and patient compliance to this SRI monotherapy were collected retrospectively.It cannot be excluded that fully responsive patients to the first SRI monotherapy could have been included in the study since the severity of depression was not assessed at the onset of the first monotherapyduring the lead-in period. However, the patients still had a mean MADRS total score at study entry of 29 points (ranging from 22 to 43 points) indicating moderate to severe depression. In the absence of data for the lead-in period, it cannot be established whether the study population was indeed limited to non responders or also included partial responders.

Lack of patient compliance to the first SRI monotherapy could have lead to inadequate response to the SRI monotherapy. However, patients were not followed during the SRI monotherapy and their compliance was therefore not assessed prospectivelybut only retrospectively by patient reporting via clinical interview. Patients' decision to change treatment and participate in the clinical trial could have been motivated by reasons other than dissatisfaction with the first SRI monotherapy.

Considering the half-lives of the SSRIs/SNRIs allowed in the lead-in period (fluoxetine was excluded) the risk of a carry-over effect of the first SRI monotherapy is considered to be minimal at the assessement of the efficacy endpoint at week 8.

The MMRM estimates for the mean change from baseline in MADRS total score at Week 8 were -16.5 and -14.4 points in the vortioxetine group and the agomelatine group, respectively, giving a mean difference of -2.16 points in favour of vortioxetine (95% CI: -3.5 to -0.81;p = 0.002). Non-inferiority was established, as the upper bound of the 95% CI for the vortioxetine and agomelatine comparison was -0.81 MADRS points, and therefore clearly below the non-inferiority margin of +2 MADRS points versus agomelatine. As the two-sided 95% CI for the difference between the means excluded zero and was in favour of vortioxetine, vortioxetine was even superior to agomelatine (which also shows that

the trial had assay sensitivity). The positive results were confirmed by the sensitivity analyses (PPS, MMRM; ANCOVA, FAS, LOCF) and the secondary efficacy endpoints. Vortioxetine was consistently statistically significantly better than agomelatine based on analyses of the secondary efficacy endpoints (MADRS total score, HAM-A total score, CGI-S score, CGI-I score) and health-related quality of life and overall functioning scores [SDS total score, EQ-5D Summary Index, WLQ Global Productivity Index, and DFFS total score]) at Weeks 8 and 12 (FAS, MMRM), except for WLQ at Week 12. The proportion of MADRS and CGI-I responders was statistically significantly higher in the vortioxetine group than in the agomelatine group at Weeks 8 and 12. At Week 12, nearly three-quarters of the patients in the vortioxetine group were responders (FAS, LOCF, logistic regression). The proportion of MADRS and CGI-S remitters was statistically significantly higher in the vortioxetine group than in the agomelatine group at Weeks 8 and 12. At Week 12, more than half of the patients in the vortioxetine group were remitters (FAS, LOCF, logistic regression).

As a conclusion, the results of this head-to-head comparison study can be considered as supportive for the claim of efficacy in this group of patients, but cannot be used to claim efficacy of vortioxetine in treatment-resistant patients, neither in patients with MDD who have responded inadequately to SRI antidepressant monotherapy since the included patient population according to the study objective was only retrospectively defined.

Study 14122A was conducted in Australia, Canada, Europe, Mexico, South Africa, and the United States. The inclusion and exclusion criteria were essentially the same as those in the other short-term MDD studies. A total of 602 patients were randomised equally (1:1:1) to placebo, Vortioxetine 10mg/day, or Vortioxetine 20mg/day for 8 weeks of double-blind treatment. Approximately 86% of the patients in each treatment group completed the study. The primary efficacy endpoint was a composite cognitive score (z-score) based on the DSST (executive function, speed of processing, and attention) and the RAVLT (learning and memory). Key secondary endpoints were the respective single scores. Vortioxetine 10 and 20mg/day were statistically significantly superior to placebo in the composite z-score ($p < 0.001$), as well as in the next pre-specified key secondary efficacy analysis of the DSST ($p < 0.001$) but not in the RAVLT (learning) score. The mean difference in z-score versus placebo was 0.36 and 0.33 for vortioxetine 10 and 20 mg respectively. However, the clinical relevant effect size of this composite score is not known and was therefore not pre-defined. The cognitive performance of the patients in the four key domains was assessed using additional neuropsychological tests, namely, TMT A (speed of processing) and B (executive function), SRT (speed of processing), CRT (attention), and STROOP (executive function). The results of the secondary analyses based on these tests supported the results of the primary analysis, that is, the patients who received vortioxetine 10 or 20mg/day improved statistically significantly more than those who received placebo on all the assessed measures, with the exception of CRT in the vortioxetine 20mg group. Vortioxetine 10 and 20mg/day demonstrated a consistent positive effect on depressive symptoms, as assessed using the MADRS: the difference to placebo in total score (FAS, MMRM) at Week 8 was -4.7 points for vortioxetine 10mg/day and -6.7 points for vortioxetine 20mg/day. The clinical relevance of this treatment effect was supported by the effect seen on the clinical global impression (CGI-S and CGI-I). Furthermore, statistically significant proportions of patients responded (defined as a ≥50% reduction from baseline in MADRS total score) or remitted (defined as a MADRS total score ≤10): 48 and 59% of the patients in the vortioxetine 10 and 20mg groups, respectively, were responders and 30 and 38% of the patients in the vortioxetine 10 and 20mg groups, respectively, were remitters at Week 8. The difference to placebo in the proportion of responders was >16 percentage points. No active comparator was included in this study, which would have been important to show that the cognitive improvement could not only be explained by the antidepressive effect. To evaluate whether the direct treatment effect on cognitive function was independent on depressive symptoms, the primary and key secondary analyses were repeated as post-hoc analyses in patients who had not responded (non-responders, that is,

patients who had a <50% reduction from baseline to Week 8 in MADRS total score) and in patients who had not remitted (non-remitters, that is, patients who had a MADRS total score >10 at Week 8).

Vortioxetine 10 and 20mg/day were statistically significantly superior to placebo in the composite z-score (p <0.001). However, if a composite endpoint is used, an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit (please refer to ICH E9, Statistical Principles for Clinical Trials, CPMP/ICH/363/96) but the applicant did not provide such an interpretation. As clinical interpretation of the primary endpoint is not possible, the evaluation of clinical relevance has to be based on the single components of the primary endpoint, which were key secondary endpoints. The Applicant argues that the clinical relevance of the cognitive effects was supported by the magnitude of the standardized effect sizes, the pre-specified path analysis and the statistical significant effect on cognitive performance in patients who were defined as non-responders or non-remitters. However, it appears questionable that clinical relevance of the effects can be robustly concluded based on these analyses: the clinical relevance of an effect size depends on the context and cannot be evaluated based on general criteria such as Cohen's d; the analysis in non-responders was a post-hoc analysis; the validity of the path analysis is not clear.
It is not clear that a path analysis is a valid model to quantify the proportion of the direct effect of Vortioxetine on cognition which is not explained by the anti-depressant effect (the proportion of direct effect depends on unverified assumptions on the functional form of the relationship between improvement on depression and cognitive symptoms in this model. Furthermore, without internal validation (i.e. without an active comparator), it is not clear whether path analysis supports a different profile compared to other antidepressants.

Clinical studies in special populations

The ninth study in the initial submission package **(12541A**) compared the efficacy of vortioxetine 5 mg vs. placebo with duloxetine 60 mg as active comparator in 453 patients aged ≥65 years. A total of 156 patients received vortioxetine 5 mg.

Subgroup analyses in the previous studies showed a decreased vortioxetine efficacy in patients aged ≥55 years, which is in line with the general observation of reduced antidepressant efficacy in older patients. Hence, the choice of a lower than recommended 10 mg dose is surprising, but was justified by the Applicant for safety reasons. In view of the lower efficacy observed in patients above the age of 55, the positive treatment effect of the 5 mg dose in elderly could not necessarily be expected.

Overall, the mean age (± SD) at baseline was 71 ± 5 years, the ratio of men to women was approximately 1:2, and the vast majority (93% to 96%) of the patients were Caucasian. The study was conducted both inside and outside the United States. In the primary efficacy analysis, vortioxetine 5 mg/day was statistically significantly (p = 0.001) better than placebo in reducing the HAM-D24 total score at Week 8, with a mean difference to placebo of -3.3 points. Vortioxetine 5mg/day was also statistically significantly (p =0.024) better than placebo in reducing the HAM-D24 total score at Week 6, with a mean difference to placebo of -2.1 points. At the non-US sites, vortioxetine 5mg/day separated from placebo (p <0.001) in the MMRM analysis of the change from baseline in MADRS total score at Week 8. The mean effect size was 5.3 points. Similar results were obtained using ANCOVA, LOCF. At the US sites (approximately one-third of the study population), vortioxetine 5mg/day separated from placebo (p <0.05) in the MMRM analysis, but not in the ANCOVA, LOCF analysis. The lack of significance probably reflects the lack of power for the subgroup analysis. The vortioxetine-placebo difference was approximately 2 points higher at the non-US sites than at the US sites, both in the MMRM and ANCOVA, LOCF analyses.

Study 12541 A had two special aspects that are highlighted subsequently. It was the only study among the 9 short-term studies that was a) conducted both in and outside the United States and b) it was the only study that included neuropsychological tests as cognition endpoints.

Taking into account the results of the 4 other US studies, two of which were negative (studies 303 and 304) and two of which showed efficacy only in the highest dose group of 20 mg (studies 315 and 316) it was of special interest to repeat primary and secondary efficacy analyses in this study separately for sites in and outside the US. The antidepressant-placebo differences in the mean changes from baseline in the MADRS and HAM-D24 (primary variable) total scores were approximately 2 points higher for the non-US than the US sites, both for Vortioxetine and duloxetine in the MMRM and ANCOVA, LOCF analyses.

For the non-US sites, Vortioxetine 5mg/day separated from placebo on all the efficacy variables (MADRS total score, HAM-D24 total score, HAM-A total score, CGI-S score, CGI-I score), both in the MMRM and in the ANCOVA, LOCF analyses. For the US sites, Vortioxetine 5mg/day separated from placebo in the MMRM analyses of the mean changes from baseline in the MADRS total score and CGI-S score and of the mean CGI-I score. In contrast no separation was reached for any parameter in the ANCOVA/LOCF analysis.

This difference between US/non-US studies was further substantiated by pharmacokinetic data from the phase II/III population showing lower and more variable LuAA21004 plasma concentrations in US patients (see PK section) and it may be concluded that US patients were less compliant to study medication.

Cognitive dysfunction is recognised as an important characteristic during the acute phase of MDD. The neuropsychological tests RAVLT (learning and memory) and DSST (speed of processing, executive function, and attention) were used in the dedicated study in the elderly, as these tests involve several of the cognitive processes that are known to be impaired in patients with MDD. The applicant´s rationale to conduct these evaluations primarily in the elderly was that cognitive dysfunction in MDD is known to be even more pronounced in the elderly than in adults and is therefore considered more sensitive to change. This is acknowledged, however for an assumed independent effect on cognition it would have been expected to show this effect in the overall population and not only in the elderly population. Vortioxetine 5mg/day and the active reference duloxetine separated from placebo ($p < 0.05$) in the RAVLT while only Vortioxetine separated from placebo ($p < 0.05$) in the DSST. This according to the applicant demonstrates the different profile versus duloxetine improving not only learning and memory capacities but also speed, attention and executive functioning and is claimed to be supported by the magnitude of the standardized effect sizes and nonclinical findings.

In addition, a path analysis was performed to assess to what extent the effect on DSST and RAVLT was a direct treatment effect, rather than an indirect effect through improvement of depressive symptoms, as measured using the primary assessment tool (HAM-D24). The results showed that Vortioxetine 5mg/day had an 83% direct effect on DSST *correct numbers* (duloxetine 26%), a 71% direct effect on RAVLT *acquisition* (duloxetine 65%), and a 72% direct effect on RAVLT *delayed recall* (duloxetine 66%).

Concerning the path analysis, the additional information and the sensitivity analyses that were provided are somewhat reassuring on the robustness of the results of this analysis. Nevertheless, the path analysis is considered a post-hoc exploratory analysis without independent replication. Compared with duloxetine, a markedly higher direct effect of Vortioxetine was observed only for one of the three parameters of the neuropsychological tests DSST and RAVLT, which does not consistently support the claim of a different profile of Vortioxetine. Furthermore, the validity of the path analysis is somewhat challenged by the path analysis for DSST using total MADRS as a mediator where a negative direct effect on cognitive symptoms was found for duloxetine, which appears contradictory.

The Applicant furthermore acknowledges that the effect on the clinician-rated cognitive symptoms (single terms of the MADRS and HAM-A) is part of the effect on the broad range of depressive symptoms.
Overall, a convincing independent effect on cognition remains to be shown.

Relapse prevention study

In the relapse-prevention study 11985A the primary efficacy analysis showed a statistically significantly superior effect of vortioxetine relative to placebo on the time to relapse of MDD during the first 24 weeks of the Double-blind Period (FAS; Cox proportional hazard model, p = 0.0035). The proportion of patients who relapsed was lower in the vortioxetine group (13%) than in the placebo group (26%). The Cox proportional hazard model gave a hazard ratio of 2.01, indicating that the risk of relapse was two times higher for placebo-treated patients than for vortioxetine -treated patients. Vortioxetine was also statistically significantly superior to placebo in the secondary analysis of time to relapse during the entire Double-blind Period using the FAS. The robustness of the results was confirmed by a number of sensitivity analyses.

Vortioxetine 5 mg or 10 mg flexible doses were effective in preventing relapse, as demonstrated both by the primary and by the secondary statistical analyses. The primary analysis of the time from randomisation to relapse within the first 24 weeks of the Double-blind Period showed statistically significant superiority over placebo with respect to time to relapse and relapse rates. The risk of relapse was twice as high in the placebo group as in the vortioxetine group.

The mean MADRS total scores were stable over time and remained close to the Baseline II level in both vortioxetine and placebo groups during the Double-blind Period. The therapeutic effect in MDD was thus maintained and stable over time during long-term double-blind period (up to 64 weeks) in both the placebo and the vortioxetine group.

Questions were raised regarding the analysis of the time to relapse in the double-blind period of the relapse prevention study (11985A). In the placebo group, mainly withdrawals due to lack of efficacy are expected whereas in the vortioxetine group mainly withdrawals due to adverse events are expected. The study considered adverse events always as primary reason for withdrawal. The Applicant clarified that all withdrawals due to lack of efficacy were considered in the analysis, that is, not only those where lack of efficacy was given as the primary reason for withdrawal. Furthermore, if a patient was not withdrawn due to lack of efficacy but had a MADRS total score ≥22, the patient was considered relapsed.

Supportive studies

Persistence of efficacy was investigated as a secondary endpoint in three completed 52-week, open-label extension studies (Studies 11492C, 11984B, and 301) and two ongoing 52-week, open-label extension studies (Studies 13267B and 314). A total of 1443 patients received vortioxetine 2.5 mg, 5 mg, or 10 mg/day. An additional 2557 patients received vortioxetine in the open-label extension studies (1443 patients in the completed studies and 1114 patients in the ongoing studies as of 29 February 2012). No placebo control was included in the 52-week, open-label extension studies.

The first extension study (11492C) evaluated the maintenance of the therapeutic effect of 5 mg or 10 mg flexible doses of vortioxetine over a period of 52 weeks in 74 patients with MDD who completed the 6-week short-term Study 11492A. After completing the 6-Week venlafaxine-controlled Study 11492A, eligible patients were switched to a 10 mg/day vortioxetine dose. After the first week, the dose was flexible (5 or 10mg/day) based on the patient's tolerability to treatment, as judged by the investigator. The mean MADRS total score decreased from 10.7 points at Baseline II to 5.3 points at Week 52, a

reduction of approximately 5.4 points, indicating maintained improvement in depressive symptoms during the extension study.

However, the data are inconclusive due to the lack of a placebo control and low numbers of patients included in each group.

The second extension study (11984B) evaluated the maintenance of the therapeutic effect of 2.5 mg, 5 mg or 10 mg flexible doses of vortioxetine over a period of 52 weeks in 535 patients with MDD who completed the 8-week short-term Study 11984A. After completing the 8-Week Study 11492A, eligible patients were switched to a 5 mg/day vortioxetine dose. After the first week, the dose was flexible (2.5, 5 or 10mg/day) based on the patient's tolerability to treatment, as judged by the investigator.

The mean MADRS total score decreased from 13.5 points at Baseline II to 5.5 points at Week 52, and the mean CGI-S score decreased from 2.7 points at Baseline II to 1.7 points at Week 52, indicating maintained improvement in depressive symptoms and the global impression during the extension study.

The third extension study (301) evaluated the maintenance of the therapeutic effect of 2.5 mg, 5 mg or 10 mg flexible doses of vortioxetine over a period of 52 weeks in 834 patients with MDD who completed the 8-week short-term Study 304 or Study 305. After completing the 8-Week Study 304 and the US-only Study 304, eligible patients were switched to a 5 mg/day vortioxetine dose. After the first week, the dose was flexible (2.5, 5 or 10mg/day) based on the patient's tolerability to treatment, as judged by the investigator.

The mean MADRS total score decreased from 16.6 to 9.3 points and the mean CGI-S score decreased from 3.2 to 2.2 points from Baseline II to the final visit, indicating maintained improvement in depressive symptoms and the global impression during the extension study.

Study 13267B is the long-term, open-label, extension study to evaluate the safety and tolerability, as well as the maintenance of the therapeutic effect, of vortioxetine at flexible doses of 15 or 20mg/day over 52 weeks in patients with MDD who had completed lead-in Study 13267A.

Lead-in study 13267A was a randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating the efficacy and safety of vortioxetine 15 and 20mg/day in the acute treatment of adult patients with MDD. A total of 607 patients were randomized equally (1:1:1:1) to placebo, vortioxetine 15 or 20 mg/day, or duloxetine for 8 weeks of double-blind treatment. The number of patients who completed the lead-in study was lower in the vortioxetine 15 or 20 mg/day treatment groups (77% and 83%, resp.) than for the duloxetine and placebo treatment groups (89% and 84%, resp.). In total, 506 patients completed the lead-in study.

The inclusion and exclusion criteria were essentially the same as those in the other short-term MDD studies, for subjects who had completed the 10 Week lead-in study.

The continuation study was originally planned to follow the safety and tolerability of 300 subjects, but only 71 were enrolled. Results obtained from a small population is not statistically significant and could be influenced by selection bias among the subjects who initially enrolled for the lead-in study, and who finally enrolled in the continuation study.

The primary objective was to evaluate the long-term safety and tolerability of flexible doses of vortioxetine (15 and 20 mg/day) over a period of 52 weeks in patients with MDD who have completed the lead-in Study 13267A. The secondary objectives were to evaluate the therapeutic effect of flexible doses of vortioxetine (15 and 20 mg/day) over a period of 52 weeks in patients with MDD as assessed

by Montgomery and Åsberg Depression Rating Scale (MADRS), Clinical Global Impression – Severity of Illness (CGI-S), and Hamilton Anxiety Rating Scale (HAM-A). Due to the open-label design of the study, the efficacy and health-related quality of life and overall functioning measures were considered exploratory and the results are presented using descriptive statistics.

The assessment of the long-term efficacy was considered as a secondary objective for this study. The results showed an improvement of depressive symptoms irrespective of previous treatment (on average, the MADRS total score decreased 10 points from Baseline II to Week 52). The highest improvement was observed in the group of previously placebo-treated patients while the less important changes were seen in the groups of patients previously treated with vortioxetine (20 mg) and duloxetine. The analysis of other efficacy measures (HAM-A, CGI-S) showed also better improvement for the previously placebo-treated patients.

The results should be interpreted very cautiously because of the low number of subjects, the potential selection bias, and the open-label nature of the design. The studies are inconclusive as to the maintenance of the clinical effect. The mean MADRS total score at Week 52 was about 5 indicating that on average, remission (MADRS≤10) was achieved in the patient population. However, the minimum and maximum values of the MADRS total score were 0 and 20, resp. This indicates that after one year treatment, some patients were total remitters (MADRS score of 0) whereas others remained depressed.

2.5.4. Conclusions on clinical efficacy

Twelve double-blind, placebo-controlled, 6/8-week, fixed-dose studies have been conducted to investigate the short-term efficacy of vortioxetine in MDD in adults (including the elderly).

Three main studies demonstrated efficacy of vortioxetine in adults based on decreasing scores on depression scales such as MADRS and HAM-D. These studies involved the 5 mg and 10 mg dose (11492A, 305) and the 15 mg and 20 mg dose (13267A) and were all performed outside the US.

In addition, one dedicated study demonstrated efficacy of vortioxetine 5 mg in patients ≥65 years (12541A). This study was performed both in- and outside the US.

The results of the primary endpoints were confirmed by CGI-I scores and responder and remitter analyses.

Short-term efficacy (at 6 or 8 weeks) of the recommended 10 mg dose was demonstrated in two of four short-term pivotal trials which were able to discriminate vortioxetine from placebo. Two of these four trials (11492A and 11984A) included an active comparator arm (venlafaxine 225 mg and duloxetine 60 mg, resp.) but one trial failed (11984A). In this latter trial, the effect of neither vortioxetine nor duloxetine was better than placebo in the primary LOCF analysis. However, the MMRM analysis showed a separation ($p<0.05$) from placebo in favour of vortioxetine 5 and 10 mg/day and duloxetine, but not for vortioxetine 2.5 mg/day, which was slightly above the clinical relevant effect size of 2 (2.5, 2.6 and 3 points for vortioxetine 2.5,2.6 and duloxetine, respectively). The other two trials were placebo-controlled trials (305 and 316) but one did not show superiority over placebo and is therefore considered negative (316).

The inclusion of 3 additional short-term studies to the initial meta-analysis of 8 short-term studies generally resulted in lower overall effect sizes in the primary and secondary efficacy endpoints. Looking

at the global data package, the effect sizes of vortioxetine treatment are lower than previously estimated on the basis of the 8 short-term studies but still separate statistically from placebo.

No specific dose adjustments are considered necessary based on patient´s age alone. However, caution should be exercised when treating the elderly especially with doses higher than 10 mg for which data are limited. The lowest effective dose of 5 mg should always be used as starting dose and patients should be carefully monitored when an increase in dose is required.

One relapse prevention study was performed, whereby responders to vortioxetine after 12 weeks of open label treatment were randomised between vortioxetine and placebo. The study demonstrated a statistically significant difference in time to relapse between vortioxetine and placebo, in favour of vortioxetine. No difference in efficacy between severely depressed patients and patients with moderate/mild depression was found.

In some of the placebo-controlled studies, an active reference was included as internal control. Although no formal comparison was conducted, , numerically larger effect sizes were observed for the active reference than for Vortioxetine, except in Studies 11492A and 11984A. The exclusion of non-responders and the inclusion of previous responders in the active reference arm could have introduced a bias in favour of the efficacy of the active reference, so differences in the efficacy of Vortioxetine versus the active reference cannot be inferred on the basis of these studies.

The long-term studies aimed at investigating clinical safety rather than efficacy and did not include a placebo control. The studies suggest maintenance of the clinical effect. The mean MADRS total score at Week 52 was about 5 indicating that, on average, remission (MADRS≤10) was achieved in the patient population. However, the minimum and maximum values of the MADRS total score were 0 and 20, resp. This indicates that after one year treatment, some patients were total remitters (MADRS score of 0) whereas others remained depressed .

To summarise:

- Vortioxetine 1 mg/day was efficacious in the one study in which it was investigated.
- Vortioxetine 2.5 mg/day was not efficacious in either of the two studies in which it was investigated.
- Vortioxetine 5 mg/day was efficacious in five of the eight studies: the results were positive in four studies (two short-term studies in adult patients, the dedicated study in the elderly, and the relapse-prevention study) and supportive in a fifth study as reflected by additional sensitivity analyses in adult patients; no effect was observed in three short-term studies in adult patients.
- Vortioxetine 10 mg/day was efficacious in seven of the eight studies in which it was investigated: the results were positive in four studies (three short-term studies and the relapse-prevention study) and supportive in the remaining three studies as reflected by additional sensitivity analyses.
- Vortioxetine 15 mg/day was efficacious in one of the three studies in which it was investigated.
- Vortioxetine 20 mg/day was efficacious in all five studies in which it was investigated; the results were positive in four studies and supportive in one study.

It can therefore be concluded that the efficacy of vortioxetine was demonstrated with at least one dosage group across 9 of the 12 studies, showing at least a 2-point difference to placebo in the Montgomery and Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale 24-item (HAM-D_{24}) total score. The clinical relevance of the effects were supported by the proportions of responders and remitters and the improvement in the Clinical Global Impression – Global Improvement (CGI-I) score. The efficacy of vortioxetine increased with increasing dose.

Panel 48 Results of the Analyses of the Primary Efficacy Variable in the Placebo-controlled Studies – Difference to Placebo in the Change from Baseline at Week 6/8 (FAS)

Study	Primary Efficacy Variable	Efficacy Analysis	Dose[a] (mg/day)					
			1[b]	2.5	5	10	15	20
11492A	MADRS total score	MMRM			-5.6***	-7.15***		
		ANCOVA, LOCF			-5.9***	-5.7***[c]		
11984A	MADRS total score	MMRM		-1.6	-2.5#[d]	-2.65#[d]		
		ANCOVA, LOCF		-1.4	-1.7[c,e]	-1.5[c,e]		
305	HAM-D_{24} total score	MMRM	-3.5***		-4.1***	-4.9***[c]		
		ANCOVA, LOCF	-3.3**		-4.0***	-4.55***		
13267A	MADRS total score	MMRM					-5.5***[c]	-7.1***[c]
		ANCOVA, LOCF					-4.4***	-5.8***
315	MADRS total score	MMRM					-1.5[c]	-2.8#[c]
		ANCOVA, LOCF					-0.8	-2.2
316	MADRS total score	MMRM				-2.2[c,f]		-3.6**[c]
		ANCOVA, LOCF				-1.7		-3.0**
14122A	Composite z-score	MMRM				0.36***[c]		0.33***[c]
		ANCOVA, LOCF				0.36***		0.32***
	MADRS[g] total score	MMRM				-4.7***		-6.7***
		ANCOVA, LOCF				-4.6***		-6.1***
CCT-002	MADRS total score	MMRM			-0.8	-2.4*		-2.4*
		ANCOVA, LOCF			-1.2[h,i]	-2.1[h,i]		-2.1[h,i]
303	HAM-D_{24} total score	MMRM			-0.8			
		ANCOVA, LOCF			-0.7[c]			
304	HAM-D_{24} total score	MMRM		-2.5*[j]	-1.0			
		ANCOVA, LOCF		-1.5	-0.6[c]			
317	MADRS total score	MMRM				-0.8[c]	-0.5[c]	
		ANCOVA, LOCF				-1.0	-0.5	
12541A	HAM-D_{24} total score	MMRM			-3.8***			
		ANCOVA, LOCF			-3.3**[c]			
11985A	Time to relapse	Cox model			Hazard ratio: 2.01**			

* p <0.05; # p <0.025; ** p <0.01; *** p <0.001

a In the studies with doses up to 10mg/day, the patients started treatment at the dose indicated; in the studies with 15 or 20mg/day, Lu AA21004 was uptitrated at the end of the first week from 10mg/day.

b Outside the testing strategy

c Primary efficacy analysis

d This study is considered supportive; when the primary efficacy analysis was repeated using MMRM, Lu AA21004 separated from placebo; in addition, Lu AA21004 separated from placebo in the majority of the secondary analyses (MMRM).

e The active reference duloxetine also did not separate from placebo in the ANCOVA, LOCF analysis.

f In this positive study, the data for the 10mg/day dose are considered supportive: Lu AA21004 separated from placebo (p <0.05) at Weeks 4 and 6; in addition, in the primary efficacy analysis, the difference was borderline statistically significant (p = 0.058).

2.6. Clinical safety

The clinical safety was investigated initially on the basis of data from 13 completed phase II/III studies in major depressive disorder (MDD).

An updated clinical safety database was provided by the Applicant with a new data cut-off as of 31st of August 2013. Overall, the updated safety database comprises 18 completed phase II/III studies in patients with MDD.

The reference treatments used in the safety clinical studies were either placebo, duloxetine (60 mg/d), venlafaxine (225 mg/d) or agomelatine (25-50 mg/d).

Patient exposure

The therapeutic dose range of Vortioxetine varies from 5 to 20 mg according to the proposed SmPC.

With respect to clinical pharmacology studies, 1169 subjects were exposed to Vortioxetine (solution or tablets) as a single dose (up to 75 mg) or repeated doses (up to 60 mg/d) calculated to 31.7 patient-years of exposure. An additional 74 subjects were reported as update of the original pharmacology studies (n_{total}= 1243). Subjects were either healthy, elderly or suffered from renal or hepatic impairment.

Patient exposure in the short-term pools (MDD short-term pool and MDD & GAD short-term pool)

MDD short-term Pool:

The 13 short-term studies included 3904 MDD patients exposed to Vortioxetine in a dose range from 1 to 20 mg per day with around 89% of subjects exposed to doses of 5 to 20 mg per day. The number of patients accounted for 527.5 p atient-years of exposure. 1968 patients were exposed to placebo and 866 subjects to active comparators (n= 753 for duloxetine and n= 113 for venlafaxine). As of the original data cut-off (29th February 2012), 67% of patients treated with Vortioxetine were women, about 11% of patients were 65 years of age and older and 81% were Caucasians.

MDD and GAD short-term Pool:

All completed short-term trials included 4972 patients exposed to Vortioxetine (671.5 patient-years of exposure), either suffering from MDD or GAD. 85% of the Vortioxetine patients received doses of 5 to 20 mg/day. 2577 patients were exposed to placebo, 113 patients received venlafaxine and 907 patients were exposed to duloxetine. Evaluation on the demographics sex, age and race was similar to the MDD short-term pool.

MDD long-term relapse prevention study 11985A

The long-term relapse-prevention study included 639 patients on Vortioxetine (127.5 patient-years of exposure) during the open-label period (12 weeks). 204 patients were exposed to Vortioxetine during the double-blind period (116 patient-years of exposure). Patients received either 5 or 10 mg of Vortioxetine. Demographics were similar to those evaluated in the short-term studies.

GAD long-term relapse prevention study 12473A

The long-term relapse-prevention study included 687 patients on Vortioxetine (222.9 patient-years of exposure) during the open-label period (20 weeks). 229 patients were exposed to Vortioxetine during the double-blind period (123 patient-years of exposure). Patients received either 5 or 10 mg of Vortioxetine. Demographics were similar to those evaluated in the short-term studies.

MDD open-label long-term pool

1443 patients from the nine short-term studies continued in the open-label long-term extension studies 301, 11492C and 11984B with flexible doses of Vortioxetine 2.5 mg to 10 mg/day (including 560 patients, who were on placebo or active control in the short-term studies). These subjects accounted for 1097 patient-years of exposure.

1105 patients on Vortioxetine had an exposure of 6 months and more and 845 patients were on Vortioxetine for at least 12 months. There is no information on the number of subjects receiving 2.5 mg, 5 mg and 10 mg for ≥ 6 and ≥ 12 months from the study reports.

MDD ongoing open-label long-term pool

Studies 13267B and 314 belong to the pool of ongoing studies and as of 26th of October 2012, 1144 patients had been exposed to 15 or 20 mg/day of Vortioxetine (813 patient-years of exposure). 391 patients had ≥ 52 weeks of exposure.

The Extent of Population Exposure to Assess Clinical Safety (ICH CPMP/ICH/375/95) is adequate: ICH E1 guidance requests data from 300 to 600 patients treated for 6 months at dosage levels intended for clinical use: 528 patients received 5 mg, 861 patients received 10 mg, 258 patients received 15 mg and 524 patients received 20 mg Vortioxetine up to 26th of October 2012. About 100 patients should receive the drug at dosage levels intended for clinical use for more at least one year. This has been adequately fulfilled for each dose level (e.g. 124 patients with 15 mg and 270 patients with 20 mg Vortioxetine).

Strategy of the overall safety evaluation:

- Clinical pharmacology integrated safety database including healthy patients and patients with renal or hepatic impairment to evaluate safety and tolerability of Vortioxetine.
- Integrated safety database from the phase II/III studies allowing pooling and comparing safety data. The primary pool for the evaluation of the short-term safety and tolerability was the MDD short-term pool, supported by the MDD&GAD short-term pool.

  Other studies in MDD and GAD have not been pooled, mainly due to a different study design and are therefore presented individually.

Pooling of studies as proposed by the applicant and separation of other studies due to a different study design (relapse-prevention studies) is reasonable.

Of note, studies 317, CCT-002, 14122A, and 14178A were completed by the new data cut off 31st August 2013, and updates on safety variables are given wherever applicable.

Patient disposition and withdrawals

Patient disposition revealed an overall consistent picture for the short-term pool with withdrawal rates of 16-23% (doses 5 to 20 mg) and for the MDD long-term pool with discontinuations between 37 and 46%. A slightly higher number (46%) of subjects withdrew from the ongoing open-label long-term pool. The most common reasons for discontinuation from treatment were adverse events and lack of efficacy. In the ongoing MDD open-label long-term pool, withdrawal of consent was the most common reason for withdrawal (11%). Fewer patients on VORTIOXETINE withdrew from the short-term pools due to lack of efficacy (1.9%) compared to long-term open-label pools (5 to 6%). Discontinuation due to adverse events during vortioxetine treatment varied less in all pools (5 to11%).

Demographic and baseline characteristics (referring to the initially submitted studies)

As was expected in this disorder, approximately two-thirds of the patients were women in the short-term pools, the MDD long-term pool and the relapse-prevention studies. The majority of the patients were Caucasian. Patients receiving duloxetine as active comparator were slightly older (49.6 ± 16 years), at least 78%.

MDD short-term pool:

In the MDD short-term pool, the mean age was 46 years in the placebo group and in the VORTIOXETINE Total group (range: 18 to 88 years [18 to 85 in the placebo group]). Patients receiving duloxetine as active comparator were slightly older (49.6 ± 16 years). A higher proportion of patients in the placebo group than in the VORTIOXETINE Total group were ≥65 years old (14% versus 10%). In the MDD short-term pool, only 30 patients (1.1 %) in the VORTIOXETINE groups were aged ≥75 year, 290 (10.5%) ≥65 year. The VORTIOXETINE 5 mg/day group was studied in elderly, resulting in a 2.6% of the population being ≥75 years of age and 19.4% ≥65 (including ≥75) for the 5 mg/day group. In the 10, 15 and 20 mg groups, only 1 patient in each group was ≥75 year. Adding the GAD short-term pool resulted in the age distribution by dose in (Table).

Table 15: Age distribution by dose in the MDD-GAD short-term pool (APTS)

	Treatment Group	Category	N	(%)	Mean	Median	SD	Min	Max
Age Group	PBO	< 65 years	1840	(88.9)					
		>=65 years	230	(11.1)					
		>=75 years	31	(1.5)					
	AA21004 1 mg	< 65 years	133	(95.0)					
		>=65 years	7	(5.0)					
	AA21004 2.5 mg	< 65 years	594	(97.2)					
		>=65 years	17	(2.8)					
		>=75 years	4	(0.7)					
	AA21004 5 mg	< 65 years	1244	(84.9)					
		>=65 years	222	(15.1)					
		>=75 years	28	(1.9)					
	AA21004 10 mg	< 65 years	814	(95.4)					
		>=65 years	39	(4.6)					
		>=75 years	8	(0.9)					
	AA21004 15 mg	< 65 years	277	(93.0)					
		>=65 years	21	(7.0)					
		>=75 years	1	(0.3)					
	AA21004 20 mg	< 65 years	424	(93.2)					
		>=65 years	31	(6.8)					
		>=75 years	1	(0.2)					
	Total AA21004	< 65 years	3486	(91.2)					
		>=65 years	337	(8.8)					
		>=75 years	42	(1.1)					
	VLF	< 65 years	113	(100)					
	DUL	< 65 years	721	(79.5)					
		>=65 years	186	(20.5)					
		>=75 years	39	(4.3)					

The mean baseline weight and **BMI** in the MDD short-term pool were similar in the placebo and VORTIOXETINE Total groups (80 and 79kg and 29 and 28kg/m^2, respectively). The proportion of patients with a BMI <25kg/m^2 was lower in the placebo group than in the VORTIOXETINE Total group (34% and 38%, respectively), consequently, the proportion of patients with a BMI ≥30kg/m^2 was higher in the placebo group than in the VORTIOXETINE Total group (35% and 31%, respectively). In the VORTIOXETINE 10mg/day group the proportion of patients with a BMI <25kg/m^2 was higher than

in the VORTIOXETINE Total group (43% and 38%, respectively). The VORTIOXETINE 20 mg/day group had a higher mean and median BMI and a higher population with a BMI above 30 kg/m^2 than the VORTIOXETINE Total group (39% and 31%, respectively).

Nearly 30 % were current smokers, approximately 15% has a diagnosis of hypertension and 3% of diabetes mellitus type I or II. For nearly 60% of the patients the baseline LDL cholesterol was above the reference range.

In the MDD long-term relapse-prevention study, the mean age was 45 years, ranging from 18 to 75 years (18 to 74 years in the Double-blind Period). There were no clinically relevant differences in weight or BMI between the placebo and VORTIOXETINE groups. Mean BMI for the FAS was 27 kg/m² for the placebo group and 26 kg/m² for the VORTIOXETINE group.

In the GAD long-term relapse-prevention study, the mean age was 44 years, ranging from 18 to 75 years. There were no clinically relevant differences in weight or BMI between the VORTIOXETINE and placebo groups.

In the open-label long-term pool, the mean age was 45 years, and 6% (n=83) of the patients were ≥ 65 years old and only 3 patients were ≥75 years old. The mean baseline BMI was 27kg/m^2 (range: 16 to 58kg/m^2).

For the MDD short-term pool, the proportions of patients with concurrent disorders at baseline were similar in the placebo and VORTIOXETINE groups (72% and 69%, respectively), ranging from 65% to 72% in the therapeutic VORTIOXETINE dose groups. At baseline, the most common concurrent disorders in all groups (occurring in ⩾20% of the patients in any group) were in the following SOCs (placebo versus VORTIOXETINE): musculoskeletal and connective tissue disorders (23% vs. 21%) and nervous system disorders (23% vs. 20%). For the MDD and GAD short-term pool, numbers of patients with concurrent disorders at baseline were similar to the MDD short-term pool.

In the MDD long-term relapse-prevention study (and similarly in the GAD long-term relapse-prevention study), 64% of the patients had concurrent disorders. The three most common concurrent disorders at baseline were metabolism and nutrition disorders (16%, mainly hypercholesterolemia and obesity), musculoskeletal and connective tissue disorders (16%, mainly back pain and osteoarthritis), and social circumstances (16%, mainly menopause). In addition, nervous system disorders (13%, mainly headache and migraine) and vascular disorders (12%, mainly hypertension) affected substantial proportions of patients at baseline.

The most common concurrent disorders for patients in the MDD Open-label Long-term Pool (Vortioxetine 2.5 to 10mg/day) (⩾10%) by preferred term were: hypertension (15%), headache (12%), and menopause (10%).

The most common concurrent disorders for patients in the MDD Ongoing Open-label Long-term Pool (Vortioxetine 15 to 20mg/day) (⩾10%) by preferred term were: headache (26%), seasonal allergy (20%), hypertension (17%), drug hypersensitivity (13%), insomnia (13%), and back pain (11%).

The short-term safety in the elderly has been investigated in study 12541A, using 5 mg/day of VORTIOXETINE.

In the MDD and GAD short-term pool (data cut-off 26th October 2012), only 38 patients in the VORTIOXETINE therapeutic dose groups (5 to 20mg/day) were aged ≥75 year, 313 patients were ≥65 years of age although depression is a common disorder in the over 65. The number of elderly patients ≥75 year was very low in the 10, 15 and 20 mg groups, with 8 patients in the 10 mg group, but only 1 patient in the 15 and 20 mg group. The number of patients ≥65 in the 10, 15 and 20 mg groups were 39, 21 and 31 respectively.

In the MDD and GAD long-term relapse-prevention studies, the mean age was 45 years and no patient was older than 75. In the open-label long-term pool (VORTIOXETINE 2.5, 5 or 10 mg/day), 6% (n=83) of the patients were ≥65 years old, of which only 3 patients were ≥75 years.

Overall, in the elderly population ≥ 65, 249 patients with MDD or GAD received VORTIOXETINE 5 mg/day, 111 patients 10 mg/day, 21 patients 15 mg/day and 42 patients 20 mg/day. A pooled analysis of the clinical safety data in elderly by dose is missing.

In the long-term studies, 37 patients were treated with the 5 mg dose, 56 with the 10 mg dose, 14 with the 15 mg dose and 24 with the 20 mg dose in elderly of 65 - ≤75 years. Only 7 patients of 75 and older have been included. Safety data for the 15 and 20 mg/day dose are limited.

Use of vortioxetine in patients aged ≥75 years is scarce.

The Applicant will initiate a post-authorisation safety study (PASS) where the frequency of certain important potential risks will be assessed. Patients with these events will be further characterised by dose and age (among others), which will provide further information on safety in elderly patients for the higher doses of 15 and 20 mg/day vortioxetine.

The SmPC has been adapted to reflect the limited data in the elderly population: The lowest effective dose of 5 mg should always be used as starting dose and patients should be carefully monitored when an increase in dose is required (see section 4.4). Particular caution should be exercised when treating elderly patients with doses higher than 10 mg/day for which data are limited.

Regarding BMI, there is no indication that the safety and tolerability of Vortioxetine are substantially different between patients with a BMI <25 or ≥30kg/m^2. There are minor imbalances in the distribution across baseline BMI categories between the Vortioxetine 10 and 20mg groups and the other treatment groups, but there is no consistent trend in terms of the nature of the adverse events or major differences in the incidences between the BMI categories.

Adverse events

Treatment emergent adverse events (TEAEs) occurring with VORTIOXETINE have been analysed for each pool.

TEAEs in the Clinical Pharmacology Studies

Clinical pharmacology studies were pooled for evaluation of TEAEs and doses of VORTIOXETINE were combined against placebo and "other substances". The SOCs with the highest percentage of TEAEs were *gastrointestinal disorders* (total VORTIOXETINE: 35.6% vs. placebo 14.2%) and *nervous system disorders* (total VORTIOXETINE: 26.2% vs. placebo 14.9%) followed by *skin and subcutaneous tissue disorders* (total VORTIOXETINE: 17.4% vs. placebo 15.3%). Preferred terms most often mentioned for subjects on VORTIOXETINE (≥ 10%) were: nausea (20%), headache (19%), and diarrhoea (13%).

Thorough QT study 104 evaluated the effect of VORTIOXETINE on cardiac repolarisation (presented in detail in section adverse events of special interest).

Single- and multiple ascending dose studies 10272 (healthy men; 10/20/30/50/75 mg) and 10467 (healthy men with 20/40/60 mg and healthy women with single doses of 60 mg, followed by washout and 12 days of exposure to VORTIOXETINE 40 mg) investigated the maximum tolerated doses of VORTIOXETINE in healthy young men and women. A cohort of elderly men and women was included in study 10467. Additional panels explored the tolerability of VORTIOXETINE at doses of 10 to 40mg/day by titration in 8 young women and at lower doses of 2.5 and 5mg/day in 16 young women over a longer period (25 days). In addition, 8 elderly men and women (aged >65 years) received VORTIOXETINE 20mg first as a single dose followed by washout and then at 20mg/day for 12 days.

As the most important results, single doses of VORTIOXETINE 60mg led to nausea and flushing in all women. Also, diarrhoea and abdominal discomfort were reported at high incidences (67%) at the 60mg dose. Tolerability of 40mg/d was not acceptable in women. This fact is referred to in section 4.8 of the SmPC. Elderly volunteers tolerated maximum doses of 20mg/d with TEAEs of procedural site reactions, headache, and sleep disorder as most common adverse events.

Adverse events reported for these three completed studies clinical pharmacology studies 14520A, 14029A, and CPH-004, as of data cut off 31st of August 2013 were in line with those previously reported in the other studies, and most frequently mentioning AEs of gastrointestinal origin. No SAEs have been reported.

TEAEs in phase II/III short-term pools

MDD short-term pool (updated)

Updated information on MDD short-term pool, including studies 317, 14122A, and CCT-002:

In the updated MDD Short-term Pool, the overall incidence of TEAEs for Vortioxetine was similar at 5mg/day (65%), 10mg/day (61%), 15mg/day (69%) and 20mg/day (65%); the incidences in the placebo and duloxetine groups were 58% and 76%. The SOCs with the highest incidences of TEAEs were *gastrointestinal disorders* and *nervous system disorders*. The two preferred terms with the highest incidences were nausea (ranging from 21 31% for 5 to 20 mg/day) and headache (ranging from 12 to 15% for 5 to 20 mg/day but similar to placebo 13%).

In general, the incidences of ***dizziness***, ***diarrhoea***, ***vomiting, and constipation*** were slightly higher for VORTIOXETINE than for placebo and slightly higher at 15 and 20mg/day than at 5 and 10mg/day.

34% of duloxetine-and venlafaxine- treated subjects reported nausea in the short-term pool.

In contrast to duloxetine, VORTIOXETINE was not associated with *insomnia*, *somnolence*, *fatigue*, or h*yperhidrosis*.

Among the less frequent TEAEs, ***abnormal dreams***, ***decreased appetite***, ***pruritus generalised***, and ***influenza*** had an incidence ≥2% and at least twice that for placebo at one or more of the VORTIOXETINE therapeutic doses.

Most of the TEAEs reported in the updated MDD short-term pool are not dose-related (e.g. nausea, headache, dizziness, etc.).

Study 14178A revealed overall consistence with the aforementioned results from the short-term studies: the incidence of AEs was similar in the two treatment groups (55% and 53% in the Vortioxetine and agomelatine groups, respectively). Nausea occurred with a higher incidence in the Vortioxetine group compared to the agomelatine group (16% and 9%, respectively). All other TEAEs with an incidence ≥5% had a higher incidence in the agomelatine group than in the Vortioxetine group and comprised headache (10% in the Vortioxetine group and 13% in the agomelatine group), dizziness (7% in the Vortioxetine group and 12% in the agomelatine group), and somnolence (4% in the Vortioxetine group and 8% in the agomelatine group).

MDD&GAD short-term pool

The pattern of TEAEs, incidences and severities were similar to that in the MDD short-term studies.

TEAEs in long-term relapse-prevention

MDD long-term relapse-prevention study 11985A

During the open-label phase of this study, the incidence of TEAEs was 70.6%. Again, the SOCs with the highest reporting rate of TEAEs were *gastrointestinal disorders* and *nervous system disorders*. Nausea was reported in 26% of patients followed by headache in 18% of patients. All other TEAEs were reported in less than 10% of patients. Of note, 5.8% of patients reported a TEAE of accidental overdose.

The majority of events were mild to moderate in severity with 13% of TEAEs being classified as severe. Severe TEAEs were headache and nausea (1.6% each), and accidental overdose (1.3%).

The overall adverse event rate in the double-blind phase of the study was similar for placebo and VORTIOXETINE-treated subjects (63.5% and 62.3%). The SOCs with the highest occurrence of TEAEs were *infections and infestations, gastrointestinal disorders and nervous system disorders*. Preferred terms in the infection and infestation SOC occurred in a similar number in placebo and VORTIOXETINE-treated subjects (nasopharyngitis: 14 and 11%; influenza: 5 and 7%; gastroenteritis: 3 and 2%). Nausea was reported nearly three times higher in the VORTIOXETINE group compared to placebo (9 and 3 %). Headache was similar in placebo and active treatment (13 and 12%), and accidental overdose was reported in 8% of placebo and VORTIOXETINE-treated patients each. The majority of events were mild to moderate in severity with 10% of TEAEs being classified as severe in both treatment groups.

A relatively high reporting rate of “accidental overdose” in study 11985A was explained by the Applicant to be caused by protocol amendment recording each overdose (accidental or intentional) at least as an adverse event. The cases depicted by the Applicant did not raise concern of intentional/suicidal background and events are similarly distributed between placebo and Vortioxetine.

GAD long-term relapse prevention study 12473A

The overall incidence of TEAEs in the open-label period of this study was 77% with *gastrointestinal disorders, nervous system disorders, and infections and infestations* being the SOCs with the highest percentage of TEAEs (43%, 30%, and 24%). Preferred terms, which contribute to these SOC rates, were nausea (27.1%), headache (17.6%), and influenza (7.6%). Results are very similar to those observed in the MDD long-term relapse-prevention study.

The overall adverse event rate in the double-blind phase of the study was similar for placebo and VORTIOXETINE-treated subjects (53.9% and 55%). Infections and infestations was the SOC with the highest rate of TEAEs in both groups placebo and VORTIOXETINE (23% and 23.6%). Twice as many subjects on VORTIOXETINE had an AE of influenza compared to placebo (12.2 vs. 6.1%).

TEAEs in the MDD open-label long-term pool

71.2% of patients included in this study had TEAEs. The SOCs with the highest percentage of TEAEs were *gastrointestinal disorders* (33.1%), *infections and infestations* (29.5%), and *nervous system disorders* (24.3%). Nausea (17.5%), headache (13.2%) and nasopharyngitis (10.5%) were the most common preferred terms. During the first two weeks of open-label treatment, the incidence of nausea was lower in patients, who continued treatment with VORTIOXETINE (6% to 9%) than those, who switched from other treatments to VORTIOXETINE (15% to 18%) when entering the extension study.

TEAEs in the ongoing MDD open-label long-term pool

At the cut-off date of 26 October 2012, 78.5% of patients included in this pool had TEAEs. The SOCs with the highest percentage of TEAEs were *gastrointestinal disorders* (41.2%), *infections and infestations* (30.2%), and *nervous system disorders* (26.8%). The TEAEs with the highest incidences (≥10%) were nausea (24%) and headache (13%).

To summarize, the most frequently reported treatment-emergent adverse events (TEAEs) occurred in the SOCs of Gastrointestinal disorders and Nervous System disorders regardless of the different pools. Clinical pharmacology studies, short-term MDD, short-term MDD and GAD, relapse-prevention studies in MDD and GAD and open-label long-term treatment with VORTIOXETINE gave an overall similar pattern of adverse events.

The most common TEAEs during short-term and long-term treatment that occurred in ≥10% of VORTIOXETINE-treated patients were *nausea and headache*. The incidence for *nausea* was constantly two- to three-fold greater than the incidence in placebo-treated patients and dose-related (up to 21 – 31% of subjects in the MDD short-term pool).

Headache (up to 20%) *and dizziness* (< 10%) were most often mentioned within the nervous system disorder SOC and also dose-related. Incidences were only slightly lower for placebo-treated subjects.

Most of the TEAEs were mild to moderate in severity. Severe adverse events were reported in a similar range in placebo and VORTIOXETINE-treated subjects (about 5-6%).

MDD short-term Pool studies serve as a basis for ADRs with a total of 3904 patients treated with Vortioxetine up to 20 mg/day and with 1968 patients receiving placebo. The causal relationship of adverse events attributed to Vortioxetine was determined by a dose-response relationship or an incidence of ≥ 1.5-times compared to placebo. Allocation to the respective frequency columns followed the SmPC guidance.

Suicidal ideation and behaviour

Patients with a significant risk of suicide were excluded from the VORTIOXETINE clinical development programme.

Suicidal ideation and self-injurious behaviour during treatment with VORTIOXETINE in the phase II/III studies was investigated based on TEAEs captured using the SMQ Suicide/Selfinjury. In addition, suicidal ideation and behaviour was captured prospectively using the Columbia-Suicide Severity Rating Scale (C-SSRS) in 3 clinical pharmacology studies, 811 phase II/III studies in MDD, and 5 phase III studies in GAD assessed suicidal ideation and behaviour using the C-SSRS. The C-SSRS scores (1 to 10) were mapped into the Columbia Classification Algorithm for Suicide Assessment (C-CASA).

In the clinical development programme for Vortioxetine, 1 completed suicide and 9 suicide attempts have been reported in patients treated with Vortioxetine, corresponding to an overall incidence of fatal and non-fatal suicide attempts of 0.34 per 100 PYE (95% CI: 0.16; 0.62).

Suicidality was evaluated for all pools and in terms of TEAEs and also using a validated rating scale. As a result, TEAEs with respect to suicide/self-injury (SMQ) were considered spontaneous and therefore, percentages were lower compared to rating scale results.

In the updated short-term MDD studies (and similarly during short-term MDD and GAD studies), 0.4% of Vortioxetine- and 0.5% of placebo-treated patients reported **TEAEs** of suicidal ideation. This number was slightly increased in the MDD open-label long-term pool (0.5%).

Suicide attempts did occur in the Vortioxetine group in the MDD short-term pool (n=4), in the MDD relapse-prevention study (n=1), in one patient from the MDD open-label long-term pool, in two patients from the MDD ongoing open-label long-term pool and in one placebo-treated subjectin the MDD short-term pool One completed suicide was reported in the clinical study program.

When using the **C-SSRS**, suicidal ideation was reported for 14.5% of Vortioxetine-treated patients and 16% of placebo-treated patients in the updated MDD short-term studies (MDD and GAD short-term studies). Elderly patients seemed to be at lower risk for suicidal ideation (12% for Vortioxetine vs. 10% for placebo). MDD open-label long-term study 301 showed a slight decrease in patients with suicidal ideation (9.6%) and during GAD long-term relapse-prevention study 12473A, suicidal ideation decreased to 2% in Vortioxetine-treated patients (vs. 3.5% placebo) during the double-blind phase of the study. Suicidal behaviour occurred in 1.3% of placebo-treated subjects and in 0.4% of Vortioxetine-treated subjects.

Suicidal ideation differs between MDD and GAD studies (lower incidence in GAD studies compared to MDD studies) suggesting the underlying disease to be the main reason for these events. The fact, that all of the reported suicide attempts happened in MDD patients, is in support of this assumption. Nevertheless, since suicidality is considered a class effect of antidepressant medication, close monitoring of suicidal events is needed. Since suicidal ideation and suicidal behaviour is a class effect known for SSRIs, SNRIs, and TCAs, it is implemented in the risk management plan as *important potential risk*.

Further adverse events of special interest

Across the clinical study program, 2 patients had **convulsions** (in both cases there was an alternative aetiology).

The potential risk for convulsions in people with a history of convulsions is included in the SmPC.

One patient in the VORTIOXETINE groups had a mild episode of **serotonin syndrome** (without neuromuscular rigidity and hyperthermia, which characterise life-threatening episodes).

No additional case of seizure or serotonin syndrome was reported in the additional 1656 patients from the updated MDD short-term pool. The clinical presentation of serotonin syndrome is variable and often aspecific, diagnosing serotonin syndrome can be challenging, particularly in mild cases. Therefore, serotonin syndrome remains a potential risk.

However, there is evidence that antidepressants could contribute to the occurrence of neuroleptic malignant syndrome (Heinemann F., Assion H.-J., Laux G. 1997). For serotonine-accented antidepressants, this could be explained by inhibitory effects on central dopaminergic neurones due to increased 5-HT activity. As a consequence, several SSRIs (sertraline, paroxetine) include a warning in section 4.4 of the SmPC.

The Applicant has added a warning on neuroleptic malignant syndrome, too.

Switching from depressive symptoms **to mania** or **hypomania** during antidepressant therapy has been reported and caution is generally advised when treating patients who have bipolar disorder or a history of mania. Patients with a history of mania or hypomania were excluded from all the studies in the VORTIOXETINE development programme. In the updated MDD short-term pool, the incidence of TEAEs captured in the SMQ Hostility/Aggression was similar in the placebo group (2.8%) and the VORTIOXETINE total group (1.9%).

Patients with a history of mania or hypomania were excluded from studies.

However, current clinical data do not indicate a switch to or induction of mania/hypomania. Therefore, patients with a history of mania/hypomania may be included as a target population. However,

VORTIOXETINE should be used with caution in this population and should be discontinued in patients entering a manic phase. A warning is added to section 4.4.

The PASS will provide more information on the use, efficacy, adverse events and withdrawals in this subpopulation.

For several antidepressants, **insomnia** and related adverse events such as **somnolence**, delayed sleep phase, and nocturnal awakening are described as common clinical problems. The incidence of insomnia and somnolence were similar to placebo, this in contrast to duloxetine which is associated with insomnia and somnolence. The updated MDD short-term pool revealed insomnia (somnolence)-related TEAEs for 3.7% (2.3%) of placebo-treated subjects and 3.9% (3.0%) of Vortioxetine-treated subjects. There was no indication of a dose-response relationship in the VORTIOXETINE groups.

Most antidepressants, including those with a serotonergic effect, are related with **sexual dysfunction**. In the clinical studies, adverse events related to sexual dysfunction were evaluated based on spontaneously reported TEAEs and, in 6 short-term studies (2.5 to 20mg), also based on the ASEX. The latter allowed identifying patients without sexual dysfunction at baseline but who developed treatment-emergent sexual dysfunction (TESD) during treatment.
In the updated MDD short-term pool, the overall incidence of sexual dysfunction TEAEs during treatment with VORTIOXETINE was low (1.6%) and similar to that in the placebo group (0.9%). It was 4.5% in the duloxetine group and 12.4% in the venlafaxine group, both are associated with sexual dysfunction. In the VORTIOXETINE dose groups (not updated), the incidence of sexual dysfunction TEAEs ranged from 0% in the 1mg group to 2.6% in the 20mg group; however, there was no dose-response relationship as the incidences in the 2.5mg, 5mg, 10mg, and 15mg groups were 2.3%, 1.6%, 1.5%, and 1.3%, respectively. Study 14178A revealed one patient with 2 AEs related to sexual dysfunction in the Vortioxetine group and no patient in the agomelatine group. In the MDD long-term relapse prevention study, during the open-label period, 2.5% of the patients had a sexual dysfunction TEAE. The most common (>2 patients) sexual dysfunction TEAEs were libido decreased (1.4%), erectile dysfunction (1.7%), and ejaculation delayed (1.2%). During the Double-blind Period, 2.0% of the patients in the VORTIOXETINE group and 1.0% in the placebo group had a sexual dysfunction TEAE. None of the events were reported by >2 patients.

Looking at treatment emergent sexual dysfunction (TESD) based on ASEX scoring for the therapeutic dose range (5mg to 20mg), there was no clear dose-response relationship in the incidence of TESD during treatment with VORTIOXETINE. However, there is an increase in TESD going from the 5 to the 20 mg group. The overall incidence of TESD during treatment with VORTIOXETINE was 38% which was slightly higher than that in the placebo group (32%). In the duloxetine group, the incidence of TESD was 48%. The incidence of TESD was 43 and 46% in the VORTIOXETINE 15 and 20 mg groups, respectively, and the latter is close to the duloxetine level. There was a tendency for the proportion of women with TESD to be slightly larger than the proportion of men with TESD for all doses and in all treatment groups, including placebo.

Increase in TESD for the 20 mg VORTIOXETINE dose group compared to placebo has been added to section 5.1 of the SmPC.

The incidence of **extrapyramidal symptoms** (akathisia and dyskinesia) may be adverse effects of psychotropic treatment. *Akathisia* is most of all believed to occur subsequently to dopaminergic/noradrenergic neurotransmission. Vortioxetine exerts its mode of action via the serotonergic system, but with minor influence on other neurotransmitter systems. In the updated MDD short-term pool, the incidence of TEAEs captured in the SMQ Akathisia and Dyskinesia were similar in the placebo group (0.6% and 0.3%) and in the VORTIOXETINE total group (0.7% and 0.3%).

Vortioxetine exerts its antidepressive mechanism solely by serotonergic regulation, similar to duloxetine, escitalopram, fluoxetine, and sertraline. Tardive dyskinesia was not observed during the clinical program. Furthermore, tardive dyskinesia is considered a long-term effect of antipsychotic treatment e.g. as augmentation to antidepressants or for treatment-resistant depression. Since this scenario does not apply for Vortioxetine, it is not relevant to add tardive dyskinesia to the SmPC.

Blood pressure and heart rate have been reviewed throughout the VORTIOXETINE clinical development programme. The vital signs evaluations did not show any relevant changes over time. In addition, searches were performed during the MDD short-term studies using the SMQ **Hypertension**. TEAEs (updated short-term pool) were similar for placebo and VORTIOXETINE (1.3% each) with preferred terms of blood pressure increased and hypertension mentioned most frequently. Nevertheless, *hypertensive crisis* was reported in one patient as SAE and in 4 additional patients on Vortioxetine as TEAE. However, there is no evidence for an increased risk of hypertensive crisis under Vortioxetine treatment.

Hyponatraemia is considered a risk in patients using antidepressants, in particular in the elderly. The harmful effects of hyponatraemia may be exacerbated in patients who take diuretics and other medications. (Moret et al., 2009). Clinical safety laboratory values have been reviewed throughout the VORTIOXETINE clinical development programme. The serum sodium values did not show any relevant changes over time. In addition, searches were performed using the SMQ Hyponatraemia/SIADH. Very few cases were reported. In MDD short-term Study 12541A in the elderly, the sodium test values showed no relevant changes over time in the VORTIOXETINE group compared to the placebo group; no patients in the VORTIOXETINE group had a potentially clinically significant low post-baseline serum sodium value.

As platelet aggregation is inhibited by serotonin transporter inhibition, drugs that inhibit the serotonin transporter may result in **increased bleeding tendencies**. Clinical pharmacology studies have been conducted to assess the potential of VORTIOXETINE to affect the anticoagulant effect of warfarin and aspirin. No significant effects have been observed. Also, to assess the potential effect of VORTIOXETINE on bleeding, blood samples for platelet count have been taken throughout the VORTIOXETINE clinical development programme. The mean platelet counts did not show any clinically relevant changes over time. In the clinical studies, the overall incidence of TEAEs related to haemorrhage was not higher for VORTIOXETINE than for placebo (updated MDD short-term pool: 1.3% for placebo and 1.4% for total Vortioxetine).

In the MDD short-term pool TEAEs were captured for the SMQ **Severe cutaneous** adverse **reactions**. The incidence was similar in the placebo and the VORTIOXETINE groups (0.2% for placebo and 0.1% for Vortioxetine).

There was no increased incidence of **osteoporosis seen from the data from the clinical studies**.

However, published data strongly point towards a serotonergic effect on bone mineral density and vortioxetine also modifies serotonergic signalling. For this reason, adequate wording on this class effect has been added to section 4.8 of the SmPC.

A potential for peripheral hypertension, or visual field effects or **glaucoma** caused by an increase in intra-ocular pressure, was not seen.

Abuse potential studies in humans have not been performed, but there was no increased reporting of drug abuse. TEAEs were evaluated using the adverse event cluster search *Abuse Liability*: In the updated MDD short-term pool, a similar number of patients in the placebo and Vortioxetine group had

AEs (4.0% and 3.7%). Most AEs were due to irritability (1.5% and 1.1%) and sedation (0.6% and 1.1%). Other pools confirmed these results.

The Applicant investigated withdrawal symptoms. The DESS were low and similar in nature as the adverse events observed during the study. These do not indicate a dependence liability.
The intake of overdose was low and mainly involved the accidental intake of 1 or 2 additional tablets.
The number of adverse events potentially related to abuse liability was low and similar in all treatment groups.
Therefore, it is agreed that a clinical abuse liability study is not necessary at the moment. The Applicant will monitor the occurrence of drug discontinuation symptoms as part of the routine pharmacovigilance activities. The newly released SMQ for Drug Abuse, Dependence and Withdrawal (MedDRA 15.0, section 2.22) will be used to identify cases.

Discontinuation symptoms

Six short-term studies (5 in MDD and 1 in GAD) and the long-term relapse-prevention studies in MDD and GAD were designed to investigate the occurrence of potential discontinuation symptoms following abrupt discontinuation of treatment with Vortioxetine.

In addition, update of study CCT-002 included a 2-week discontinuation period following abrupt discontinuation of placebo or Vortioxetine 5mg, 10mg, or 20mg/day.

Overall, there was no evidence of clinically relevant discontinuation symptoms that warranted a dose tapering of Vortioxetine. *Due to the long plasma elimination half-life of 66 hours and the gradual elimination from the central 5-HT transporter, there is a relatively long natural down-taper*.

At this time, discontinuation symptoms are referred to in the SmPC as not relevant for Vortioxetine and subsequently, there seems to be no need for gradual dose reduction of the substance.

Serious adverse events and deaths

Deaths

There were no deaths in the clinical pharmacology studies.

As of updated cut-off date 31st August 2013, 6 deaths had been reported in the clinical development programme, all patients were in the Vortioxetine study groups. Deaths were reported consequently due to cancer (2), suicide (1), morphine intoxication (1), and accidents (2). According to the investigator, there was no apparent pattern in the causes of death and were not clearly related to the study medication.

Unfortunately, the Applicant could not further clarify the circumstances of two death cases suspect of a suicidal background (morphine intoxication and fall from a balcony) and one completed suicide. However, one could assume from the narratives of these cases that at least the subject who fell from a balcony has a suicidal background.

Other serious adverse events

In the completed **clinical pharmacology** studies, 4 of the 1243 subjects exposed to Vortioxetine had 5 SAEs; 1 subject while exposed to placebo and 3 of the subjects while exposed to 10mg Vortioxetine: abortion spontaneous, chest discomfort and dyspnoea – at discontinuation of Vortioxetine treatment, traumatic fracture.

In the updated **MDD short-term pools**, the incidence of SAEs was similar in the placebo group (1.0% [19 patients]) and Vortioxetine Total group (1.1% [41 patients]); there was no dose-response relationship in the Vortioxetine dose groups.

The SAEs that occurred in ≥2 patients in the Vortioxetine Total group were: convulsion, depression, suicidal ideation, and suicide attempt.

During long-term treatment with Vortioxetine, the incidence of SAEs was 3.4% in the double-blind Period of **MDD relapse-prevention Study 11985A**. In the open-label period, no SAE occurred in >1 patient, except for d*epression* which occurred in 2 patients, the other SAEs occurred in only 1 patient, among which *accidental overdose*, *serotonin syndrome* and a *suicide attempt*.
During the open-label period of the **GAD relapse-prevention Study 12473A** there were 2 psychiatric disorders: one *depressive disorder* and one *panic attack*; 2 renal and urinary disorders; one *atrial fibrillation* and one *ECG prolonged QT-interval*; one *cholelithiasis*; one *appendicitis*; one *migraine*; one *allergic rhinitis*. During the double-blind phase there was one *anaphylactic reaction*, one patient with *major depression*, one *nasal septal operation*.

The SAE incidence was 3.3% in the **MDD open-label Long-term Pool**. As of 26 October 2012, the incidence of SAEs in the MDD ongoing open-label long-term Pool was 2.4%. The only SAEs that occurred in ≥2 patients were *breast cancer female, cholelithiasis* and *suicide attempt* (2 patients each). One patient has acute cholecystitis and one cholecystitis. All other SAEs occurred in single patients only and did not follow a specific pattern.

During the **MDD ongoing open-label long-term studies** (314 and 13267B, data cut-off date as of 26th October 2012), 28 out of 1144 patients (2.4%) have been reported with an SAE. 6 of these 28 patients with SAEs (21%) were from the neoplasm SOC. The Applicant adequately summarised the individual risks for these patients, which could be clearly traced back for five of these patients (prior carcinomas or other risks for developing carcinomas). None of these events were classified as related to study drug, which can be accepted.

There was no discernible pattern or trends in the types of events within or between treatment groups.

Several SAEs have been investigated and discussed in the section on *adverse events of special interest*.

Laboratory findings

The clinical safety laboratory test results indicate that short- or long-term treatment with Vortioxetine is not associated with clinically relevant changes in any of the tests that were assessed. The mean changes and the proportions of patients with shifts from normal values at baseline to out-of-range values at last assessment or with potentially clinically significant (PCS) values were at placebo level.

Liver and kidney toxicity

The liver function test results were further evaluated using additional outlier criteria and the results showed no impact of Vortioxetine on liver function as compared to placebo. In addition, the adverse events were analysed for signals of effects on renal or liver function and no indication of such effects were seen.

Weight and lipid values

In general, the proportion of patients with abnormal lipid values was high. In the MDD Short-term Pool, the LDL cholesterol value at baseline was above the reference range in nearly 60% of the patients. However, both during short- and long-term treatment with Vortioxetine, the mean changes

were at placebo level, and the proportion of patients with shifts from normal at baseline to a value above the reference range was not higher than that with placebo.

During long-term treatment in the Double-blind Period of the relapse-prevention study in MDD, the mean weight increase for Vortioxetine (0.4kg) was also at placebo level (0.6kg). These results were supported by those in the relapse-prevention study in GAD and the open-label, long-term studies.

QT-interval prolongation

A thorough QT study has been conducted to evaluate the potential of Vortioxetine to cause QTc-interval prolongation. The administration of Vortioxetine 10 or 40mg/day for 14 days to healthy men had no clinically significant effect on cardiac repolarisation using the ICH E14 definitions. Although, the study shows a clear tendency of the higher dose of Vortioxetine 40 mg/day to increase the QT interval. The upper bound of the two-sided 90% CI around the least squares (LS) mean, time-matched, baseline-adjusted difference to placebo for QTcNi, QTcF, QTcB, and QTcFm was <10ms for both doses of Vortioxetine at all assessment time points. The pre-specified primary endpoint was the largest time-matched baseline-adjusted LS means difference for QTcNi (linear) to placebo at post-treatment ECG collection times. The maximum mean difference to placebo in QTcNi (linear) was 1.4ms (90% CI: -2.1; 4.9) for VOR 10mg/day and 4.4ms (90% CI: 0.9; 7.9) for Vortioxetine 40mg/day. The positive control moxifloxacin confirmed the sensitivity of the study. No correlations between the time-matched, baseline-adjusted QTc and the plasma concentrations of Vortioxetine or its metabolites Lu AA34443 and Lu AA39835 were observed. In the categorical analysis of ECG outlier events, the occurrence of QTcNi (Linear) values >450 ms was observed in one patient receiving Vortioxetine 10 mg/day at day 14, 5hr postdose. No subject experienced QTcNi (Linear) >480 and 500 ms or change from Baseline >60 ms. Few patients in the Vortioxetine group showed an increase in QTcNi interval from baseline >30ms.

ECGs have been reviewed throughout the clinical development programme. In the MDD short-term pool, the incidence of PCS high RR interval values was 1.2% in the placebo group and ranged in the therapeutic Vortioxetine dose groups from 1.1% in the 15mg group to 2.6% (25 patients) in the 5mg group. The incidence of PCS low PR interval values in the placebo group was 2.1% and ranged in the therapeutic Vortioxetine dose groups from 2.7% in the 10mg group to 4.6% in the 15mg group.
In the MDD relapse-prevention study, during the double-blind period, the incidences of PCS ECG parameter values were low. PCS ECG parameter values with an incidence ≥2% in either treatment group were:

- low PR interval (placebo group: 4.3%; Vortioxetine group: 3.0%)
- high QTcB (placebo group: 1.1%; Vortioxetine group: 2.0%)
- high RR interval (placebo group: 3.2%; Vortioxetine group: 1.5%)

In the ongoing open-label long-term safety pool, at the cut-off of 26 October 2012, the ECG parameter values with an incidence of PCS values ≥2% were high RR interval (2.4%) and low PR interval (3.9%).

Searches were performed using the SMQ Torsade de Pointes/QT Prolongation.
In the MDD short-term pool, the majority of the events captured in this SMQ were ECG QT prolonged. All the events were non-serious and none of them were reported as arrhythmias or torsade de pointes. No events in the placebo or Vortioxetine dose groups resulted in withdrawal from the study. One patient in the Vortioxetine 10 mg group had syncope; one patient in the Vortioxetine 2.5mg group had loss of consciousness (severe event; concurrent with an accident). In the MDD & GAD Short-term Pool, MDD long-term relapse-prevention Study 11985A, and the MDD Open-label Long-term Pool, the incidences and pattern of TEAEs in the SMQ Torsade de Pointes/QT Prolongation were similar to those

in the MDD Short-term Pool. A total of 5 patients had **syncope**: 3 patients who received Vortioxetine 2.5mg/day in short-term studies in GAD and 2 patients during long-term treatment with Vortioxetine; 1 event was mild, 3 events were moderate, and 1 event was severe; 1 patient withdrew due to syncope and 9 other events. In addition, 3 patients withdrew from open-label treatment with Vortioxetine due to **electrocardiogram qt prolonged**. In GAD long-term relapse-prevention Study 12473A, 1 patient had **ventricular tachycardia** on Day 5 of the Open-label Period, was withdrawn from the study, and recovered from the event; the patient had a history of obesity, ventricular extrasystoles, and hypertension and received beta blockers and angiotensin II antagonists. In addition, 1 patient had an SAE of **electrocardiogram qt prolonged** and electrocardiogram **T wave inversion** (non-serious) reported in the Open-label Period; the patient completed the study. In the Double-blind Period, 1 patient in the Vortioxetine group had electrocardiogram qt prolonged.

In the clinical studies, the incidences of potentially prolactin-related TEAEs were at the placebo level during short- and long-term treatment with Vortioxetine. The data do not suggest that treatment with Vortioxetine is associated with an increase in serum prolactin.

Safety in special populations

Sex

Pharmacokinetic assessment with respect to sex revealed exposure increases of up to 30% in women. In the MDD short-term pool, the incidence of TEAEs leading to withdrawal was similar between men and women in the Vortioxetine 5mg group. In the Vortioxetine 10mg, 15mg, and 20mg groups, the incidences of TEAEs leading to withdrawal was higher for women (6.5%, 9.5%, and 9.3%, respectively) than for men (4.5%, 5.2%, and 6.3%, respectively). In the MDD Short-term Pool, the incidences of TEAEs were similar between men and women, except for nausea, which was consistently lower in men than in women in the therapeutic Vortioxetine dose groups, the active reference groups, and the placebo group. The incidence of nausea increased in a dose-dependent manner in both men (from 17% in the 5mg group to 22% in the 20mg group) and women (from 23% in the 5mg group to 35% in the 20 mg group).

The incidence of TEAEs and more specifically of nausea is higher in women than in men, which is referred to in section 4.8 of the SmPC. The pharmacokinetically observed slightly higher exposure in women than in men possibly contributes to this effect.

Age

Age-related differences were found in pharmacokinetic studies with subjects aged ≥65 years having approximately 30% higher exposure to Vortioxetine compared to subjects aged 45 years and younger after treatment with multiple doses of 10 mg/d.

In the dedicated study in the elderly **≥65 years** of age (Study 12541A), treatment with VORTIOXETINE **5mg/day** was safe and well tolerated and the **safety profile was not different from that in patients aged <65** years. For VORTIOXETINE, the changes in the clinical safety laboratory results, vital signs, weight, or ECGs were at placebo level. In the updated MDD short-term studies (including the study in the elderly), in which approximately 9% of the patients were aged ≥65 years, there was no consistent trend in the safety profile between patients aged < or ≥65 years. When looking at the therapeutic VORTIOXETINE doses, patients aged <65 years had a higher incidence of TEAEs in the VORTIOXETINE 5 mg and 10 mg group compared to patients aged ≥ 65 years. In contrast, more patients aged ≥ 65 years had TEAEs in the higher dose groups of VORTIOXETINE 15

and 20 mg. In the VORTIOXETINE **20mg group**, the **incidences of nausea and constipation were higher in patients aged ≥65 years** (42% and 15%, respectively); than in patients aged <65 years (27% and 4%, respectively). These are issues of tolerability rather than safety. Of note, patients aged ≥ 65 years had a nearly twofold higher incidence of TEAEs leading to withdrawal from study (5.1%, 14.7%, 14.3%, and 15.2% for Vortioxetine 5mg, 10mg, 15mg, and 20mg) compared to patients <65 years of age (4%, 4.6%, 7.4%, and 6.4% for Vortioxetine 5mg, 10mg, 15mg, and 20mg).

In the new Study 14178A (Vortioxetine versus agomelatine), 19 patients with an age ≥ 65 were on VORTIOXETINE treatment. More elderly patients had SAEs and AEs leading to withdrawal than in the whole study population (5.3% vs 1.2% and 15.8% vs 5.9%, respectively). However, this population is too small to draw conclusions.

The **MDD open-label long-term pool and the ongoing open-label long-term pool** do not indicate a difference in the incidence of AEs, SAEs and AEs leading to withdrawal between patients > 65 and ≤65. The number of patients included for the 15mg/day and 20 mg/day doses are limited.

Table presents the incidences of the TEAEs by age group for Vortioxetine (5 to 20mg/day) and placebo in the MDD Short-term Pool.

Table 16: Summary of TEAEs, entire study period, by treatment and age group (APTS) – MDD short-term pool

	Age <65				Age 65-74				Age 75-84				Age 85+			
	PBO		AA21004 5-20 mg		PBO		AA21004 5-20 mg		PBO		AA21004 5-20 mg		PBO		AA21004 5-20 mg	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of Patients	1257		2037		176		245		27		27		1		2	
TEAEs	765	(60.9)	1374	(67.5)	105	(59.7)	154	(62.9)	18	(66.7)	18	(66.7)	0	(0.0)	2	(100)
Serious TEAEs	11	(0.9)	23	(1.1)	3	(1.7)	4	(1.6)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
-Death	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
-Hospitalization or prolonged hosp	7	(0.6)	18	(0.9)	3	(1.7)	3	(1.2)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)
-Life Threatening	2	(0.2)	3	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
-Disability	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
-Other	3	(0.2)	4	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
AE leading to drop-out	45	(3.6)	124	(6.1)	8	(4.5)	20	(8.2)	2	(7.4)	5	(18.5)	0	(0.0)	0	(0.0)
Psychiatric Disorders (SOC)	144	(11.5)	240	(11.8)	12	(6.8)	22	(9)	1	(3.7)	2	(7.4)	0	(0.0)	0	(0.0)
Nervous System Disorders (SOC)	315	(25.1)	554	(27.2)	44	(25)	50	(20.4)	8	(29.6)	5	(18.5)	0	(0.0)	2	(100)
Accidents and Injuries (SMQ)	34	(2.7)	64	(3.1)	3	(1.7)	9	(3.7)	4	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac Disorders (SOC)	29	(2.3)	34	(1.7)	6	(3.4)	4	(1.6)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)
Vascular Disorders (SOC)	24	(1.9)	47	(2.3)	3	(1.7)	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebrovascular Disorders (SMQ)	4	(0.3)	2	(0.1)	1	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and Infestations (SOC)	176	(14)	312	(15.3)	20	(11.4)	25	(10.2)	5	(18.5)	1	(3.7)	0	(0.0)	0	(0.0)
Quality of Life Decreased (PT)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Fall and Fainting (AE cluster)	88	(7)	163	(8)	12	(6.8)	21	(8.6)	5	(18.5)	2	(7.4)	0	(0.0)	2	(100)
Ataxia (AE cluster)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Osteoporosis/Osteopenia (SMQ)	0	(0.0)	4	(0.2)	0	(0.0)	0	(0.0)	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)

Dictionary: MedDRA 14.1

Lu AA21004 IDB Final Q189_D120 14MAR2013:09:10:32 SADs Build Number: 12.1

A PASS is planned to also cover elderly patients above 75 years of age. An update regarding the MDD short-term pool was presented including newly generated data on patients 65 years and above (see Panel 27).

Panel 27 Summary of TEAEs, Core Treatment Period, by Dose and Age Group (APTS) - Updated MDD Short-term Pool

	PBO n(%)	AA21004 5 mg n(%)	AA21004 10 mg n(%)	AA21004 15 mg n(%)	AA21004 20 mg n(%)	DUL n(%)
Total						
Number of Patients	1968	1157	1042	449	812	753
PYE	263	149	143	61	113	101
Patients with AEs	1140(57.9)	749(64.7)	636(61.0)	309(68.8)	529(65.1)	571(75.8)
Patients with AEs leading to Withdrawal	70(3.6)	48(4.1)	51(4.9)	35(7.8)	55(6.8)	66(8.8)
Patients with SAEs	9(0.5)	9(0.8)	8(0.8)	1(0.2)	3(0.4)	6(0.8)
Deaths	0	1(<0.1)	0	0	0	0
64 years or below						
Number of Patients	1754	960	1008	421	779	567
PYE	233	122	139	57	108	76
Patients with AEs	1012(57.7)	630(65.6)	620(61.5)	287(68.2)	501(64.3)	425(75.0)
Patients with AEs leading to Withdrawal	61(3.5)	38(4.0)	46(4.6)	31(7.4)	50(6.4)	47(8.3)
Patients with SAEs	9(0.5)	8(0.8)	7(0.7)	1(0.2)	3(0.4)	4(0.7)
Deaths	0	0	0	0	0	0
65 years or above						
Number of Patients	214	197	34	28	33	186
PYE	30	27	4	4	4	25
Patients with AEs	128(59.8)	119(60.4)	16(47.1)	22(78.6)	28(84.8)	146(78.5)
Patients with AEs leading to Withdrawal	9(4.2)	10(5.1)	5(14.7)	4(14.3)	5(15.2)	19(10.2)
Patients with SAEs	0	1(0.5)	1(2.9)	0	0	2(1.1)
Deaths	0	1(0.5)	0	0	0	0

Lu AA21004 IDB Final aTEAE_sum_M1I2 19AUG2013:16:59:09 SADs Build Number: 13.0

The short-term safety in the elderly has been investigated in study 12541A, using 5 mg/day of VORTIOXETINE while the currently recommended dosage in the SmPC is 10 mg once daily.

PK data indicate an increased exposure in the elderly aged ≥65 years (approximately 30%) compared to subjects aged 45 years and younger after treatment with multiple doses of 10 mg/d. On this basis, no dose adjustment in elderly is required, although a higher number of AEs can be expected.

A dose of 5mg/day was shown to be safe and well tolerated in the elderly population.

Data from the MDD short term pool indicate that the 10 mg/day dose does not lead to larger amount of TEAEs, but to a higher number of study withdrawals due to TEAEs. In the MDD open-label long-term pool (5 and 10 mg/day), the incidence of nausea was slightly higher in patients aged <65 years than in patients aged ≥65 years (18% and 11%, respectively).

For the 15 mg/day dose, the number of patients is too small to draw clear conclusions (n=21 for short term and n=14 for long term). In the MDD short-term pool, the incidences of TEAEs and TEAEs leading to withdrawal were increased. For the 20 mg/day dose, the long term data are also limited (n=25). In the updated MDD short-term pool an increase in TEAEs, especially nausea and constipation was observed, as well as an increase in TEAEs leading to withdrawal. The incidence of nausea increased in the 20 mg/day group from 27% in patients below 65 years to 42 % in patients ≥ 65. In the MDD ongoing long-term pool (15 and 20 mg/day) data are too scarce to draw conclusions.

The use of doses above 10mg/day in the elderly population shows limitations regarding the number of patients studied with these doses. At this moment no major safety concerns in the elderly population have been observed, however due to the limited data in the elderly population for doses above 10 mg/day, the increased exposure in elderly and an increase in TEAEs and TEAEs leading to withdrawal

for the 15 and 20 mg/day dose in the short term pool, a dose increase should be undertaken only with particular caution, as reflected in the SmPC.

Few elderly patients were treated with the higher doses during the long–term studies. There are generally more adverse effects in patients >65 years of age, e.g. those leading to treatment discontinuation.

BMI

In the MDD Short-term Pool, the incidence of TEAEs leading to withdrawal, the overall incidence of TEAEs, and the types of TEAEs with an incidence ≥5% in the VORTIOXETINE groups were generally similar among the different BMI categories.

Genetic polymorphisms in cytochrome P450 enzymes

A phase I population pharmacokinetic analysis, indicated that CYP2D6 extensive metabolisers have an approximately 2-fold higher oral clearance than poor metabolisers (PMs). Therefore, an analysis of tolerability in CYP2D6 PMs versus CYP2D6 non-PMs from the clinical pharmacology studies was conducted.

Of the 41 PMs, 20, 15, and 7 subjects received at least one dose of VORTIOXETINE ≤10mg, 15 to 30mg, and ≥40mg, respectively. The mean duration of exposure in these dose categories was 10.6, 7.4, and 6.5 days, respectively. Of the 879 non-PMs, 518, 242, and 162 subjects received at least one dose of VORTIOXETINE ≤10mg, 15 to 30mg, and ≥40mg, respectively. The mean duration of exposure in these dose categories was 9.3, 5.3, and 8.5 days, respectively.

The incidences of TEAEs leading to withdrawal were 4.9% (2 subjects) and 2.4% (21 subjects) in the PM group and the non-PM group, respectively. The TEAEs leading to withdrawal in the PM group were vomiting and angioedema. In the non-PM group, the most common TEAE leading to withdrawal was vomiting (4 subjects); all other TEAEs leading to withdrawal did not occur in >2 subjects. The TEAEs with an incidence ≥5% in both groups were: nausea, diarrhoea, headache, and dizziness.

Nausea, dizziness, pruritus and pruritus generalised were higher in the PM group than in the non-PMs.

An approximately two-fold increase in VORTIOXETINE exposure was seen following coadministration of bupropion (a strong CYP2D6 inhibitor). When bupropion was added to VORTIOXETINE 10mg/day at steady state, a higher incidence of adverse events was observed than when VORTIOXETINE was added to bupropion at steady state. This may be explained by pharmacodynamic or combined pharmacodynamic/pharmacokinetic effects following CYP2D6 inhibition with bupropion, which seem to be more pronounced when the inhibition is initiated when VORTIOXETINE is in steady state than before VORTIOXETINE is administered. Depending on the individual patient response, a lower dose of VORTIOXETINE may be considered if strong CYP2D6 inhibitors are added to VORTIOXETINE treatment.

The frequency of some adverse effects is doubled in the PM group, like for dizziness and pruritus. Probably, the dose will also have an influence. Therefore, this additional aspect should be taken into account in this analysis of PMs versus non-PMs. However, analysis based on grouping by genotype of patients in the phase II/III studies is not possible as no genotyping was performed. Blood sampling for plasma concentrations of Vortioxetine was performed in patients from Studies 11492A, 11984A, 12541A, 13267A, 305, 315, and 316, which allows for a pooling of adverse events by average plasma concentration (Cav). 10% of patients with the highest C_{av} were a substitute for low clearance and the 10% of patients with the lowest C_{av} for high clearance.

Only in the 20 mg VORTIOXETINE group, the incidence of adverse events was higher in the low-clearance group than in the normal-clearance group. Globally, the overall incidence of adverse events was similar in patients categorised as having low or normal clearance.

Section 5.2 of the SmPC has been updated to specify: CYP2D6 poor metabolisers: As for all patients, depending on individual patient response, a dose adjustment may be considered. In section 4.2, highlights that “depending on individual patient response, the dose may be increased to a maximum of 20 mg daily or decreased to a minimum of 5 mg daily”.

Hepatic and renal impairment

Patients with hepatic and renal insufficiency have been excluded from the phase II/III studies. We refer to study 114 and 112, investigating the effect of hepatic and renal impairment on the pharmacokinetics of VORTIOXETINE.

Pregnant and lactating women

A total of 36 women who received VORTIOXETINE became pregnant during or shortly after stopping treatment with VORTIOXETINE. For the majority of these pregnancies, the mother had an elective abortion or gave birth to a healthy infant with no birth or developmental birth defects.
Some of these outcomes are still unknown; however, the data presented do not give raise to a specific concern and are therefore acceptable.

In lactating rats, VORTIOXETINE-related material was distributed to the milk. It is expected that VORTIOXETINE will be excreted into human milk.

Overdose

In Study 10272, single ascending doses of VORTIOXETINE 10, 20, 30, 50, or 75mg were explored in 36 healthy young men. There was a slightly higher proportion of TEAEs in the two highest dose groups, with more frequent GI disorders, in which nausea had the highest incidence, the other AE in this SOC were diarrhoea and abdominal pain. Also dizziness was more frequently observed in the highest dose groups.

In Study 10467, multiple ascending doses of VORTIOXETINE 20, 40, or 60mg/day for 12 days were explored in 18 healthy young men. The most common TEAEs reported by subjects receiving VORTIOXETINE were diarrhoea (33-67% vs. 11% for placebo), abdominal discomfort (33-67% vs. 22% for placebo), headache (33-50% vs. 44% for placebo) and procedural site reactions (33-50% vs. 33% for placebo). The subject incidence of headache and procedural site reaction were similar in all of the treatment groups (VORTIOXETINE and placebo). **Diarrhoea, abdominal discomfort** and abdominal pain were more common in subjects receiving VORTIOXETINE compared with those receiving placebo. For diarrhoea and abdominal discomfort the incidence was generally **higher at the highest dose** (60 mg). It is of note that 13 of the 18 men receiving active treatment had abdominal discomfort, abdominal pain or diarrhoea during the first 3 days of dosing. In most subjects these adverse events were transient and had resolved by Day 4. **Generalised pruritus** was reported for 3 out of 6 patients for 60 mg and not for the other doses.
In addition, 6 healthy young women received single doses of 60mg followed by washout and 12 days of exposure to VORTIOXETINE 40mg/day. The single dose of 60 mg VORTIOXETINE (Day 1) was not well tolerated by the young women; therefore the dose was reduced to 40 mg for multiple dosing on Days 5 to 16. The most common TEAEs in subjects receiving VORTIOXETINE were **nausea** (83-100% vs. 0% for placebo), **flushing** (33-100% vs. 0% for placebo), **dizziness postural** (67-33% vs. 33% for placebo), **headache** (83-33% vs. 0% for placebo), **abdominal discomfort** (33-67% vs. 0% for placebo), **dizziness** (50-33% vs. 0% for placebo), **somnolence** (67-0% vs. 0% for placebo), **diarrhoea** (0-67% vs. 0% for placebo) and **pruritus generalised** (17-50% vs. 0% for placebo).

Effects on ability to drive or operate machinery or impairment of mental ability

In driving performance Study 12689A, single and multiple doses of VORTIOXETINE 10mg/day did not impair driving performance compared to placebo as assessed using the standard deviation of lateral position and standard deviation of speed during an on-the-road driving test.
Based on a pharmacodynamic test battery assessing psychomotor and cognitive effects, VORTIOXETINE 10mg/day administered in the evening yielded no residual effects, whereas mirtazapine yielded moderate residual effects in the acute phase.

In the MDD Short-term Pool, the incidences of insomnia, somnolence, fatigue, and sedation in the VORTIOXETINE Total group were similar to those in the placebo group. However, the incidence of dizziness increased slightly with increasing dose.

Safety related to drug-drug interactions and other interactions

Potential drug-drug interactions were investigated in 11 pharmacology studies. The majority (8 studies) were cytochrome P450 interaction studies (bupropion, rifampicin, ketoconazole/fluconazole, omeprazole, cocktail [caffeine, tolbutamide, dextromethorphan, and midazolam], combined oral contrazeptive [ethinyl estradiol and levonorgestrel], warfarin, diazepam). There were 3 other interaction studies with ethanol, aspirin and lithium.

Significantly higher incidences of AEs were observed when bupropion 150 mg BID was added to the VORTIOXETINE 10 mg QD monotherapy (related AE from 60 to 89%). No corresponding increase in the incidence of AEs was observed when VORTIOXETINE 10 mg QD was added to the bupropion 150 mg BID monotherapy. AEs with the greatest incidence were nausea (60% and 30% respectively), headache (43 and 47%), vomiting (33 and 23%), insomnia (33 and 7%), palpitations (20 and 13%), hyperhidrosis (20 and 10%), constipation (23 and 0%), dizziness (23 and 13%), postural dizziness (23 and 13%), dyspepsia (13 and 10%) and tremor (13 and 10%).

According to the results from bupropion interaction Study 117, CYP 2D6 plays a major role in metabolism of Vortioxetine and CYP 2D6 inhibitors like bupropion increase exposure to Vortioxetine (in terms of AUC) with concomitantly increased rates in adverse events, e.g. vomiting, nausea, insomnia, dizziness. Patients concomitantly treated with other strong CYP 2D6 inhibitors, e.g. paroxetine, and fluoxetine, are also considered at increased risk for adverse events.

The Applicant stated correctly that strong antidepressant inhibitors were not allowed during the clinical studies. A search was conducted including strong CYP 2D6 inhibitors others than antidepressants and a total of six patients were found with strong inhibitors, mainly with terbinafine. No new adverse events were reported which could lead to the assumption of an altered safety profile of Vortioxetine. However, since data on concomitant administration with other strong CYP2D6 inhibitors like fluoxetine and paroxetine are lacking, no final conclusion can be drawn at this time. The Applicant included further potent CYP2D6 inhibitors to SmPC section 4.2 in regard to dose reduction while on combination therapy with potent CYP2D6 inhibitors.

Study 115 evaluated the potential interaction of Vortioxetine and rifampicin (a broad inducer of CYP isoforms): Co-administration of Vortioxetine 20 mg and rifampicin 600 mg following multiple doses of rifampicin 600 mg, led to a 72% reduction in AUC(0-tlqc), a 77% reduction in AUC(0-inf), and a 51% reduction in the Cmax of Vortioxetine. The majority of adverse events were associated with the administration of rifampicin 600 mg QD alone on Days 15 to 24.

There were no significant exposure changes and increases in adverse events throughout the other interaction studies.

Discontinuation due to AES

If an adverse event was contributory to withdrawal, the adverse event was regarded as the primary reason for withdrawal.

In the updated MDD Short-term Pool, the incidence of treatment-emergent adverse events (TEAEs) leading to withdrawal was higher in the VORTIOXETINE therapeutic dose groups (5 to 20mg/day) and in the duloxetine group (8.8%) than in the placebo group (3.6%); in the VORTIOXETINE therapeutic groups, the incidence increased with dose from 4.1% in the 5 mg group to 7.8% in the 15 mg group. The incidence of adverse events leading to withdrawal in the 20 mg Vortioxetine group was lower (6.8%). The updated MDD short-term pool showed up to be similar to the original data.

During long-term treatment with VORTIOXETINE in the Double-blind Period in MDD relapse prevention Study, the incidence of TEAEs leading to withdrawal was 6.9% in the VORTIOXETINE group and 1.0% in the placebo group. In the open-label extension studies, the incidence of TEAEs leading to withdrawal during long-term treatment with 2.5 to 10mg/day was 6.2% (MDD Open-label Long-term Pool) and the incidence during long-term treatment with 15 or 20mg/day (MDD Ongoing Long-term Pool) was 10%.

Nausea was the most common TEAE leading to withdrawal in each of the active treatment groups and more frequently compared to the placebo group. For VORTIOXETINE, the incidence of nausea leading to withdrawal increased with dose and, for the therapeutic doses, it ranged from 1.1% at 5mg/day to 3.8% at 15mg/day. Nausea as an AE leading to withdrawal was reported in 3.3% of subjects from the 20mg Vortioxetine dosing group. The majority of the patients who withdrew due to nausea did so within the first 3 weeks of treatment. No other pattern was seen in the TEAEs leading to withdrawal.

-The withdrawal due to adverse events in the double-blind period of the GAD relapse prevention study is lower than in the MDD relapse prevention study. No apparent explanation was found on this difference in withdrawal due to AEs.

- Several adverse events are related to the disorder itself, like depression, suicidal ideation, depressive symptom, major depression, insomnia, depressed mood, suicide attempt and are related to a lack of efficacy. However, only very few patients withdrew due to depression-related TEAEs (as primary or contributory reason).

Discontinuations from study treatment due to adverse events were slightly higher for Vortioxetine compared to placebo in all pools using placebo controls giving an overall consistent picture. The most common adverse event leading to withdrawal was nausea. The risk for this event leading to treatment discontinuation was highest during the first weeks of treatment.

The incidences of nausea with 5 mg and 10 mg Vortioxetine (21% and 23%) are similar and also withdrawal due to nausea (1.1% and 1.4%) regarding the updated MDD short-term pool. This is substantiated by the fact that a similar number of patients on 5 mg and 10 mg Vortioxetine withdrew within the first week of treatment (1% and 0.9%; original MDD short-term pool data). Based on these data, titration of Vortioxetine is not considered beneficial in the adult population.

2.6.1. Discussion on clinical safety

Population exposure

The integrated safety database for Vortioxetine refers to 18 completed clinical phase II/III studies in adult subjects with MDD and 5 completed phase III studies in subjects with GAD. Studies were pooled either to the MDD short-term pool, the GAD short-term pool, the MDD and GAD short-term pool, the MDD open-label long-term pool or the MDD ongoing open-label long-term pool. Individual studies were not pooled and results were presented separately for MDD relapse-prevention study, GAD relapse prevention study, several MDD short-term studies, which are ongoing, and one MDD open-label long-term study (OCT-001), which is also ongoing. At day 180, data have been added from a recently completed double-blind 12-week active-comparator study with flexible doses of 10 to 20 mg/day (study 14178A) and studies 317, 14122A, and CCT-002. An update was also presented for the MDD ongoing open-label long-term studies 13267B and 314.

The Extent of Population Exposure to Assess Clinical Safety (ICH CPMP/ICH/375/95) is adequate. In the MDD-GAD short term pool, 1466 patients received 5 mg/day, 853 10mg, 298 15mg and 455 20mg. As of the new data cut-off date August 2013, an additional 144 (497, 151, and 357) patients contributed to the overall short-term safety of Vortioxetine 5mg (10mg, 15mg, and 20mg). ICH E1 guidance requests data from 300 to 600 patients treated for 6 months at dosage levels intended for clinical use, which has been adequately presented by the Applicant: 528 patients received 5 mg, 861 patients received 10 mg, 258 patients received 15 mg and 524 patients received 20 mg Vortioxetine up to 26th of October 2012. About 100 patients should receive the drug at dosage levels intended for clinical use for more at least one year. This has been adequately fulfilled for each dose level (e.g. 124 patients with 15 mg and 270 patients with 20 mg Vortioxetine).

Currently, data on the elderly population is limited. The Applicant committed to perform a drug utilisation study which will provide further information on safety in elderly patients >75. Hyponatraemia is considered a field of interest in the elderly, especially in those treated with antidepressants,.

Patient disposition

Patient disposition revealed an overall consistent picture for the short-term pools with withdrawal rates of 16-23% for doses of 5 to 20 mg/day and for the MDD long-term pools with discontinuations between 37 and 46%. A slightly higher number (46%) of subjects withdrew from the ongoing open-label long-term pool. The most common reasons for discontinuation from treatment were adverse events and lack of efficacy. In the ongoing MDD open-label long-term pool, withdrawal of consent was the most common reason for withdrawal (11%). Fewer patients on Vortioxetine withdrew from the short-term pools due to lack of efficacy (1.9%) compared to long-term open-label pools (5 to 6%). Discontinuation due to adverse events during vortioxetine treatment varied less in all pools (5 to11%).

TEAEs

The system organ classes (SOC) with the highest proportion of patients with AEs were Gastrointestinal disorders and Nervous System disorders. Within these SOCs, most AEs were rated mild to moderate in severity.

The most frequent adverse event is nausea (up to 31% with no clear dose-relationship). Headache (up to 20%) and dizziness (< 10%) were most often mentioned within the nervous system disorder SOC. A relationship to dose could not be established with these events.

The incidences of dizziness, diarrhoea, vomiting and constipation were slightly higher for Vortioxetine than for placebo and slightly higher at 15 and 20mg/day than at 5 and 10mg/day. Among the less frequent TEAEs, abnormal dreams, decreased appetite, pruritus generalised, and influenza had an incidence ≥2% and at least twice that for placebo at one or more of the Vortioxetine therapeutic doses.

With respect to TEAEs included in section 4.8 of the SmPC, the causal relationship of adverse events attributed to Vortioxetine was determined by a dose-response relationship or an incidence of ≥ 1.5-times compared to placebo.

Suicidal ideation and behaviour

At this time, there seems to be no increased risk for suicidality under Vortioxetine treatment compared to other antidepressants with a similar mode of action. Nevertheless, further investigation is needed also because suicidal ideation and suicidal behaviour is a class effect known for antidepressants. The PASS study, will specifically evaluate completed suicides and suicide attempts.

SAEs

The occurrence of serious adverse events under Vortioxetine treatment was in the same range compared to placebo in the short-term studies (around 1%). Within each pool, no accumulation of SAEs of specific preferred terms could be seen. Nevertheless, single SAEs recurring over all analysed pools were spontaneous abortion, depression, suicidal ideation/attempt/completed suicide. Of note and special interest, 21% of SAEs in the ongoing open-label long-term pool with 15 and 20 mg Vortioxetine were from the neoplasm SOC, which is considered a high number. For 5 of these 6 patients prior carcinomas or other risks for developing carcinomas were identified.

Adverse events of special interest

Convulsions, serotonin syndrome and neuroleptic malignant syndrome remain a potential risk.

Patients with a history of mania or hypomania were excluded from studies, therefore the possible switch from depression to mania as a result of Vortioxetine treatment has not been investigated. . Vortioxetine should be used with caution in this population and should be discontinued in patients entering a manic phase.

The incidence of insomnia and somnolence were similar to placebo, this in contrast to duloxetine which is associated with insomnia and somnolence.

In the updated MDD short-term pool, the overall incidence of sexual dysfunction TEAEs during treatment with Vortioxetine was low (1.6%) and similar to that in the placebo group (0.9%). Looking at treatment emergent sexual dysfunction (TESD) based on ASEX scoring for the therapeutic dose range (5mg to 20mg), there was no clear dose-response relationship in the incidence of TESD during treatment with Vortioxetine. However, there is an increase in TESD going from the 5 to the 20 mg group. The overall incidence of TESD during treatment with Vortioxetine was 38% which was slightly higher than that in the placebo group (32%). In the duloxetine group, the incidence of TESD was 48%.

The incidence of TESD was 43 and 46% in the Vortioxetine 15 and 20 mg groups, respectively, which is close to the duloxetine level. The latter is associated with sexual dysfunction.

No significant effects have been observed for extrapyramidal symptoms, hypertension, hyponatraemia, increased bleeding tendencies, severe cutaneous reactions, osteoporosis or glaucoma. The risk for bone fractures (osteoporosis) in SSRIs and TCAs is a known class effect and has been added to the SmPC (see CMDh/PhVWP/020/2010).

Abuse potential

The Applicant investigated withdrawal symptoms. The DESS were low and similar in nature as the adverse events observed during the study. These do not indicate a dependence liability. The intake of overdose was low and mainly involved the accidental intake of 1 or 2 additional tablets. The number of adverse events potentially related to abuse liability was low and similar in all treatment groups.
Therefore, a clinical abuse liability study is not necessary at the moment. The Applicant will monitor the occurrence of drug discontinuation symptoms as part of the routine pharmacovigilance activities. The newly released SMQ for Drug Abuse, Dependence and Withdrawal (MedDRA 15.0, section 2.22) will be used to identify cases.

Discontinuation symptoms

Some patients may experience discontinuation symptoms with Vortioxetine, particularly if treatment is stopped abruptly. Discontinuation symptoms were assessed by looking at the TEAEs emerging after Week 1 and Week 2 following stop of treatment. Results were inconsistent in the single clinical studies neither indicating an absence of discontinuation symptoms nor a marked effect of Vortioxetine on the emergence of discontinuation symptoms. Discontinuation symptoms were also assessed in three MDD short-term studies using the discontinuation-emergent signs and symptoms checklist (DESS). The overall DESS scores in the Vortioxetine groups were slightly higher compared to placebo after Discontinuation Week 1 and 2. DESS single items were similar to the discontinuation TEAEs (incidence of 10% and more: irritability, fatigue/tiredness, trouble sleeping/insomnia and increased dreaming and nightmares).

At this time, discontinuation symptoms are not considered to be of significant concern and a gradual dose reduction of the substance is not supported by data.

Laboratory findings

The effects of Vortioxetine on laboratory results of haematology, clinical chemistry and urinalysis did not raise any clinically relevant concerns. Clinically relevant abnormalities in hepatic analytes have been rarely detected for AST and ALT and were not different from placebo. Therefore, no safety concern is raised on the alteration of liver function.

In general, the proportion of patients with abnormal lipid values was high. In the MDD Short-term Pool, the LDL cholesterol value at baseline was above the reference range in nearly 60% of the patients. However, both during short- and long-term treatment with Vortioxetine, the mean changes were at placebo level, and the proportion of patients with shifts from normal at baseline to a value above the reference range was not higher than that with placebo.

The vital sign and electrocardiogram (ECG) data from the controlled short- and long-term studies did not raise any tolerability or safety concerns and did not indicate that treatment with Vortioxetine is associated with changes therein. In the thorough QT Study, the administration of Vortioxetine 10 or 40mg/day for 14 days to healthy men had no clinically significant effect on cardiac repolarisation using the ICH E14 definitions. Although, the study shows a clear tendency of the higher dose of Vortioxetine 40 mg/day to increase the QT interval. Furthermore, the adverse events did not raise any signals of QT prolongation or arrhythmias. Tachycardia was reported to occur at a higher incidence in Vortioxetine-

treated subjects compared to placebo (3.5% for Vortioxetine 10 mg and 2.4% for Vortioxetine 40 mg vs. 1.2% in placebo-treated subjects). These results were confirmed in the phase II/III clinical studies.

Special populations

Pharmacokinetic assessment with respect to sex revealed exposure increases of up to 30% in women. The incidence of TEAEs and more specifically of nausea is higher in women than in men.

The short-term safety in the elderly has been investigated and proven in study 12541A, using 5 mg/day of Vortioxetine.

PK data indicate an increased exposure in the elderly aged ≥65 years (approximately 30%) compared to subjects aged 45 years and younger after treatment with multiple doses of 10 mg/d. On this basis, no dose adjustment in elderly is required, although a higher number of AEs can be expected.

Data from the MDD short term pool indicate that the 10 mg/day dose does not lead to larger amount of TEAEs, but to a higher number of study withdrawals due to TEAEs. In the MDD open-label long-term pool (5 and 10 mg/day), the incidence of nausea was slightly higher in patients aged <65 years than in patients aged ≥65 years (18% and 11%, respectively).

For the 15 mg/day dose, the number of patients is too small to draw clear conclusions (n=28 for short-term and n=14 for long-term). In the MDD short-term pool, the incidences of TEAEs and TEAEs leading to withdrawal were increased. For the 20 mg/day dose the long term data are limited (n=25). In the MDD short-term pool an increase in TEAEs, especially nausea and constipation was observed, as well as an increase in TEAEs leading to withdrawal. The incidence of nausea increased in the 20 mg/day group from 27% in patients below 65 years to 42 % in patients ≥ 65. In the MDD ongoing long-term pool (15 and 20 mg/day) data are scarce.

The use of doses above 10mg/day in the elderly population has limitations regarding the number of patients studied with these dosesand therefore, particular caution should be exercised when using doses above 10 mg/day.

From an **interaction** point of view, Vortioxetine was shown to undergo CYP isoenzyme biotransformation via CYP2D6, CYP2C9, CYP2C19, CYP3A, and CYP2A6. Of these, CYP2D6 plays a major role in Vortioxetine metabolism. The frequency of some adverse events doubles in the poor metabolizer (PM) group, but few patients were included in the PM group. The increased exposure in CYP2D6 PM can be managed by dose reduction if tolerability issues arise.
An analysis based on grouping by genotype of patients in the phase II/III studies is not possible as no genotyping was performed. Instead, a pooling of adverse events by average plasma concentration (Cav) was performed. 10% of patients with the highest Cav were a substitute for low clearance and the 10% of patients with the lowest Cav for high clearance. In the 20 mg Vortioxetine group, the incidence of adverse events was higher in the low-clearance group than in the normal-clearance group. Globally, the overall incidence of adverse events was similar in patients categorised as having low or normal clearance.

Bupropion is a potent CYP2D6 inhibitor and led to increased Vortioxetine exposure and subsequently AE reporting when concomitantly treated. Patients concomitantly treated with other strong CYP2D6 inhibitors, e.g. paroxetine, and fluoxetine, are also considered at increased risk for adverse events and a dose reduction of vortioxetine should be considered.

Current data presented do not give rise to a specific concern on pregnancies. However, exposure to serotonergic medicinal products during the third trimester has been associated with medication withdrawal symptoms in the newborn and with an increased risk of persistent pulmonary hypertension

in the newborn, which is a serious condition with a mortality rate of about 10%. These potential risks have been highlighted in the SmPC.

2.6.2. Conclusions on the clinical safety

Treatment with Vortioxetine at therapeutic doses (5 to 20 mg/day) was safe and well tolerated in adults. The incidence of nausea, the most common adverse event, was shown to be higher at doses of 15 and 20 mg/day compared to doses of 5 and 10 mg/day and typically had an onset within the first week of treatment and on average had a duration of 1 to 2 weeks. Nausea was the most common adverse event leading to withdrawal and more so with the higher doses. Other common adverse events were headache, dry mouth, dizziness, and diarrhoea. In the long-term pools, the incidence of TEAEs in Vortioxetine-treated patients confirms the safety profile obtained in the short-term pools.

The use of doses >10mg/day in the elderly population, especially in patients 75 years of age and older, shows limitations regarding the number of patients studied with these doses and the SmPC has been adapted to reflect this issue.).

At this time, there seems to be no increased risk for suicidality under Vortioxetine treatment compared to other antidepressants with a similar mode of action. Nevertheless, further investigation will be conducted as part of the PASS study. Suicidal ideation and suicidal behaviour is a class effect known for antidepressants.

Vortioxetine seems to underlie variable pharmacokinetics and various parameters affect the systemic exposure (e.g. gender, age, race, CYP2D6 status, and drug-drug interactions).

A non-interventional post-authorisation safety study (PASS) of vortioxetine in Europe will be carried out to collect information on important missing information (off-label use regarding indication, off-label paediatric use, use in pregnant women, use in patients aged ≥75 years, use in patients with a history of mania/hypomania, use in patients with Alzheimer's disease, Parkinson's disease, multiple sclerosis and stroke, use in patients with severe renal or hepatic impairment, misuse for illegal purposes like abuse/dependance) as well as to describe patterns of use of vortioxetine in clinical practice and to further characterize important potential risks (suicidal ideation and behavior; convulsions/seizures, severe renal or hepatic disorders due to precipitation of metabolites in kidney and liver).)

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 3.0, the PRAC considers by consensus that the risk management system for Vortioxetine (Brintellix) for the treatment of major depressive episodes in adults is acceptable. The following points should be taken into account in the next Risk Management Plan update:

1. The assessment of dependence (drug abuse) should be included in the scope of the planned PASS;

2. Information on the safety and tolerability of the 15 and 20 mg/day dose of vortioxetine on the long term in patients > 65 years of age should be captured;

3. The quality of the analysis of adverse events reports should be enhanced.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Precipitation of metabolites in kidney and bile ducts • Convulsions/Seizure • Effects on reproduction • Suicidal ideations and behaviours • Serotonin Syndrome • Hyponatraemia • Haemorrhage • Persistent pulmonary hypertension in the newborn (PPHN)
Missing information	• Use during pregnancy and lactation • Use in patients with severe renal or hepatic impairment • Misuse for illegal purposes • Off-label use • Off-label paediatric use • Overdose • Use in patients aged ≥ 75 years • Use in patients with comorbid Alzheimer's disease, Parkinson's disease, multiple sclerosis, and stroke • Use in patients with history of mania/hypomania

The PRAC agrees

- **Pharmacovigilance plans**

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the proposed drug utilisation study is sufficient to monitor the effectiveness of the risk minimisation measures.

The CHMP endorsed this advice but recommended that the PASS also captures withdrawals due to lack of efficacy for the different dosages, with the aim to collect additional information in the elderly as shown below.

Table 2.2: Ongoing and planned studies in the PhV development plan

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
A non-interventional post-authorisation safety study (PASS) of vortioxetine in Europe (non-interventional cohort, 3)	1) To describe extent of use of vortioxetine in clinical practice by collecting information on *important missing information* 2) To further characterise the safety profile of vortioxetine by assessing the frequency of the certain events related to *important potential risks* in patients treated with vortioxetine. 3) To perform exploratory assessment of the frequency of events of abuse/dependence for detection of potential signals 4) To collect information on withdrawal due to lack of efficacy in patients aged 75 and over	*Important potential risks:* o Suicidal ideations and behaviours • Convulsions/ seizures • Severe renal or hepatic disorders due to precipitation of metabolites in kidney and liver *Important missing information:* • Off-label use in terms of indication • Off-label paediatric use • Use in pregnant women • Use in patients aged ≥ 75 years • Use in patients with a history of mania/hypomania • Use in patients with Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke, • Use in patients with severe renal or hepatic impairment • Misuse for illegal purposes (Abuse/ Dependence)	Draft Protocol Synopsis submitted to PRAC (Part VII, Annex VI)	Final Study Report April 2018

- **Risk minimisation measures**

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Potential risks		
Precipitation of metabolites in kidney and bile ducts	Information on the nonclinical finding in section 5.3; Prescription-only medicine	None
Convulsions/Seizure	Warning on the potential risk of convulsions and information on how to ensure patient safety in patients with previous convulsions in section 4.4; Information on the preclinical finding in section 5.3; Prescription-only medicine	None
Effects on reproduction	Information on the nonclinical finding in section 4.6 and 5.3; Prescription-only medicine	None
Suicidal ideations and behaviours	Warning on the risk for suicidal ideation in depression and MDD and information on how to ensure patient safety in patients with suicidal ideation and behaviours in section 4.4; Prescription-only medicine	None
Serotonin Syndrome	Warning on the potential risk of serotonin syndrome and information on how to ensure patient safety in section 4.4; Information on potential for drug interaction with drugs that increase serotonin in section 4.5; Prescription-only medicine	None
Hyponatraemia	Warning on the potential risk of Hyponatraemia and information on how to ensure patient safety in section 4.4; Prescription-only medicine	None
Haemorrhage	Warning on the potential risk of Heamorrhage and information on how to ensure patient safety in section 4.4; Information on potential for drug interaction with other drugs affect platelet aggregation and coagulation in section 4.5; Prescription-only medicine	None
Persistent pulmonary hypertension in the newborn (PPHN)	Warning on the potential risk of PPHN with SSRIs in section 4.6; Prescription only medicine	None
Missing information		
Use during pregnancy and lactation	Information on nonclinical and clinical experience during pregnancy and lactation in section 4.6; Information on the nonclinical finding in section 5.3; Prescription-only medicine	None
Use in patients with severe renal or hepatic impairment	Information on treatment in these patients in section 4.4; Information on study results in patients with renal or hepatic impairment in section 5.2; Prescription-only medicine	None
Misuse for illegal purposes	Prescription-only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Off-label use	Information on the authorised indication section 4.1; Prescription-only medicine	None
Off-label paediatric use	Information on the authorised indication in section 4.1; Information on lack of experience with paediatric use in section 4.2; Warning on the risk with use of other antidepressants in section 4.4; Information on waiver obtained for investigating efficacy and safety in children younger than 7 years in section 5.1; Prescription-only medicine	None
Overdose	Information on experience with overdose in section 4.9; Prescription-only medicine	None
Use in patients ≥75	Information on treatment in the elderly in section 4.2; Warning on limited experience in the elderly in section 4.4; Information on adverse events in the elderly in section 4.8; Information on study results in the elderly in section 5.1 and 5.2; Prescription-only medicine	
Use in patients with a history of mania/hypomania	Warning on the use in patients with a history of mania and information on how to ensure patient safety in this subpopulation in section 4.4; Prescription-only medicine	None
Use in patients with comorbid Alzheimer's disease, Parkinson's disease, multiple sclerosis, and stroke	Information on treatment in the elderly in section 4.2; Warning on the potential risk of convulsions and information on how to ensure patient safety in patients with previous convulsions and warning on limited use in elderly in section 4.4; Information on the potential for drug interaction with selegiline and rasagiline in section 4.5; Information on adverse events in the elderly in section 4.8; Information on study results in the elderly in section 5.1 and 5.2; Prescription-only medicine	None

The PRAC having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Twelve double-blind, placebo-controlled, 6/8-week, fixed-dose studies have been conducted to investigate the short-term efficacy of vortioxetine in MDD in adults (including the elderly). The efficacy

of vortioxetine was demonstrated with at least one dosage group across 9 of the 12 studies, showing at least a 2-point difference to placebo in the Montgomery and Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale 24-item (HAM-D_{24}) total score.

Treatment with vortioxetine for 6 or 8 weeks at doses of 5, 10 or 20 mg had moderate effect on depression in patients suffering from MDD included in the clinical development programme. These doses were found to be superior compared to placebo as demonstrated by a significant reduction of baseline MADRS or HAM-D24 total score after 6 or 8 weeks of treatment and the clinical relevance of the effect was supported by the proportions of responders and remitters and the improvement in the CGI-I score.

In the meta-analyses, the average effect size of the MADRS versus placebo ranged between -2.6 points (p=0.008) for the lowest therapeutic dose (5mg/day) and -4.6 points (p <0.001) for the highest therapeutic dose (20 mg/day). The average effect size was -4.1 points (p <0.001) for the 10 mg/day doses. The 15 mg/day dose did not separate from placebo in the meta-analysis, but the mean difference to placebo was -3.5 points. Therefore, a dose-dependent effect has been reasonably shown. The addition of the placebo-controlled studies 317, 14122 A and CCT-002 that were completed after MAA submission did not change the conclusions with respect to dose. In the meta-analysis including these studies the overall mean difference to placebo across the studies remained statistically significant: -2.3 points (p = 0.007), -3.6 points (p <0.001), and -4.6 points (p <0.001) for the 5, 10, and 20 mg/day doses, respectively; again, the 15mg/day dose did not separate from placebo in the meta-analysis, but the mean difference to placebo was -2.6 points.

Whilst the inclusion of the above mentioned 3 additional short-term studies in the the meta-analysis initially only including the 8 short-term studies generally resulted in lower effect sizes in the primary and secondary efficacy endpoints, results are still in favour of vortioxetine, as supported by the pooled responder analysis.

The efficacy of vortioxetine 10 or 20 mg/day was further demonstrated in a 12-week, double-blind, flexible-dose comparative study versus agomelatine 25 or 50 mg/day in patients with MDD. Vortioxetine was statistically significantly better than agomelatine as measured by improvement in the MADRS total score. Clinical relevance of the effect was supported by the proportions of responders and remitters and improvement in the CGI-I scores.

In one relapse prevention study, the risk to relapse was two times higher for placebo-treated patients than for vortioxetine-treated patients, and there was a statistically superior effect of vortioxetine 5 and 10 mg/day relative to placebo on the time to relapse of MDD.

In addition, maintained efficacy of vortioxetine was also supported by four open-label extension studies

Uncertainty in the knowledge about the beneficial effects

A dose range from 5 to 20 mg/day with a starting dose of 10mg/day is considered to be justified for patients < 65 years, however since data are limited in patients ≥ 65 years for doses higher than 10mg/day particular caution should be exercised, and the starting dose should be 5 mg/day in the elderly.

Concerning depression history, relatively slight imbalances between treatment arms were reported across studies for the median number of previous episodes and duration of the current episode. Since there is no indication that randomization and allocation concealment were compromised during the conduct of the studies, these imbalances most likely reflect a random process.

The mechanism of action of vortioxetine in patients is not totally clarified. The claimed multimodal effects of vortioxetine acting at several receptor targets and at the 5-HTT is considered responsible for

the antidepressant effect. However overall, a convincing independent effect on cognition and function (HrQoL) (beyond antidepressant effect)remains to be shown.

Risks

Unfavourable effects

The types of AEs were generally comparable to those seen for the antidepressant duloxetine. Up to one-third of all patients reported nausea as most common adverse event under Vortioxetine treatment being of highest occurrence during the first weeks of treatment. The incidence of nausea was shown to be higher at doses of 15 and 20 mg/day compared to doses of 5 and 10 mg/day. However, similar numbers were seen in the comparator groups venlafaxine and duloxetine. There seems to be a slight reduction in nausea during long-term treatment with Vortioxetine. For the TEAEs dizziness, diarrhoea, and vomiting, the incidences in the Vortioxetine groups were higher compared to placebo. The severe / discontinuation due to AEs were predominantly in the gastrointestinal disorder (GI), nervous system disorder, and psychiatric disorder organ class (SOC). Serious AEs recurring over all analysed pools were spontaneous abortion, depression, suicidal ideation/attempt/completed suicide.

Suicidality has been comprehensively addressed in the dossier as requested by the Draft Guideline on Clinical Investigation of Medicinal Products in the Treatment of Depression (EMA/CHMP/185423/2010, Rev 2). Suicidal events have not been reported for the clinical pharmacology studies neither in terms of TEAEs nor in terms of validated rating scales. Exposure-related differences do not indicate an increased risk for suicidality under Vortioxetine treatment compared to placebo and duloxetine (0.1% vs. 0% each in the controlled MDD short-term pool) and at this time, there seems to be no increased risk for suicidality under Vortioxetine treatment compared to other antidepressants with a similar mode of action. Nevertheless, the proposed PASS study will further caractherise this potential risk. A warning on suicidality is placed in section 4.4 of the SmPC.

Convulsions, serotonin syndrome and neuroleptic malignant syndrome are referred to as potential risk.

Vortioxetine seems to be benign in terms of EPS effects, QT prolongation, renal and hepatic toxicity, body weight. Sexual dysfunction was similar to placebo and lower compared to venlafaxine with no negative effect on long-term treatment. However, looking at treatment emergent sexual dysfunction (TESD) based on ASEX scoring, there is an increase in TESD going from the 5 to the 20 mg group. The incidence of TESD was 43 and 46% in the Vortioxetine 15 and 20 mg groups, respectively, and the latter is close to the duloxetine level, which is associated with sexual dysfunction.

In the elderly study, treatment with Vortioxetine 5mg/day was safe and well tolerated and the safety profile was not different from that in patients aged <65 years. In the pooled studies, in the Vortioxetine 20 mg group, the incidences of nausea and constipation were higher in patients aged ≥65 years (42% and 15%, respectively); than in patients aged <65 years (27% and 4%, respectively). These are tolerability rather than safety issues. The TEAEs led more often to withdrawal from the study in the elderly (≥65 years).

Uncertainty in the knowledge about the unfavourable effects

The short-term safety data in the elderly has been mainly investigated using 5 mg/day of Vortioxetine. Less data was provided with doses of 10 to 20 mg/day. The incidence of TEAEs and rate of discontinuation due to adverse events during the short-term experience was slightly higher compared to younger subjects for higher doses of 10 to 20 mg/d. A very low number of patients > 75 years have

been included in the clinical studies. These patients may be additionally affected by hyponatraemia while receiving co- medication (e.g. diuretics).

Patients with a history of mania or hypomania were excluded from the studies; therefore the possible switch from depression to mania as a result of Vortioxetine treatment has not been investigated. A PASS will provide further information on the use, efficacy, adverse events and withdrawals in patients with (a history of) mania/hypomania.

Vortioxetine treatment was not associated with an increased risk of suicidal ideation or behaviour, based on the TEAEs and C-SSRS, although patients with a significant risk of suicide were excluded from the Vortioxetine clinical development programme.

Balance

Importance of favourable and unfavourable effects

Short and long-term efficacy of vortioxetine for the treatment of major depressive episodes in adult patients has been established. From a safety point of view, the types of adverse events reported were similar to those already known from other serotonin-accented antidepressants.

Remaining uncertainties will be addressed in a non-interventional PASS study, covering the important potential risks of suicidal ideation/behaviour, convulsions/seizures, severe renal and hepatic disorders as well as important missing safety information, which pertains to off-label use (indication), off-label use in paediatrics, use in pregnant women, use in patients aged ≥75 years, use in patients with a history of mania/hypomania, use in patients with Alzheimer`s disease, Parkinson`s disease, MS and stroke, and use in patients with sever renal or hepatic impairment. Additional information on the safety and tolerability (including withdrawal rate due to AEs) of the 15 and 20 mg/day dose of vortioxetine on the long-term in patients 65 years and older will also be captured within the RMP. In addition, data on withdrawals due to lack of efficacy/loss of efficacy will be collected.

Benefit-risk balance

The overall Benefit /Risk of Brintellix is positive for the 5 to 20 mg/day dose range in adults aged <65 years of age. Caution is advised when treating patients ≥ 65 years of age with doses higher than 10 mg vortioxetine for which data are limited.

Discussion on the benefit-risk assessment

This new medicine provides an additional alternative for the treatment of patients with MDD. Efficacy of Vortioxetine *versus* placebo was demonstrated in 9 (7 positive and 2 supportive) of the 12 short-term studies and in the long-term treatment of MDD in adults and the elderly. About one-third of the studies were either failed or negative in the primary analysis. However, negative studies are not uncommon in MD due to the lack of sensitivity.

Efficacy was shown on the broad spectrum of depressive symptoms and in patients with severe MDD. The clinical relevance was supported by the proportions of responders and remitters and the improvement in the CGI-I score. However, specific effects due to the postulated new mechanism of action on cognition and function have not yet been convincingly demonstrated and remain to be shown.

Uncertainties pertaining to long-term efficacy data of the higher doses and dose range in the elderly are addressed with appropriate warnings in the SmPC.
Uncertainties including the largely unexplained lower response in the US remain although efficacy in the treatment of MDD is considered to be proven.

The safety profile of vortioxetine was shown to be comparable to other serotonin-accented antidepressants. Unfavourable effects are mainly those pertaining to tolerability issues like GI disorders, especially nausea, and to nervous system disorders, especially headache and most commonly reported adverse events are rather mild in nature. Suicidality remains a potential important risk in line with other antidepressants that will be further addressed by means of the PASS study and referred to as a class warning in the SmPC.

The elderly are considered an important part of the treated population. The evaluation of vortioxetine in the very old population (>75) is limited but will be covered by the PASS. In addition, the Applicant committed to capture information on the safety and tolerability of the 15 and 20 mg/day dose of vortioxetine during short- and long-term treatment in patients ≥ 75 years of age within the scope of the RMP.

To conclude, the overall benefit risk profile of Vortioxetine in the treatment of major depressive episodes is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Brintellix in the treatment of major depressive episodes in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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 data on the quality properties of the active substance, the CHMP considers that Vortioxetine is qualified as a new active substance.