24 February 2022
EMA/187589/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

QUVIVIQ

International non-proprietary name: daridorexant

Procedure No. EMEA/H/C/005634/0000

Note

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

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List of abbreviations

BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human use
CFU	Colony forming units
CQA	Critical quality attribute
EC	European Commission
EU	European Union
GC-HS	Gas chromatography headspace
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
MAH	Marketing authorisation holder
NMR	Nuclear magnetic resonance
PAR	Proven acceptable range
Ph. Eur.	European Pharmacopoeia
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QC	Quality control
QTPP	Quality target product profile
RH	Relative Humidity
rpm	Revolutions per minute
SmPC	Summary of product characteristics
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Idorsia Pharmaceuticals Deutschland GmbH submitted on 2 March 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for QUVIVIQ, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 April 2020.

The applicant applied for the following indication

the treatment of adult patients with insomnia to improve sleep and daytime functioning

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

The application submitted is

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Regulation (EC) No 1901/2006, the application included an EMA Decision P/0131/2020 on the agreement of a paediatric investigation plan (PIP) and on the granting of a deferral and on the granting of a waiver.

The PDCO issued an opinion on compliance for the PIP and a deferral and a waiver, EMEA-002121-PIP03-19.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

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

1.6. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Ondřej Slanař

The application was received by the EMA on	2 March 2021
The procedure started on	25 March 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 June 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 June 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 July 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	29 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 December 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 December 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 February 2022
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 QUVIVIQ on	24 February 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	24 February 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5, 2013), insomnia disorder is defined as "a predominant complaint of dissatisfaction with sleep quantity or quality with one (or more) of the following symptoms:

(i) difficulty initiating sleep,

(ii) difficulty maintaining sleep characterized by frequent awakenings or problems returning to sleep after awakenings,

(iii) early-morning awakening with inability to return to sleep.

The sleep disturbance causes clinically significant distress or impairment with detrimental effects on daytime functioning, including social, occupational, educational, academic, behavioural, or other important areas of functioning".

Similar diagnostic criteria for insomnia disorder were defined in the International Classification of Sleep Disorders. 3rd Edition (ICSD-3, 2014).

Insomnia is associated with an abnormal state of hyperarousal that overrides the normal control of sleep. Orexin is a central promotor of arousal and vigilance.

2.1.2. Epidemiology

Population-based studies across several European countries in the last 20 years have found an insomnia prevalence between 5 and 19%.

Insomnia disorder occurs in all age groups. There is no clear relationship between insomnia prevalence and age, with several studies yielding conflicting results. Insomnia disorder occurs more frequently in females than in males.

Longitudinal studies in Europe and US have found an annual insomnia incidence of 2–5%. For the elderly adult population, no incidence data are available for insomnia disorder.

Predisposing factors and factors that facilitate the development of insomnia include demographic variables, familial/hereditary conditions, psychological factors, and health related factors.

In addition to female sex, poor physical and mental health are main risk factors for insomnia. Individuals with certain psychological features, such as increased anxiety and depressive symptoms, worries, and lower ability to cope with stressful events are more prone to develop insomnia. Stress exposure in the form of severe and chronic life events is also a risk factor for the onset of insomnia. Chronic conditions with pain often precede the development of insomnia. A history of insomnia in first-degree family members also represents a risk factor, with genetic and epigenetic factors involved in the aetiology and pathophysiology of insomnia, although the genetic basis for insomnia is not well characterised.

2.1.3. Clinical presentation, diagnosis

The diagnosis of insomnia on a clinician's assessment of a patient's conditions consistent with the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5, 2013) or the International Classification of Sleep Disorders. 3rd Edition (ICSD-3, 2014).

Insomnia disorder is defined as "a predominant complaint of dissatisfaction with sleep quantity or quality with one (or more) of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep characterized by frequent awakenings or problems returning to sleep after awakenings, early-morning awakening with inability to return to sleep.

The sleep disturbance causes clinically significant distress or impairment with detrimental effects on daytime functioning, including social, occupational, educational, academic, behavioral, or other important areas of functioning".

The definition of insomnia within the ICSD-3 largely follows that of the DSM-5 with the importance of the impact on daytime functioning. The patient complaint is an important part of the diagnosis leading to the importance of taking into account subjective criteria for drug efficacy assessment, as mentioned in the European Guideline on medicinal products for the treatment of insomnia (EMA, 2011).

2.1.4. Management

According to treatment guidelines from the US and Europe, the first-line treatment is Insomnia-specific cognitive-behavioural therapy (CBT-i). Pharmacological intervention can be offered when CBT-i is not effective or not available.

Use of hypnotic drugs is currently mostly recommended for short-term treatment, or as a temporary adjunct to CBT-i, due to safety limitations of existing drugs.

Pharmacological treatment consists of benzodiazepines, non-benzodiazepine GABA-A receptor agonists, melatonin receptor agonists, and drugs that are administered off-label (e.g., sedating antidepressants, antihistamines).

Two Dual Orexin Receptor Antagonist DORAs (the drug class of daridorexant) are approved in some regions for the treatment of insomnia characterised by difficulties with sleep onset and/or sleep maintenance: suvorexant has been approved since 2014 in some regions, including the US, Japan, Canada and Australia, while lemborexant has been approved since 2019 in some regions including the US, Japan and Canada. In Europe, no DORA is currently approved for the treatment of insomnia.

In addition, several over-the-counter herbal medicines and devices are used by people with insomnia.

2.2. About the product

Daridorexant, also known as ACT-541468, is a specific and potent DORA acting on both orexin 1 (OX1) and orexin 2 (OX2) receptors. The orexin neuropeptides (orexin A and orexin B) act on orexin receptors to promote wakefulness. It could therefore be hypothesized that daridorexant will act both on sleep maintenance and on sleep latency in contrast with hypnotics such as benzodiazepines and z-drugs which act mainly on sleep latency.

2.3. Type of Application and aspects on development

This is a complete and independent application.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 25 or 50 mg of daridorexant as active substance. The product contains the hydrochloride salt.

Other ingredients are:

Tablet core: mannitol, microcrystalline cellulose, povidone, croscarmellose sodium, silicon dioxide and magnesium stearate

Film-coat: Hypromellose, microcrystalline cellulose, glycerol, talc, titanium dioxide, iron oxide red, iron oxide black and iron oxide yellow (50 mg tablets only).

The product is available in polyvinyl chloride (PVC) coated with polyvinylidene chloride (PVdC) and laminated with PVC film blister sealed with an aluminium foil as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of daridorexant hydrochloride is [(*S*)-2-(5-chloro-4-methyl-1*H*-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl](5-methoxy-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride corresponding to the molecular formula $C_{23}H_{23}ClN_6O_2$.HCl. It has a molecular mass of 450.93 g/mol (free base) or 487.38 g/mol (salt) and the following structure:

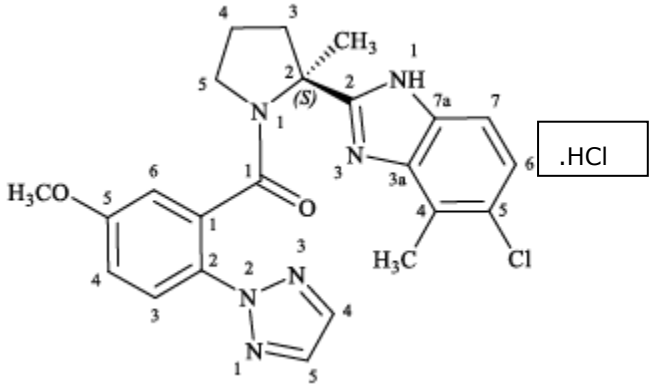

Figure 1: active substance structure

The chemical structure of daridorexant hydrochloride was elucidated by a combination of ^{1}H and ^{13}C, NMR spectroscopy, mass spectrometry, infrared spectrophotometry, and elemental analysis. The solid-state properties of the active substance were measured by thermogravimetric analysis, differential scanning calorimetry, gravimetric vapour sorption and x-ray powder diffraction (XRPD).

The active substance is a white to light yellow non-hygroscopic crystalline powder, very slightly soluble in acidic media but insoluble at neutral pH. Particle size is controlled in the active substance specification following the micronisation step. The proposed manufacturing process routinely delivers the desired polymorphic form. Daridorexant contains a single chiral centre. Enantiomeric purity is controlled routinely by chiral HPLC in the active substance specification.

Manufacture, characterisation and process controls

Daridorexant hydrochloride is synthesized in 3 main steps using well defined starting materials with acceptable specifications.

Although several impurities which originate upstream of the starting materials, were listed in the active substance specification, the synthetic routes for the starting materials had not been described in sufficient detail and the control of impurities, including those which are potentially mutagenic, was deemed insufficient. In addition, a raw material representing a significant structural fragment of the active substance, was not originally proposed as a starting material but as a reagent. Therefore, the CHMP raised two major objections in relation to the definition of and control strategy for the initially proposed starting materials. Firstly, the MAH was asked to re-define the proposed starting materials and secondly, to provide more detail on their routes of synthesis including reagents and catalysts used, as well as on their impurity profiles and the subsequent fate and purge of these impurities.

In response, the applicant explained how the impurities which originate upstream of the starting materials and carry over into the active substance can be considered "impurities that persist" according to ICH Q11 Q&A 5.8. They are structurally similar to the active substance and thus are not readily purged. Limits for these impurities in the starting materials were tightened, rather than re-defined the starting materials. Furthermore, a detailed description of the actual and potential impurities in the starting materials was provided, including an explanation of the control of mutagenic impurities which are controlled according to ICH M7. The Applicant also defined another starting material. The CHMP considered the applicant's approach acceptable.

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

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The control strategy for impurities was justified by provision of extensive fate and purge data. Acceptable limits have been set in raw materials, intermediates, and the active substance. Critical steps were discussed and suitable process parameter controls are in place to ensure the purge of key impurities.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. The same principle route was used throughout with optimised conditions introduced as development progressed.

Material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification shown in **Error! Reference source not found.** includes tests for appearance, colour, sulphated ash (Ph. Eur.), water content (KF), identity (IR, HPLC), identity of chloride (Ph.

Eur.), chloride content (titration), residual solvents (GC-HS), impurities (HPLC), assay (HPLC), enantiomeric ratio (chiral HPLC), particle size distribution (laser diffraction) and microbial quality (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Limits for specified and total impurities were tightened during the procedure following a request from CHMP.

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

Batch analysis data from 12 pilot to production scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH), for up to 24 months under intermediate conditions (30 ºC / 65% RH) and for up to 9 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, colour, water content, impurities, assay, enantiomeric ratio, particle size distribution and microbial quality. The analytical methods used were the same as for release and are stability indicating. No significant changes to any of the measured parameters were observed under all three conditions and no trends were noted.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. The active substance is photostable in the solid state.

Forced degradation studies were conducted on the solid active substance and in solution.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container without specific storage conditions.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is an immediate release triangle-shaped film-coated tablet, approximately 7 mm in diameter and 4 mm in thickness. The 25 mg and 50 mg strengths are the same size and weight and are distinguished by colour and debossing. The 25 mg tablet is light purple and debossed with “25” on one face. The 50 mg tablet is light orange and debossed with “50” on one face. Both tablets are debossed with the MAH logo on the other face (Figure 2).

Figure 2: finished product appearance

The goal of pharmaceutical development was an immediate release tablet with a rapid disintegration time and a high dissolution rate in acidic media. The most stable of the known crystalline forms has been selected.

All excipients are well known pharmaceutical ingredients and their quality (or the quality of the components of the film-coating mix) 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 and in paragraph 2.4.1 of this report. The amounts of excipients used in the composition have been adequately justified. The development approach is based on an understanding of the relationship between formulation inputs and manufacturing process parameters on the critical quality attributes (CQAs) of finished product such as appearance, content uniformity, assay, related substances, dissolution rate, shelf life and microbiological contamination defined according to the quality target product profile (QTPP). An overview of the formulations used in clinical trials was presented, including hard and soft gelatin capsules used in phase 1 and phase 2. Triangular 7 mm film-coated tablets were developed at strengths of 2.5, 5, 10, 25 and 50 mg for use in pivotal phase 3 trials and for commercialisation. Clinical and the commercial tablets have a different appearance but this is not expected to impact their *in vivo* performance.

The discriminatory power of the QC method was investigated using finished product manufactured with active substance with different particle sizes and with batches manufactured with meaningful changes in relevant parameters (e.g. over-granulated, change on granulation liquid content, different amounts of excipients). The proposed dissolution method was able to reject mis-manufactured batches and is thus considered as acceptable. The proposed release and shelf-life dissolution limits, some of which were tightened during the procedure, are considered acceptable. However, the applicant is recommended to tighten the shelf-life limit of the 50 mg tablet once additional real time stability data has been generated.

Optimisation of the manufacturing process was carried out using elements of the QbD approach for the granulation step. A traditional approach was used for the optimisation of the final blending and tableting steps. Target set-points have been defined for all process parameters with PARs assigned to others. The proposed PARs have been adequately justified. For each process step, only one process parameter at a time can be varied within its PAR while others are maintained at the defined target.

The development experiments are considered satisfactory for optimising the manufacturing process, for challenging the scaling-up and also for showing the robustness of the proposed manufacturing process. The overall control strategy is considered adequate for this type of formulation and manufacturing process.

The commercial process will be run on a larger scale than that used for clinical batches and as a result, some parameters for granulation, drying, compression and film coating steps needed to be modified to accommodate scale and equipment changes. However, comparative dissolution profiles between the clinical and proposed commercial batches were not provided in the initial submission. In response to the resultant

major objection raised by the CHMP, the parameters for the planned validation campaign were adjusted accordingly results from one validation batch were provided.No impact on dissolution rate was observed between biobatches and those used for scale-up and validation using the quality control (QC) dissolution method. The primary packaging is polyvinyl chloride (PVC) coated with polyvinylidene chloride (PVdC) and laminated with PVC film blister sealed with an aluminium foil. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process and in-process controls consists of four main steps: blending of intra-granular excipients and granulation; blending with extra-granular excipients; compression; film-coating. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on 3 pilot scale batches of each strength tablet by the proposed manufacturer. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. An acceptable process validation scheme has been submitted, explaining how the process will be validated on 3 productions scale batches of each tablet strength prior to commercialization.

Product specification

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

The finished product specifications are in line with ICH Q6A. Limits for impurities are acceptable according to ICH Q3B.

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data from 15 batches was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed considering root causes mentioned in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). However, some of the potential root causes applicable to Quviviq had been omitted resulting in a major objection. In response, the applicant provided a comprehensive risk assessment covering all potential sources of nitrosamines, which were considered satisfactory. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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

Batch analysis results are provided for 3 production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

Stability data from three production scale batches of each strength of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH), for up to 18 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, colour, water content, dissolution, assay and degradation products. The analytical procedures used are stability indicating. An increase in water content was observed, along with a decrease in dissolution rate, under all storage conditions, more so at higher humidity and temperature. The changes are small and both parameters remained within specification throughout the studies. No trends to any of the other measured parameters were observed.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not photosensitive. Additional studies under stressed conditions indicate the finished product is not sensitive to light, to heat, basic stress and high and frozen temperature cycles whereas some degradation occurs on exposure to acidic and oxidative stress conditions.

Based on available stability data, the proposed shelf-life of 30 months (section 6.3) is acceptable.

Adventitious agents

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

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

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

The major objections relating to the choice of starting materials was resolved by providing additional information on impurity origin, fate and purge and by defining an additional starting material. Provision of comparative dissolution data between biobatches and batches manufactured on commercial scale resolved a major objection relating to comparability of batches made by different processes. Finally, the applicant provided additional risk assessment and purge data relating to the potential formation of nitrosamines impurities to resolve the fourth major objection.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendation for future quality development

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

- The applicant is recommended to tighten the dissolution shelf-life limit of the 50 mg tablet once additional real time stability data has been generated.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical testing strategy was based on the ICH M3 guideline and other applicable nonclinical ICH guidelines. Daridorexant was formulated in the *in vivo* non-clinical studies to comply with the clinical route. Drug substance investigated in the non-clinical programme is the hydrochloride salt of Daridorexant.

Non-clinical development of daridorexant (ACT-541468) included an exhaustive programme. Dedicated studies were included to support plasma profiles of metabolites in humans and to investigate their pharmacological properties. Species selection was based on pharmacologically relevant binding to Orexin receptors in humans and in these non-clinical species with high selectivity and potency, metabolically relevant pathways in these species are similar to those in humans, as well as close plasma protein binding properties for some species only. Doses for the pharmacodynamic studies were chosen to evaluate a range of dose-response activity that was considered to include both primary and secondary effects. Consistent with ICH M3, the high doses for toxicity studies were selected to provide substantial challenge to the test animals and cause systemic pharmacological and toxic effects. Low doses were selected to provide no-observed-effect and/or no-observed-adverse-effect levels (NOEL, NOAEL).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Low Log D value of Daridorexant (ACT-541468) supported a brain penetration potential, that was experimentally confirmed in a pharmacology wake-sleep Wistar rat model, in which Daridorexant was demonstrated to cross blood-brain-barrier at doses pharmacologically active (resulting in -26% and -74% of the total sleep time following oral administration of 30 and 100mg/kg, respectively). Whole brain concentration of ACT-541468 reached 3206ng/g (71nM brain-free) and 5201ng/g (115nM brain-free) 1h following oral administration of 30 and 100mg/kg, respectively.

In cell-based assays, Daridorexant antagonized orexin-A–induced calcium release at OX1 and OX2 receptors, with similar high potencies at human, rat, and dog orexin receptors.

The 3 major human metabolites acted also as dual antagonists at both the OX1 and OX2 receptors, with free apparent Kb values ranging from 28 to 1035 nM and from 7.0 to 458 nM, respectively. These Kb values for human OX1/OX2 receptors were greater than those of ACT-541468A: at least 44/8-fold for M3, 81/47-fold for M1, 1545/555-fold for M10. Then M3 had the highest potency among metabolites and M1 had the lowest potency on both receptors. On the whole, metabolites showed higher selectivity for OX2 receptor (3.9(M3), 2.26(M10), 1.4(M1)-fold), then these metabolites, displayed significantly lower potency at both OX1R and OX2R than daridorexant. Given free apparent Kb at OX2 for the parent is at least 10-fold lower than for metabolites, the contribution of metabolites to an OX2-mediated activity may be low. Considering their abundance in human plasma, the high binding to plasma proteins, substrate potential for f P-gp which would limit their brain penetration, and lower potency on OX1R and OX2R compared to parent drug, unbound concentrations of the these metabolites in the brain would not contribute to *in vivo* sleep-promoting activity in animals and humans

Daridorexant dose-dependently decreases wakefulness and promotes sleep in rats and dogs, with onset of somnolence within the first hour after administration and the effect of ACT-541468 on sleep lasted for 6 h at least. In both species, it decreases the latency to persistent non-REM sleep and increases both non-REM and REM sleep times; the proportion of non-REM and REM sleep within the total sleep time is not affected by daridorexant treatment.

The lowest pharmacological dose, which achieved statistically significant decreasing effects on home cage activity, total sleep and total wake times, and latency to persistent non-REM sleep, was 30 mg/kg, and the effects lasted at least 6 h. At this dose, during the first 6h night period post administration, the home cage activity decreased by 30.9% and the time spent in active wake by 21.9% (32min). Total sleep time increased by 39.2% (34 min; including 21 min of non-REM sleep and 13 min of REM sleep). At 30mg/kg, free concentrations in the brain reached 71nM at 1h following administration, with a brain/plasma ratio of 218%. Latency to the first persistent episode of non-REM sleep was markedly decreased from the lowest dose tested of 10 mg/kg (17 min compared with 61 min latency with vehicle), whereas total sleep time, total wake time or home cage activity were not significantly changed at this dose. Analysis of the EEG spectral frequencies within the sleep/wake stages showed that the spectral pattern of the different stages was not altered by ACT-541468 at the highest dose of 300mg/kg in contrast to the GABAA receptor modulator zolpidem. It can be concluded that ACT-541468 decreases wakefulness and compensates by increasing total sleep without altering the general sleep architecture of adult rats.

ACT-541468A did not induce muscular weakness in the activation test with food upon awakening, and did not affect motor performance in the rotarod and grip strength tests at any dose (10-100 mg/kg) that were effective on sleep-wake cycle. Zolpidem impaired motor performance in the tests in a dose-dependent manner. It means that rats under ACT-541468A treatment that are woken up from sleep are able to perform normally on the rotarod and grip strength tasks, then motor function upon awakening is expected not affected in humans at clinically effective dose in contrast to drugs for insomnia, which are GABAA receptor modulators and known to elicit a number of side-effects such as residual sleepiness, motor incoordination, memory and cognitive impairment, and abuse liability. Then sleep promoted by ACT-541468 can be considered surmountable in rats as no next day residual occurred.

2.5.2.2. Secondary pharmacodynamic studies

ACT-541468A and its major metabolites M1, M3, and M10 were tested against a large and usual panel of ion channels, receptors, transporters, and enzymes. Concentration of ACT-541468, M1 and M3 able to result in

off-target activities are considerably higher than the human free Cmax reached at 50mg/day highest clinical dose. As the mean free human Cmax of ACT-541468 at clinical dose of 50 mg/day is 3.0ng/mL (6.7 nM), effective concentrations on the dopamine transporter, the adrenergic β3 receptor, and PDE4 are 2134-, 2493-, and 1493-fold higher, respectively. Considering the mean free human Cmax of M1 at ACT-541468 clinical dose, effective concentrations on the AT1, NK3, and OP2 receptors were approximately 44,000-, 37,000- and 27,000-fold higher than M1 human free Cmax, respectively. As the mean free human Cmax of M3 at ACT-541468 clinical dose of 50 mg/day is 2.12 ng/mL, effective concentrations on the dopamine transporter was approximately 4,700-fold higher than M3 human free Cmax. No off-target is anticipated during human use.

2.5.2.3. Safety pharmacology programme

In the usual GLP-hERG assay, Daridorexant led to a concentration-dependent reduction of inward and outward K+ currents. IC_{20} is at least >1000-fold higher than the free Cmax observed in humans at clinical dose of 50mg/day. The risk for daridorexant-induced QT prolongation in humans is considered low given the large safety margin to the hERG channel blockade. The 3 major human plasma metabolites accounting for 28.9% (M3), 12.7% (M1), and 9.0% (M10) of total drug-related material are intrinsically covered taking into account %Fu.

Telemetred Beagle dogs administered by the oral route up to the dose 100mg/kg, did not relevantly modify the arterial blood pressure (mean, systolic and diastolic) and the duration of the QTc intervals and of the QRS complex, and body temperature during the 24h period following administration when compared with vehicle values. Considering the low amplitude and no dose-dependent changes in heart rate and PR, RR and QT interval durations, the NOAEL was established at the maximal dose of 100 mg/kg in this GLP study. The free Cmax values at this dose were at least 120-fold higher than exposure at clinical dose of 50mg/day in humans. These data do not support high risk for a clinical safety concern due to large safety margin and low amplitude effects. This is in line with the clinical TQT study, which results excluded QTcF prolongation >10ms up to supratherapeutic plasma concentrations of daridorexant. Given known metabolites exposure in the 39-week study in dogs, exposure multiples are from 15 to 118-fold compared to human exposure at 50 mg/kg, then no further study is needed.

Effects on hemodynamic and cardiac parameters, body temperature, and locomotor activity were also investigated in non-GLP studies in conscious normotensive versus spontaneously hypertensive rats (SHR) and in anesthetized guinea pigs. Transient and low amplitude effect on these parameters occurred at mean Cmax value 52-fold above the human exposure at the 50mg/day dose in normotensive rats. ACT-541468A induced a slight decrease in heart rate and mean arterial pressure, heart rate, body temperature) in SHRs at Cmax 62-fold higher than human exposure at highest clinical dose. The NOEL for cardiovascular function in guinea pigs was established at 30mg/kg, corresponding to a mean Cmax of 23,265 ng/mL that is largely higher than human exposure at clinical dose of 50mg/kg. Data suggest also a low risk in hypertensive patients.

Single oral administration of Daridorexant up to 1000 mg/kg was associated with reduced activity and arousal within 0.5-5h, supported by the observation of several hyporeactive rats in each test item-treated group, increased palpebral closure and tremor scores, decreased postural and arousal scores, and lower exploratory activity during a GLP-compliant Irwin test. Most effects disappeared within following 24h after dosing, only exploratory activity remained still lower at 1000mg/kg. When animals were stimulated, their behavioural responses did not noticeably differ from those noted in animals from the vehicle group. None of the signs adversely affected the health of the animals up to 300 mg/kg based on temperature, body weight gain, activity/CNS excitability, autonomic functions, gait and muscle tone, motor and sensory reflexes, then NOAEL

is estimated 300mg/kg. An increased incidence and severity of tremors from 100 mg/kg, and lower body weight gain may be secondary to hyporeactivity and increased immobility. Findings are related to the pharmacological activity of daridorexant, and such effects occurred in rats and dogs at free Cmax >86-fold human free Cmax at clinical dose of 50 mg/day. It is unclear whether rectal temperature decrease up to -2.1°C/-1°C at 1000 mg/kg may be cause or consequence of CNS-related effects.

Similarly, daridorexant up to the dose of 1000mg/kg, did not exert any biologically relevant effect on the tidal and minute volumes, the respiratory rate, the inspiratory, expiratory and relaxation times, the peak inspiratory and expiratory flows, and on the enhanced pause as evaluated by whole-body plethysmography in freely moving rats. This study supports no expected respiratory adverse effect in human at clinical dose.

2.5.3. Pharmacokinetics

The disposition of ACT-541468 has been studied in (Wistar) rats and (Beagle) dogs, which are the species used in pharmacology and toxicology programmes. The concentrations of ACT-541468 were at least quantified in plasma samples from at least toxicology relevant species, rat and dog, using validated LC-MS/MS method.

Absorption

Absorption parameters were mainly characterized after a single dose and after oral multiple doses in rats and dogs, which are the species used in pharmacology and toxicology programmes.

Single dose studies indicated that:

-Mean plasma clearance was 49-74 mL/min/kg in the rat and 9.8 mL/min/kg in the dog, the volume of distribution was in large excess of total body water, and terminal half-lives were in the range of 0.5-2.1h in the rat and 2.5-4.1h in the dog.

-Oral absorption of Daridorexant was rapid in rats and dogs, with Cmax at 0.3h post-dose in the rat, 0.8-2h in the fasted dog versus 2.5h in the fed dog (Cmax and AUC0 was 1.3-fold higher). Oral bioavailability was in the range of 10-30% and 31-58% in rats and dogs, respectively. Oral bioavailability of Daridotrexant in rats is not dose-dependent, but oral bioavailability increased with dose in dogs.

-In rats, AUC generally increased in a more than proportional manner with increasing oral doses from 1 to 30mg/kg. As a significant first-pass extraction was observed, saturation of metabolic processes during oral absorption might contribute to the observed non-linear PK. In dogs, exposure to Daridorexant increased in a broadly linear manner with respect to oral doses. Higher inter-animal variability in plasma exposure occurred in dogs than in rats. This variability is believed to depend on intrinsic factor as Daridorexant plasma clearance in the dog showed similar inter-animal variability.

- In contrast to dogs, some gender effect was observed in rats, with females exhibiting slightly lower clearance, but highest oral bioavailability, Cmax and AUC values.

Pharmacokinetics of Daridorexant after multiple doses were documented from 4-week toxicity studies in rats and dogs, but metabolites were not measured. Slight more than dose-proportionally increase in exposure is globally observed in rats and dogs. Some gender-related effect had been identified in rats, females being generally more exposed to ACT-541468 with increasing doses. No accumulation (week 4/day 1 ratio) was observed in rats. In the dog, a slight gender effect may be possible. Daridorexant accumulated by about 2-fold

at 30-100mg/kg over the 4-week treatment period. Daridorexant may slightly accumulated between administrations for dogs (with week 4/day ratio around 1.4-2), with lowest accumulation at highest dose.

Distribution

Vss of Daridotrexant was measured in PK studies superior to the body water volume and increased with dose in rats and dogs, supporting distribution in tissues. High unbound plasma concentrations facilitate also drug partitioning into tissues. This in a favour to achieve high exposure for free concentration of Daridorexant on the toxicological species used in pivotal repeat-dose toxicity studies (rat and dog).

Interspecies differences occurred for Daridorexant as maximal unbound fractions ranged from 0.3–0.5% (rabbits and humans) to 2.4–2.8% in rodents and dogs, with some concentration-dependent plasma protein binding (non-linearity due to protein binding saturable at lower concentration and decreased binding with increasing concentration) in *in vitro* assay. Variability of human plasma binding was low as assessed from clinical sample from the single-ascending dose study AC-078-101 with subjects treated 25 mg and 200 mg (mean plasma protein binding ranged 99.7–99.9%). Then free plasma fraction are the lowest in humans and range for humans/non-clinical species from 0-1-0.3%/ 0.4-1.5% for M1, 0.4-1.4%/6.2-12% for M3 and 4.0-7.8%/19.0-31.0% M10 respectively. The non-linear human plasma binding in vitro was also observed as in non-clinical species. Free plasma fraction are the lowest in humans and range for humans/ on-clinical species/ from 0-1-0.3%/0.4-1.5% for M1, 0.4-1.4%/6.2-12% for M3 and 4.0-7.8%/19.0-31.0% M10 respectively. Strong *in vitro* plasma protein binding for the parent compound is at least attributable to serum albumin and α1-acid glycoprotein (>93.9% and >70.2%, respectively) in humans.

As a remark, as Daridorexant is highly bound to plasma sample from human subjects administered 50-200 mg Daridorexant (with no evidence of significant inter-subject and dose-related variability in human plasma protein binding properties) and in plasma of non-clinical species, calculation of exposure ratio based on free Cmax and AUC is agreed for discussion of safety margins within the safety programme.

The blood/plasma ratios were concentration-dependent, likely as a consequence of the increased unbound concentrations in plasma: 1.33 and 1.67 in mouse, 2.07 and 2.32 in rat, 0.82 and 1.15 in rabbit, 0.67 and 0.96 in dog, 0.54 and 1.06 in human at 0.5 and 20µg/mL. In human blood, the mean percentage of radioactivity associated with red blood cells and blood/plasma ratios increased steadily from 1.1% to 50%. The blood/plasma partitioning ratios support that daridorexant did not significantly partition into blood cells in rabbits, dogs and humans (50%<) contrary to rodents (>50%). These blood/plasma ratios were concentration-dependent, likely as a consequence of the increased unbound concentrations in plasma. To conclude the non-linear plasma binding manifests as dose-dependent increases in the volume of distribution at steady state and prolonged half-lives.

Quantitative whole-body autoradiography in the albino versus pigmented rats indicated that Daridorexant was rapidly absorbed in all tissues with highest total radioactivity at 0.5h post dose, mainly in the gastrointestinal mucosa, the liver and kidney, adrenal gland, brown fat, and myocardium. The radioactivity decreased to the limit of quantification at 24h post dose in most tissues and blood except the liver and the gastrointestinal tract, and no remaining radioactivity was detected 7 days post-dose in any tissue. The fact radioactivity remained important in the mucosa of the gastrointestinal tract up to 72h may correlate to usual gastrointestinal tract transit times after an oral administration. The presence of Daridorexant-associated radioactivity in the kidney pyramid and urinary bladder up to 24h, as well as in bile ducts up to 4h, suggest that renal and biliary elimination occurred. Autoradiograms support also a rapid brain penetration within the 0.5h post-dose to 34% of the respective levels of blood, and no accumulation in rats. The choroid plexuses from one of the interfaces

that control the brain microenvironment by regulating the exchanges between the blood and the central nervous system, and it was confirmed rapid exposure of cerebrospinal fluid after oral administration as radioactivity was detected only at this time at choroid plexuses. Brain/plasma ratios reached up to 218% after oral in a pharmacology study in rats, and the achieved brain concentrations were demonstrated appropriate in rats to decrease active wake time and increased total sleep time. Unchanged parent drug, M1, M2, M3, M5 and M13 were detected in their brain.

Given there were no significant differences in tissue distribution and elimination of radioactivity in pigmented versus albino rats, and no retention of radioactivity in the uveal tract/retina and pigmented skin, this may suggest daridorexant (or metabolites) is not able to bind to melanin and a low concern for risk associated to phototoxicity.

Metabolism

A total of 77 metabolites of daridorexant were identified in human plasma, urine, and feces. Three metabolites accounted each for 9% or more of the total drug-related material in human plasma: M3 (28.9%), M1 (12.7%), and M10 (9.0%). Non-clinical exposure to these 3 metabolites was confirmed appropriate to support at least equivalent level in toxicology programme. Daridorexant was metabolized along several metabolic pathways:

1) Aliphatic hydroxylation of the methyl benzimidazole moiety yielded M3. The alcohol M3 underwent further stepwise oxidation to its aldehyde M1 and its acid M2. Other downstream products of M3 resulted from O-demethylation to M12, Odemethylation and oxidation to the carboxylic acid M13, and glucuronidation to M30.

2) O-demethylation of daridorexant led to the phenol M4. Downstream products of M4 included M31 as a product of formal addition of water. M31 is subsequently oxidized to M22. M4 is also glucuronidated to M9, which is further hydroxylated to M17. Hydroxylation of M4 at the triazole ring followed by glucuronidation yields M20.

3) Hydroxylation of daridorexant at the α-carbon position of the pyrrolidine ring produced M5. This initial product then ring-opened to an aminoaldehyde, and finally yielded a piperidinol via re-cyclization of the aldehyde with the benzimidazole moiety. Downstream metabolites of M5 were M7 resulting from O-demethylation, and M10 resulting from aliphatic hydroxylation of the methyl benzimidazole moiety. The alcohol M10 was further oxidized to the corresponding acid M21.

4) Hydroxylation of daridorexant at the anisole ring yielded M11, which underwent further glucuronidation to produce M6.

5) Hydroxylation of the anisolyl triazole moiety followed by glucuronidation resulted in metabolite M8. The primary biotransformation product of this pathway was not detected.

6) Double hydroxylation on the triazole ring followed by glucuronidation produced M14. The primary biotransformation products of this pathway were not detected.

7) Hydroxylation of the methylpyrrolidinyl benzimidazole moiety and subsequent glucuronidation led to M29. Further oxidation resulted in metabolite M18.

Beyond daridorexant, M1, M2, M3, M4, M5, M7, M9, M10 and M30 were observed in human plasma. Metabolites M1-M10 were identified from human hepatocytes. M11, M12, M13, M14, M17, M18, M20, M21, M22, M29 and M31 were structurally characterized in rat bile and faeces samples.

Rat shared with human, M1, M3, M4, M5, M6, M8, M9 and M10, thus supporting appropriateness of this specie for toxicology studies. Among the non-rodent species, dog showed the best coverage with 9/10 human metabolites and is best suited non-rodent species for toxicity testing. There were species differences in the rate of Daridorxant metabolism in liver microsomes. Under initial rate conditions, i.e. during the first 10min of incubation, Daridorexant turnover was only 19 % with human liver microsomes and thus the slowest among all species studied here. Little differences were observed between rat, dog, monkey and rabbit with turnover in the range of 29-45 %. Metabolism was fastest in the mouse with a 45% turnover in only 5min.

Rat hepatocytes yielded 14 metabolites, with M1, M3, M4, M5, M6, M8, M9 and M10 also generated in human hepatocytes. Dog hepatocytes produced 8 metabolites (M1, M2, M3, M4, M5, M7, M9 and M10) that were also found in humans. As for microsomes, there were species differences in the rate of Daridorexant metabolism, leading to 21-34% differences in turnover 1h. The fastest metabolism was for mouse hepatocytes as 70% turnover was reached (only 1h).

Sex differences in the metabolic pattern of Daridorexant were investigated in the rat liver microsomes. There was no difference in the nature of metabolic products between male and female rats. However, the rate of metabolite formation was 2-3 times slower with liver microsomes of female rats, as Daridorexant turnover was only 12 % after 10 min compared to 29 % with liver microsomes from male animals. Sex differences in metabolic competence is a well-known phenomenon in the rat and generally of no relevance for man. Similarly to liver microsomes, sex differences were evident in experiments with hepatocytes from male and female rats. Turnover was higher with liver cells from male rats with 71% turnover after 4h versus 42% in female.

Based on enzyme kinetic analysis of Daridorexant with human liver microsomes and recombinant P450 enzymes, CYP3A4 was the major enzyme responsible for daridorexant metabolism accounting for 89% of metabolic clearance.

Excretion

Excretion pathways were deducted from QWBA study in rats, in which Daridorexant-derived radioactivity remained important in the mucosa of the gastrointestinal tract up to 72h, and up to 24h in the kidney pyramid and urinary bladder. This supports the usual gastrointestinal tract transit times after an oral administration, with subsequent renal and biliary elimination. Additional characterization comes from the metabolic profiling study in bile duct cannulated Wistar rats: excretion of radioactivity was fast with almost complete recovery achieved within 24h after oral ^{14}C-Daridorexant (>90%), and within 4h after intravenous administrations (>77%). The radioactivity recovered from bile (87%), urine (2%) and feces (1%) upon oral absorption.

Irrespective of the route of administration, biliary secretion was the main excretion pathway whereas the role of renal excretion was negligible. Unchanged parent drug represented less than 1 % of the dose. Small amounts of radioactivity were found in faeces after intravenous dosing, indicating a minor degree of direct secretion of drug-related material from blood into the gastro-intestinal lumen. Daridorexant was extensively metabolized into 23 metabolites. Eighteen metabolites were observed in rat bile, of which M6 and M9 were the main products, both being glucuronides of the primary metabolites M11 and M4. Five metabolites were observed in rat urine, none exceeding 0.3% of dose. Daridorexant, M1, M2, M3, M5 and M13 were the most prominent entities observed in plasma and were also detected in the brain. M1 that derived from M3 was not found in urine, faeces or bile.

In lactating female rats Wistar following a single oral gavage administration at 30 mg/kg, Daridorexant and the 3 major human metabolites were excreted wihin the first two hours into milk. Daridorexant, concentrations in

milk exceeded those in plasma by 14- to -20-fold while milk plasma ratios of the metabolites did not exceed 1.6-fold.

Inhibition, induction and drug-drug interactions

Nonclinical data may support that daridorexant is not a substrate of OATP uptake transporters and the efflux pumps P-gp/MDR-1 or BCRP, no in vivo DDI study evaluating the effects of inhibitors/inducers of these transporters on daridorexant was conducted. Metabolites were demonstrated as possible in vitro substrates for PgP, but considering their low unbound peak plasma concentrations, they would not affect the disposition of concomitant drugs whose disposition is drug transporter-dependent.

The drug-drug interaction (DDI) potential of daridorexant was investigated in vitro toward CYP450 enzymes and drug transport proteins (human liver microsomes, recombinant P450 enzymes, and cellular systems or membrane vesicles overexpressing human transport proteins). CYP450 induction was investigated on the level of PXR activation and upregulation of CYP mRNA in human hepatocytes.

Daridorexant (and to a smaller extent, M1 and M3) mainly inhibited CYP3A4, and showed time-dependent inhibition of CYP3A4. The clinical relevance of in vitro findings was assessed clinically with midazolam and rosuvastatin, and the study demonstrated Daridorexant is neither a CYP3A4 inhibitor or inducer, nor an inhibitor of BCRP. Daridorexant also inhibited in vitro a number of drug transport proteins, in particular BCRP, P-gp, MATE2K and MATE1. The clinical relevance of putative victim or perpetrator potency was investigated through a physiology-based pharmacokinetic modelling-based predictions of DDI (see clinical assessment report). The conclusion for the clinical doses in this model are: (i) Daridorexant may be a victim of CYP3A4 inhibitors and inducers; (ii) Daridorexant may be a weak CYP3A4 inducer at clinical doses.

However, based on interpretation of results in line with the EMA Guideline, in vivo inhibition of P-gp cannot be also completely excluded. Clinical relevance of CYP2C9 and CYP2C19 inhibition as well as whether daridorexant can be transported or not by the OATP1B1, OATP1B3, P-gp and BCRP at clinically relevant concentrations, and data regarding inhibition of the BSEP transporter were discussed at clinical level for convenient interpretation with regard to clinical exposure.

Daridorexant activated human PXR that resulted in CYP3A4 mRNA expression upregulaton in human hepatocytes. In addition Daridorexant exposure after multiple dosing in the rat and in the dog resulted in a dose-dependent upregulation of rat cyp3a1 and dog cyp3a12 mRNA in the livers, as well as rat ugt1a1 and ugt1a6 mRNA. Then Daridorexant has a potential for induction of Drug Metabolizing Enzymes, in line with known cyp3a and ugt enzymes regulation via the nuclear PXR.

2.5.4. Toxicology

2.5.4.1. Repeat dose toxicity

Rats and dogs are pharmacologically species relevant for daridorexant, as the orexin system is highly conserved across mammalian species, and as activity on sleep parameters had been clearly demonstrated. Additionally Daridorexant crossed the brain of rats during pharmacology studies, leading to significant brain/plasma ratios support the activity. Major human metabolites were found in the plasma of rats and dogs

The multiple of exposure for the parent compound and M1, M3 and M10 major human metabolites calculated as the ratio of free Cmax and free AUC in male and female rats and dogs at NO(A)ELs versus plasma exposure in humans at 50 mg/day showed high safety margins for Daridorexant, M1, M3, and M10. Margins appeared higher in females than males of both species. The lowest margin of safety relative to human maximum recommended dose was established at 14/40- (M/F) and 18/50-fold in dogs, 72/121-, and 80/152-fold in rats for free AUC and Cmax, respectively. The lowest exposure ratio for free AUC and free Cmax of M1, M3 and M10 are more than 147-, 238- and 73- fold at least for rats. These exposure ratio are more than 19-, 8.4- and 45-fold for M1, M3 and M10 in dogs. Theses margins may be sufficient to derisk non-clinical findings in the 26-week and 39-week repeat dose studies and limit their translation to humans.

In rats

Daily administration of Daridorexant for 26 weeks (with 8-week recovery period) resulted in central nervous system at all dose levels associated to exacerbated pharmacology at supra-pharmacological doses or related to the sleep-promoting effect of Daridorexant at pharmacological doses. Hypersalivation at all doses is considered related to poor oral palatability of the formulation. Other findings are reversible then toxicological significance is considered low (changes in hematology parameters, body weight gain, increase in gamma glutamyl transferase, triglycerides, cholesterol). In addition the increase of plasma cholesterol, interpreted as related to drug-metabolizing enzymes induction and activation of human PXR by Daridorexant was not observed in humans with insomnia treated with daridorexant in clinical studies

Reversible microscopic findings in the liver and in the thyroid gland occurred at doses ≥ 50mg/kg/day and can be considered non-adverse as hepatocellular hypertrophy is commonly considered as an adaptation phenomenon in rodents and non-rodents and the hypertrophy of thyroid follicular cells could be secondary to hepatocellular hypertrophy. Regarding the liver findings, there was no evidence of effect of daridorexant on hepatic function in humans, no marked laboratory abnormalities were reported, and all hepatic TEAEs were non-serious, considered not medically relevant and none led to study treatment discontinuation. The liver findings correlated with the changes in clinical chemistry (increased gamma glutamyl transferase, decreased T4 levels)) and the follicular cell hypertrophy in the thyroid gland correlated with variations in thyroid hormone levels (slight increase in circulating TSH levels). Findings related to thyroid and hormones (and importantly, cell hypertrophy of the pars distalis in the anterior pituitary gland at 1000mg/kg in a 4-week study) may have no clinical relevance due to species differences in thyroid hormone transport, metabolism, and elimination, with rats and dogs being more sensitive than humans to thyroid changes and alterations of the hypothalamo-pituitary-thyroid axis. Follicular cell hypertrophy of the thyroid gland in rats often results from its overstimulation due to increased TSH production in the pituitary gland, which is a compensatory reaction to increased metabolic clearance of thyroid hormones through ugt2b enzyme induction. Based on the clinical review of both thyrotropin abnormalities and AE pertaining to thyroid dysfunction during clinical trials, only AE attributable to the subjects' medical history and/or thyrotropin levels already elevated at baseline were found. No relationship with daridorexant treatment was suggested, and no dose-dependent signal was detected in these patients.

The kidney findings in females at 450 mg/kg/day (increased formation of tubular hyaline casts) were still present at the end of the treatment-free period, but considered non-adverse as such lesions are representative of chronic progressive nephropathy that is a common lesions in the aging rat, and do not correlate with nephrotoxicity or renal injuries in humans. Then NOAEL can be established at 450 mg/kg/day, leading to safety margins relative to human maximum recommended dose at 72/121- and 80/152-fold in rats for free AUC and Cmax, respectively. Free AUC and Cmax for M1, M3 and M10 are also superior to free exposure in humans at 50 mg/day. The lowest exposure ratio for free AUC and free Cmax of M1, M3 and M10 are more than 147-,

238- and 73- fold at least for rats compared to the human clinical exposure. These data suggest low safety concern for non-reversible findings.

If findings similar to those in the 26-week study were found in the 13-week GLP toxicity study (followed by a 4-week treatment-free period) and in shorter studies (3 days to one month) with higher maximal dose, the administration of 1000 mg/kg/day led to deaths distended abdomen, severe hypothermia resulting in severe hypoactivity and bradycardia that likely contributed to death at high dose in rats (see mechanistic studies). Finally on the possible relationship between orexin receptor antagonism at very high doses and death related to gastrointestinal dysfunction and hypothermia, this is not considered clinically relevant as findings occurred at free Cmax largely exceeding free human exposure at clinical dose of 50mg/day.

In dogs

In Beagle dogs were administered 10, 30, or 100mg/kg/day Daridorexant for 39 consecutive weeks, and followed by 8 weeks of recovery period, there were no test item-related deaths and no daridorexant-related clinical signs at 10mg/kg/day.

The CNS-related clinical findings consisted mainly to exaggerated pharmacology-driven effects as decubitus, lying down, loss of balance, unsteady gait, clumsy movements, unable to stand and/or immobility. They were observed in the exercise area after positive stimulation, approximately 1-2 h after dosing from Week 7 for the majority of animals given 100 mg/kg/day and for a few animals given 30mg/kg/day. While they were no more observed from the beginning of the recovery period, these clinical signs can be considered as adverse due to their severity. Hypersalivation, and a higher incidence of vomiting and/or regurgitation occurred at 100 mg/kg/day for both sexes that were probably related to the poor palatability of the formulation. Daridorexant lowered food consumption for males given 100 mg/kg/day, without impacting body weight. These findings were considered non-adverse since there was no impact on the global health condition of the dogs.

Daridorexant related changes in clinical chemistry parameters consisted mainly of increased alkaline phosphatase (ALP) activity at 30 and 100 mg/kg/day and decreased albumin concentration and in total bilirubin concentrations in both sexes at 100 mg/kg/day. These variations were no longer present at the end of the treatment-free period and were considered as non-adverse. One female treated at 100 mg/kg/day had high ALT, GLDH, AST and GGT activities without histological features. These changes were reversible, then considered non-adverse. There were no Daridorexant-related changes at the low dose level of 10 mg/kg/day.

Absolute and relative liver weight increased up to 100 mg/kg/day in both sexes, without histologic evidence of hepatocellular hypertrophy. Following the treatment-free period, changes fully reversed. There were no histological changes at 10 mg/kg/day. It was shown in a non-GLP morphometry study, that the liver weight increase was due to a moderate and homogeneous enlargement of hepatocytes probably secondary to drug metabolizing enzymes induction (see mechanistic studies). At clinical level, there was no evidence of any effect of daridorexant treatment on hepatic function in humans.

A slight increase in presence of adipocytes in the sternal bone marrow was observed in males and females at 100mg/kg/day, and was considered non-adverse due to reversibility during the treatment-free period.

Increased amount of luminal secretory material in the gallbladder of females at 30 mg/kg/day, and males and females at 100 mg/kg/day. As no gallstone developed, and no histological alteration of the gallbladder occurred at any dose level and time, and finding were reversible at recovery, observed functional excretory changes may be considered not adverse and unlikely to translate in humans at 50 mg/day clinical dose (exposures multiple around 134-and 780-fold in females and males, respectively).

Finally the NOEL was established at 10 mg/kg/day in both sexes, corresponding to a test item AUClast of 5180/6410 ng.h/mL (male/female) on Day 1 and 9100/17500 ng.h/mL (male/female) in Week 39. The multiple of exposure for the parent compound and M1, M3 and M10 major human metabolites calculated as the ratio of free Cmax and free AUC in male and female dogs at NOEL versus plasma exposure in humans at 50 mg/day showed high safety margins for ACT-541468, M1, M3, and M10: the margin of safety relative to human maximum recommended dose was established at 14/40-(male/female) and 18/50-fold for free AUC and Cmax, respectively. The lowest exposure ratio for free AUC and free Cmax of M1, M3 and M10 are more than 19-, 8.4- and 45- fold. Theses margins may be sufficient to derisk non-clinical findings and limit their translation to humans.

2.5.4.2. Genotoxicity

Usual battery of *in vitro* and *in vivo* GLP compliant-tests in line with ICH S2 guidelines were performed to assess the genotoxic potential based on *in vitro* gene mutations test, chromosomal aberrations test in human lymphocytes, as well as the micronucleus assay in bone marrow cells from rats treated Daridorexant. *In vitro* tests were performed also under metabolic activation or not, using appropriate concentration range and maximal concentration, and with sufficient replicates/counts in appropriate cell/strains systems. S9 fraction was from a specie from which metabolism was demonstrated in ADME studies. In contrast to positive controls, Daridorexant was considered to be non-clastogenic in this chromosome aberration test, when tested up to cytotoxic and/or precipitating concentrations (52.2 µg/mL), and non-mutagenic in the Salmonella typhimurium reverse mutation assay up to 5000 µg/plate, neither in the presence nor absence of S9 metabolic activation. Regarding *in vivo* study, plasma concentrations in animals dosed with Daridorexant at 2000 mg/kg b.w. ranged from 4.70 to 12.5µg/mL that is at least 47-fold higher than human exposure at clinical dose considering free Cmax. These animals exhibited a reduction of spontaneous activity without statistically significant increase of micronucleus frequency, in contrast to cyclophosphamide. By extension M1, M3 and M10 metabolites are intrinsically considered to not display genotoxic potential as metabolites were generated in this study at levels superior to human exposure with plasma concentrations of 53-, 11- and 19-fold respectively relative to human free Cmax at the 50mg clinical dose.

2.5.4.3. Carcinogenicity

A slightly higher body weight gain was seen in males treated Daridorexant at 150mg/kg/day, and weight of the liver increased up to +26% and +42% in males and females, respectively. Weight of the thyroid glands also increased up to +43% in males and +23% in females. Marked thyrotropin abnormalities and thyroid dysfunction were found in clinical trials only in subjects with medical history and/or thyrotropin levels already elevated at baseline. Then thyroid changes in rats can be considered not clinically relevant.

Non-neoplastic findings were observed in females treated at 150mg/kg/day and consisted of increased incidence and/or severity of bile duct hyperplasia, karyocytomegaly / multinucleated hepatocytes, and centrilobular hepatocellular hypertrophy in the liver. These effects were detected also in the pivotal 6-month repeat-dose toxicity study in rats. An increased incidence of chronic progressive nephropathy was observed. Chronic progressive nephropathy is a common lesions in the aging rat, and literature may suggest that such nephropathy in rats may not lead to nephrotoxicity or renal injury in humans. Finally the results in patients without and with severe renal impairment showed that daridorexant can be administered to subjects with any

degree of renal function impairment without the need for dose adjustment. Then findings in rats are not clinically relevant.

There were no Daridorexant-related effects on the incidence of pre-neoplastic and neoplastic microscopic findings. Masses were primarily located in the thoracic and ventral/dorsal abdominal regions and to a lower extent in the urogenital region. The neoplastic findings were considered unrelated to Daridorexant and within the spectrum of the spontaneous histopathological variation in this species in view of their nature and incidence. The number of adenomas of pars distalis and follicular adenomas in the thyroid gland in males treated at 150 mg/kg/day was higher than in the control groups, but without statistical significance upon Peto analysis of tumor incidences. In the pathology report, higher incidence of cysts was reported in the ovaries of females treated at 150mg/kg/day. The ovarian cysts were generally focal and unilateral and were considered likely part of the spontaneous histopathological background variation in aging female rats based on litterature review. To conclude, daily administration of ACT-541468A by once daily oral gavage to the Wistar rat up to 150mg/kg/day for 104 weeks did not induce significant neoplastic changes. Given the safety margins, there are no safety concern.

The 26-week carcinogenicity assay in Tg.rasH2 mice daily administered by oral gavage with t 100, 200/300 (females/males) or 1000 mg/kg/day of Daridorexant was conducted according to ICHS1 under GLPs. Selection of high dose for carcinogenicity study should be 50-fold ratio (AUC) in TgrasH2 mice according to ICHS1, however the multiple of exposure ratio for the 1000 mg/kg high dose are only 8.5-4.37 fold (males-females) for Daridorexant, and comprised between 5.3 and 7.7 fold for metabolites. This high dose may be accepted considering possible limiting toxicity for a 26-week treatment duration based on liver necrosis from the 4 week-DRF study at 1500 mg/kg/day. Oral administration of Daridorexant resulted in minor test-article related decreased body weights and body weight gain in males at ≥300 mg/kg/day and non-neoplastic findings limited to increased liver weights in males at ≥300mg/kg/day and females at 1000 mg/kg/day and corresponding hepatocellular hypertrophy in males at ≥ 100mg/kg/day and females at 1000 mg/kg/day. This hepatocellular hypertrophy, also occurring in other GLP toxicity studies, was considered to be an adaptive and non-adverse change. All these findings were known from other pivotal repeat-dose toxicity studies in rodents. There was a lack of a dose response in the incidence of non-neoplastic findings. N-Nitroso-N-methylurea, as positive control resulted in induction of neosplastic lesions to validate the study. Daridorexant did not induce any significant neoplastic changes and therefore was considered not carcinogenic.

2.5.4.4. Reproductive and developmental toxicity

Fertility studies were conducted in male rats mated to untreated female rats at oral doses up to 450 mg/kg/day, and in female rats mated to untreated male rats at oral doses up to 300 mg/kg/day. No treatment-related adverse effect was observed on male mating behaviour and fertility, reproductive organ weights and sperm parameters at doses up to 450 mg/kg/day. In females, there was no treatment related effect on estrous cycle, mating behaviour and reproductive indices. However, the number of implantations was decreased at 300 mg/kg, causing reductions in the number of live embryos and in gravid uterine weight and an increase in the pre-implantation loss. The NOAEL for male and female reproduction is therefore set at 450 mg/kg/day and 100 mg/kg/day, respectively, corresponding to safety margins of >30 based on free AUC levels suggesting that effects seen in females are of minor concern for clinical use.

Embryo-fetal development toxicity studies were conducted in rats and rabbits. Treatment-related effects on embryo-foetal survival or foetal malformations were not reported in any species. A decrease in fetal weight was seen in rabbits at 88-fold the clinical exposure (based on free AUC levels) and would therefore be of minor

concern for clinical use. At the developmental NOAELs of 300 mg/kg/day in rats and 60 mg/kg/day in rabbits, safety margins were ≥46 based on free AUC levels.

In the pre- and post-natal development study, there was no treatment-related effect on post-weaning development of F1 rats including sexual maturation, behavioral tests, and mating performance and fertility at doses inducing exposure levels 123-fold higher than those reached in patients. (based on free AUC levels) The body weight of F1 animals at the high dose level of 300 mg/kg was lower than that of controls from birth (males: -4.6%; females: -5.33%) to weaning (males: -7.5%; females: -6.54%). In males, this effect persisted during the postweaning period up to termination on PND98 (-4.5%), whereas it reversed between PND56 and PND77 in females. The changes were considered as non-adverse notably since the reported values lied within the historical control range, and because there was no consequence on the animals' clinical condition and sexual maturation.

Juvenile toxicity

Although the current application is for adult patients, a 9-week juvenile toxicity study was conducted in rats aged 21 days dosed orally at 0, 50, 150 and 450 mg/kg/day to further support development in paediatric patients from 2 years of age. To resume, the non-adversity of increased motor activity noted at ≥150 mg/kg had been discussed further, since the data point to a treatment-relationship in all treated groups**.** Moreover, the treatment-relationship of the increased incidence and severity of interstitial cell vacuolation in the ovary observed in treated animals. Otherwise, thyroid and liver findings reported in this study were in line with those seen in studies initiated in sexually mature animals.

Motor activity: the applicant relies on the variability of motor activity measures which may be caused by non-treatment-related factors (time of the day, state of wakefulness, age, level of anxiety, etc.). This is acknowledged. However in the context of the juvenile animal study (JAS), such inter-individual sources of variability should have been limited between control and treated animals. Historical data were provided, showing notably that motor activity measures for high dosed males were outside of the historical control range for both basic (4532 vs. 1660-4094) and fine (3659 vs. 1343-3255) movements. At the mid dose level, the reported motor activity for males were within the highest historical control range (basic: 4136; fine: 3283). Therefore, a treatment-related effect cannot be excluded at the high dose level. Nevertheless, the unchanged pattern of overall motor activity as well as the reversibility of the reported findings are noted. In addition, since they were observed at a high exposure ratio (x85 clinical exposure) with sufficient safety margin (x29), it can be concluded that the clinical relevance is most likely remote. Inclusion in the SPC 5.3 is therefore not needed at this stage.

Histopathological findings in ovaries: interstitial cell vacuolation is reported as having been over-diagnosed in the current study due notably to technical (location of histological cut) and biological (stage of estrous cycle) factors. However, historical control data indicate that interstitial cell vacuolation was reported in none of 19 JAS conducted for the past 5 years at the CRO where the current JAS study was performed. Since procedures applied in a given facility are expected to be similar from a study to another, over-diagnosis of a particular finding in a single study would not be expected.

In the definitive JAS study, the incidence of interstitial cell vacuolation in ovaries at end of treatment was 1/10, 4/10, 6/10, and 9/10 (10%, 40%, 60%, and 90%) in the control, low, mid, and high dose groups. At the end of recovery, these values were 4/6, 1/6, 2/5, and 3/6 (66%, 17%, 40%, and 50%). Therefore, it is considered that the incidence of this lesion was in the study control range (10-66%) in all groups, except in high-dosed females at end of treatment. Similarly, the severity of the lesion was in general similar in the control, low and

mid dose groups (minimal) and increased at the high dose level at the end of treatment (minimal to mild). Therefore, the NOAEL for this ovary finding could be set at the mid dose level of 150 mg/kg/day, from which a safety margin of x29 can be derived based on unbound AUC levels. The histopathological finding noted at 450 mg/kg/day had no functional correlate since there was no treatment-related effect on estrous cycles, mating performance, and fertility. Considering the high exposure ratio at this dose level (x85), and the other nonclinical data in adult rats showing no drug-related effect on ovaries, estrous cycle, fertility, and tissues with high expression of orexin receptors, it is considered that the clinical relevance of this effect is most likely remote and therefore does not require to be included in the SPC 5.3.

2.5.4.5. Toxicokinetic data

Interspecies comparison of the exposure profiles showed tendency to similar shape for the parent and major metabolites upon chronic treatment with dose dependent exposure levels and with significant less than dose proportionality in the range of higher doses. A tendency for less-than-dose-proportional increase in exposures was observed in non-clinical species in the range of lowest-moderate doses and could be interpreted as related to saturation of first-pass metabolism that may result in full saturation of first-pass metabolism when doses increase. Interestingly, exposure ratios between daridorexant and the sum of metabolites (M1, M3, M1 changed slightly in favour of the parent, supporting occurrence of metabolism saturation when Daridorexant doses increase.

Daridorexant, M1, M3, and M10 circulate in plasma of these species and cover human exposure at all doses equal to or greater than human exposure levels, excepted for mice for with exposure level are the lower relatively to other species. A plausible explanation for the lower exposure level in mice compared to other species may be that the main metabolic pathways are significantly different in mice which generated rather M4 and M9 than M1, M3, and M10, then changing exposure daridorexant: metabolite in favour to metabolites.

Daridorexant may slightly accumulated between administrations in all species. Auto-induction of CYP450 enzymes may be responsible for such phenomenon as upregulation of cyp2b1/2 and cyp3a1 had been demonstrated in liver, at least in rats and dogs, but this slight accumulation may traduce also a saturation of clearance processes.

Exposure at the lowest-moderate doses for both parent and metabolites generally led generally to higher exposure in females compared to males in dogs, whereas exposure in mice and rat females was generally the higher than in males whatever the dose. This gender effect was more characterized in dogs and rats for which the sex difference rarely exceeded 2-fold for ACT-541468. As ACT-541468 is primary metabolized by CYP450 enzymes, this gender difference may be explained at least by known sexual dimorphism (in rats and dogs) regarding the phase I metabolism pathway.

Mechanistic studies

Mechanistic studies for liver findings were conducted given the hepatotoxicity findings toxicity studies in mice, rats and dogs (exploratory and definitive repeat-dose toxicity studies, including carcinogenicity programme). A non-GLP study aimed at investigating the direct cytotoxic potency of daridorexant in primary-cultured CD-1 mouse and human hepatocytes through the lactate dehydrogenase (LDH) assay demonstrated Daridorexant had no direct cytotoxic potential up to 50 µM, corresponding to a 22/7500-fold the total/free plasma concentrations at the clinical dose of 50 mg/day. Then it is considered daridorexant is not directly cytotoxic against hepatocytes at clinically relevant exposure.

2.5.4.6. Other toxicity studies

Dependence potential

Because Daridorexant is a centrally penetrant, CNS-active drug, the potential risk of abuse was evaluated in non-clinical studies. On one hand, Daridorexant treatment was associated with signs of sedation in pharmacology and toxicology studies. On the other hand, Daridorexant did not displayed a novel mechanism of action as two DORAs are presently marketed, but the background on the class may be considered low that supports the need of drug abuse and liability studies for Daridorexant at non clinical level. As a complement, off-target profiling included CNS targets known to be associated with substance abuse, including cannabinoid receptors, opioid receptors, serotonin receptors, GABA receptors, monoamine transporters, glutamate NMDA receptors, and various ion channels. Data from human receptor-ligand binding assays related to neuronal systems evidenced some agonism or antagonism of the parent or M1 metabolite for : angiotensin II receptor type 1, adrenergic β3 receptor, human tachykinin receptor 3, opiate OP2 receptor, and human dopamine transporter, that may be related to abuse. Given IC_{50} and clinical exposure, off-target effects of Daridorexant and metabolites are considered to not activate any abuse-related molecular CNS targets at clinically relevant concentrations. Then the Applicant' strategy was to investigate Drug Discrimination studies followed by behavioural assessment of dependence through the withdrawal syndrome and self-administration test. The plasma exposure reached during these experimental procedures were within the concentration range known to cause inhibition of orexin receptor signalling in the brain and to decrease wakefulness in rats, and compatible with the target exposure in humans at clinical dose of 50 mg. The level of M1, M3 and M10 in plasma was also compatible with the clinical exposure in humans. In the three GLP-compliant abuse liability studies, daridorexant had no potential for self-administration in rats with a previous history of cocaine self-administration and did not generalize to the effects of zolpidem in rats trained to discriminate zolpidem from placebo. Furthermore, there were no changes in physiological, neurobehavioral, or locomotor activity parameters associated with the withdrawal syndrome after treatment discontinuation in rats. Taken together, based on animal studies, daridorexant did not reveal any sign indicative of physical dependence or drug abuse potential.

Metabolites

The safety profiles of major human metabolites (M1, M3 and M10) were obtained from pivotal oral toxicology studies with daradorixant wherein metabolites exposures were equal or greater to the human clinical exposure at 50 mg/day. Each major metabolite was detected at least 50% of human exposure at the 50 mg dose in multiple species, consistent with ICHM3 (R2, Q&A, 2012).

Impurities

The assessment of genotoxic impurities is consistent with the recommendations of ICH M7. All potential, confirmed or known mutagenic impurities in the final substance are below the thresholds of toxicological concern, below the limit of detection in batches, or estimated as negligible amount due to large purge factors. Regarding non mutagenic impurities, specifications were extrapolated from oral GLP-repeat dose toxicological studies with batches of Daridorexant hydrochloride containing sufficient amount of impurities. Then all relevant impurities were qualified *in vivo* according to ICHM3/S3 guidelines, and the Applicant proposed specifications below the qualification thresholds. No safety concern is anticipated.

Phototoxicity

Daridorexant is not of concern for phototoxicity as (i) it did not display any phototoxic effects on BALB/c 3T3 cells under the experimental conditions compliant with ICHS10; (ii) there were no significant evidence of binding to melanin based on tissue distribution studies in pigmented versus albino rats.

2.5.5. Ecotoxicity/environmental risk assessment

Log octanol-water partition coefficient was experimentally determined below the trigger value of 4.5 at environmentally relevant pH's, then daridorexant is not considered to be a persistent (P) and bioaccumulative substance, or a very (T) and very 'B) substance. But based the active substance should be considered vP (due to persistence in sediment according to OECD 308), not B and not T. PEC_{SW} was determined above the action limit of 0.01 µg/L (0.25 µg free base/L), then a Phase II environmental fate and effects analysis was conducted by the Applicant with a total residue approach to cover environmental fate and toxicity of metabolites and parent compound. During Phase II assessment, shifting to the sediment in the water-sediment degradation test was observed. Risk assessments for the surface water, sediment and sewage treatment plant allowed to conclude that daridorexant (and metabolites) do not represent a risk for the aquatic environment, the groundwater, soil and sediment compartments, micororganisms, plants and biota.

Table 1. Summary of main study results

Substance (INN/Invented Name): Daridorexant			
CAS-number : 1505484-82-1 (free base)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	GLP compliant OECD 107 shake flask study Non-GLP study Microspecies distribution generated using MarvinSketch.	-The octanol/water partitioning coefficient = 2.9, 3.0 and 2.9 at pH values of 5, 7 and 9, respectively. - logKow = 3.9 at pH 7 - at pH 5 the logKow values should be regarded as logDow value and at pH 7 and pH 9, the logDow is equal to the logKow as it shows the value of the neutral species.	As the logKow is below the trigger of 4.5, the substance is not considered to be a PBT or a very persistent and very bio-accumulative (vPvB) substance, and therefore a definitive PBT assessment is not required.
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		
	BCF		
Persistence	DT50 or ready biodegradability		
Toxicity	NOEC or CMR		
PBT-statement :	As the logKow for the weakly basic daridorexant is below the trigger of 4.5, the compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC $_{surfacewater}$	0.25	µg free base/L			The calculated PECSW > action limit of 0.01 µg/L, therefore a standard Phase II environmental fate and effects analysis is needed.
Other concerns					
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption/desorption with 3 soils and 2 sludges	OECD 106	Organic carbon-normalized Freundlich adsorption coefficient: Sludge KF,oc= 645 and 774 L/kg Soil KF,oc = 1155, 1334 and 1420 L/kg			-The reported Freundlich exponents (1/n) of the Freundlich adsorption isotherms were 0.92 for both sludges and between 0.79 and 0.82 for the 3 soils. Do not trigger further studies as Koc for the two sludges < the trigger value of 1000 L/kg
Ready Biodegradability Test	OECD 301B	Replicate values: 4% and 9% biodegradation.			Not readily biodegradable
Water sediment study= Aerobic and Anaerobic Transformation in Aquatic Sediment system (radiolabelled-daridorexant in two water/ sediment systems (*Schoonrewoerds Wiel [SW] and Middle Pond [MP]) at 20 ± 2 °C in the dark for 102 days*)	OECD 308	Daridorexant as % AR in sediment at or after Day 14 Schoonrewoerdse Wiel: 55/56/45/31 % AR at day 14/ 28/ 63/102 Middle Pond:63/70/68/63 % AR at day 14/ 28/ 63/102 DT50 of daridorexant= 67 days in the SW total system and 201 days in the MP total system. The half-life calculated for the water layer was not a degradation DT50 but a dissipation half-life and was 6.3 days in SW water and 6.5 days in MP water. For sediment, no calculations could be performed. DT90 values for the total system = 222 days (SW) and 779 days (MP).			-significant shifting of the drug substance to the sediment. -need for further investigation of effects on sediment-dwelling organisms (Chironomus sediment water toxicity test performed)
Phase II Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test (*Raphidocelis subcapitata*)	OECD 201	NOEC EC_{10}	0.48 0.72	mg free base/ L	Statistically significant inhibition of growth rate was found at test concentrations of 0.48 mg free base/L and higher. However, growth rate inhibition recorded at 0.48 mg free base/L was well below 10% (3.5%) and is therefore considered to be biologically not relevant. The NOEC for algae growth rate inhibition was thus set at 0.48 mg free base/L and the EC10 was 0.72 mg free base/L.
Daphnia reproduction Test	OECD 211	NOEC EC_{10}	1 1.8	mg free	Statistical analysis showed that the reproduction of the daphnids was significantly

<table>
<tr><td></td><td></td><td></td><td></td><td>base/ L</td><td>reduced at test substance concentrations of 4.6 mg free base/L and higher. Statistically significant reduction of growth (body length) was found at the test substance concentration of 2.2 mg free base/L (i.e., 22% of a saturated solution prepared at a loading rate of 10 mg free base/L) and higher. The overall NOEC from the study was 1.0 mg free base/L. The EC10 for reproduction was 1.8 mg free base/L.</td></tr>
<tr><td>Fish, Early Life Stage Toxicity Test (Pimephales Promelas)</td><td>OECD 210</td><td>NOEC
EC_{10}</td><td>0.11
0.4</td><td>mg free base/ L</td><td>Statistical analysis showed that the time of hatching and hatching success were not significantly different in any of the treatments when compared to the pooled controls. Post-hatch survival was not statistically significantly affected at 1.1 mg free base /L and below but was significantly reduced at the highest test concentration. Larval growth, as measured by weight and length, was statistically significantly reduced at 0.23 mg free base/L and above when compared to the pooled controls. Based on these results, the overall NOEC from this study was 0.11 mg free base/L and the EC10 was 0.4 mg free base/L.</td></tr>
<tr><td>Activated Sludge Bacteria, Respiration Inhibition Test</td><td>OECD 209</td><td>NOEC
EC_{10}</td><td>3.2
3.4</td><td>mg free base/ L</td><td>At 1.0, 3.2, 10, 32,100, 320 and 1000 mg free base/L, respiration was inhibited by 4.8%, 11%, 14%, 17%, 42%, 45% and 52%, respectively. As no statistically significant inhibition of the respiration rate of the sludge was recorded at or below 3.2 mg free base/L, the NOEC from this study was 3.2 mg free base/L. The EC10 was 3.4 mg free base/L.</td></tr>
<tr><td>Sediment-Water Chironomid Toxicity Test Using Spiked Sediment for 28 days.</td><td>OECD 218</td><td>NOEC
LOEC</td><td>154
278</td><td>mg free base/ kg sediment dry weigh t</td><td>-No significant statistical effect compared to the pooled control in the three lowest test concentrations. At 497 mg free base/kg sediment dwt, the highest concentration at which only two midges emerged, the observed effect on development rate was statistically significant compared to the pooled control.
- NOEC = 154 mg free base/kg sediment dwt and the EC10 = 278 mg free base/kg sediment dwt.
According to the EMA Q&A document, the NOEC from the study with spiked sediment should be recalculated into an endpoint for standard sediment (std) with an organic carbon content of 10%,
<table>
<tr><th>Study</th><th>Measured value</th><th>$f_{OC,std}$</th><th>$f_{OC,measured}$</th><th>Standard value</th></tr>
<tr><td>Sediment-spiked NOEC</td><td>154 mg free base/kg dwt</td><td>0.10</td><td>0.019</td><td>811 mg free base/kg dwt</td></tr>
<tr><td>Sediment-spiked EC_{10}</td><td>278 mg free base/kg dwt</td><td>0.10</td><td>0.019</td><td>1464 mg free base/kg dwt</td></tr>
</table></td></tr>
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Bioaccumulation in fish	OECD 305	BCFssL BCFkL	721 ± 132 in the 1µg/L group; 355± 84 in the 10µg/L group; 695 in the 1µg/L treatment group; 365 in the 10µg/L group	L/kg L/kg	As the logKow of daridorexant was ⩾ 3, an aqueous bioconcentration study was performed. -BCFssL = lipid-normalized steady-state bioconcentration factor; BCFkL = lipid-normalized kinetic bioconcentration factor; -corrected for fish lipid content -BCFssL and the BCFkL were similar at both target concentrations; BCFssL and BCFkL values of daridorexant were far below 2000 L/kg = not considered to be bioaccumulative in fish.
Ratio	**PEC**	**PNEC**	**PEC/PNEC**	**Trigger**	**Remarks**
$PEC_{SURFACEWATER}/PNEC_{WATER}$	0.25 µg free base/L	40 µg free base/L	0.00625	1	As the ratio is < 1, further testing in surface water is not required and it can be concluded that daridorexant is unlikely to represent a risk to the aquatic environment
$PEC_{Sewage\ treatment\ plant}/PNEC_{MICROORGANISM}$	0.25 µg free base/L	340 µg free base/L	0.00740	1	As the ratio is < 1, further testing in surface water is not required and it can be concluded that daridorexant is unlikely to represent a risk to microorganism & sewage treatment plant compartment
$PEC_{GROUNDWATER}/PNEC_{GROUNDWATER}$	0.063 µg free base/L	4 µg free base/L	0.01575	1	As the ratio is < 1, further testing in surface water is not required and it can be concluded that daridorexant is unlikely to represent a risk to the groundwater compartment
$PEC_{SEDIMENT}/PNEC_{SEDIMENT}$	0.034 (mg free base/kg dry weight	14.64 mg free base/kg dry weight	0.0023	1	As the ratio is < 1, further testing in surface water is not required and it can be concluded that daridorexant is unlikely to represent a risk to the sediment compartment.
$PEC_{BIOTA}/PNEC_{BIOTA}$	0.174 mg free base/kg	4 mg free base/kg food	0.0435	1	-As the BCFkL at target concentrations of 1 and 10 µg/L were 695 and 365 L/kg, respectively, a further assessment for secondary poisoning was performed. The potential for secondary poisoning should also be assessed if the BCFk>100 L/kg. -$PNEC_{BIOTA}$ is derived from the most relevant mammalian toxicity study. -As the ratio is < 1, it is concluded no risk for secondary poisoning (birds and mammals resulting from consumption of contaminated fish or other aquatic organisms).

2.5.6. Discussion on non-clinical aspects

The main toxicology, toxicokinetic, and safety pharmacology studies were performed in accordance with Good Laboratory Practice (GLP) regulations and were conducted in countries that are signatories to the Organization for Economic Cooperation and Development (OECD) mutual acceptance of data (MAD) agreement and at laboratories that are members of their national GLP compliance programme. Other pharmacodynamic and

pharmacokinetic studies do not fall under these regulations. Applicable International Conference for Harmonisation (ICH), Committee for Medicinal Products for Human Use (CHMP), or Food and Drug Administration (FDA) guidance documents were also referenced during the design of the toxicology, toxicokinetic, and safety pharmacology studies. When deviations to protocols were identified, they were considered to have no or minimal impact on study outcomes.

Proof-of-concept for the indication was sufficiently demonstrated in *in vivo* primary pharmacology studies using as usually naive rats and dogs as models. Daridorexant exerted its activity from the brain at clinically achievable concentration. Selective antagonism on OX1 and OX2 receptors was the primary mode of action on OX1 and OX2 receptors from *in vitro* calcium mobilization studies. Daridorexant behaved very similarly the approved drug Suvorexant, with similar range of Kb and apparent occupancy half-life on human OX1 receptor and OX2 receptor. It can be concluded that daridorexant induced surmountable and rapid sleep-wake effects, the overall non-REM and REM sleep times being increased without the wake period did not exceed the natural sleep period, without next-day residual effect, as animals can be awakened and able to perform normally in various motor tasks. The 3 major human metabolites M1, M3 and M10 exhibited Kb values for human OX1/OX2 receptors several order greater than those of Daridorexant supporting metabolites are not expected to significantly contribute to sleep effect. Such dual OX1 and 2 receptor antagonism would therefore promote slow sleep (NREM), and paradoxical sleep (REM) in insomniac humans.

Secondary pharmacology investigation showed that Daridorexant, M1, M3, and M10 do not bind to or inhibit the activity of a large panel of target receptors, channels, and enzymes, and for the few observed *in vitro* off-target, the large multiple of exposure at the clinical exposure at clinical dose, allow to consider off-target risk is not considered relevant for humans for daridorexant and its major human metabolites at clinical exposure.

Findings from dedicated GLP- and ICH7-compliant safety pharmacology studies in rats and dogs, and additional non-GLP studies in guinea pigs, are considered of low concern for translation in humans given large safety margins. Daridorexant (and major human metabolites) plasma concentrations well covered clinical human exposure. No relevant adverse effects for human were observed on respiratory system, central nervous system, or cardiovascular function at Cmax values more than 50-fold above the human exposure at the 50mg/day dose. Data suggest also a low risk in hypertensive patients. Non-adverse reduction of activity and arousal occurred in rats and dogs as pharmacology-driven effects. Only severe hypothermia at highest dose occurred in animals, but any similar finding was reported in clinical studies.

ADME studies demonstrated that daridorexant is rapidly orally absorbed, and distributed in all tissues, mainly in the gastrointestinal mucosa, the liver and kidney, adrenal gland, brown fat, and myocardium. The radioactivity decreased to the limit of quantification at 24h post dose in most tissues and blood except the liver and the gastrointestinal tract, and no remaining radioactivity was detected 7 days post-dose in any tissue. Excretion routes were renal and biliary elimination. Exposure generally increased in a more than proportional manner with increasing oral doses but a significant first-pass extraction was observed, saturation of metabolic processes during oral absorption that might contribute to non-linear PK at highest dose. PK profiles in subjects with insomnia and healthy subjects showed that the exposure was approximately dose proportional up to the maximum therapeutic dose of 50 mg with no influence of sex on daridorexant PK parameters, and no accumulation, in contrast to non-clinical species, which slight accumulation or gender effect were observed. Daridorexant is highly bound to plasma of human subject and non-clinical species, and with no significant variability within human plasma sample, allowing to calculate exposure ratio based in free Cmax and AUC.

Daridorexant crosses the blood-brain barrier and local concentration had been correlated to sleep-promoting activity in rats. Significant plasma binding properties were evinced among non-clinical species and humans, then implying to consider %Fu to compare exposure within species and to calculate safety margin/multiple of

exposure. The non-linear plasma binding manifests as dose-dependent increases in the volume of distribution at steady state and prolonged half-lives, as higher unbound plasma concentrations facilitate drug partitioning into tissues. This in a favour to achieve high exposure for free concentration of ACT-541468 on the toxicological species used in pivotal repeat-dose toxicity studies (rat and dog). No significant differences in tissue distribution and elimination of radioactivity in pigmented versus albino rats suggesting ACT-541468A (or metabolites) is not able to bind to melanin and a low concern for risk associated to phototoxicity (the usual phototoxicity test in on BALB/c 3T3 was negative). Major human metabolites were generated at sufficient level in non-clinical species. Phase I metabolism (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) as well UGTs were found to mediate the metabolism of Daridorexant, CYP3A4 being the major enzyme responsible for ACT-541468 metabolism accounting for 89% of metabolic clearance. Then from the ADME and pharmacology point of view, the rat and dog can be then considered relevant species for non-clinical efficacy and safety studies. As a remark, the standard analytical methods used for the ADME programme are considered appropriate and validated for their purpose. However, long-term stability testing of daridorexant and its metabolites in rat and rabbit plasma will only be completed in June 2022. The applicant commits to provide the missing data once available.

Based on experiments with human liver microsomes and recombinant P450 enzymes, CYP3A4 inhibitors and inducers are expected to modify daridorexant pharmacokinetics in man. Daridorexant is an inhibitor of several P450 enzymes tested in vitro, the strongest effect was observed on CYP3A4. Daridorexant was also a weak time-dependent CYP3A4 inhibitor. The clinical relevance of CYP3A4 inhibition was further investigated in vivo and/or through physiology-based pharmacokinetic modelling-based predictions. The inhibitory potential of the metabolites showed a similar pattern but was generally weaker compared to parent drug. In vitro studies were performed to investigate whether daridorexant induces enzymes, daridorexant upregulated CYP3A4 mRNA expression in human hepatocytes: Daridorexant and its metabolites elicited a concentration-dependent activation of human PXR. Daridorexant has a potential for induction of Drug Metabolizing Enzymes, cyp3a and glucuronyltransferases enzymes regulation via the nuclear PXR. These observations were also confirmed in vivo.

Nonclinical data also suggested that daridorexant may be not a substrate of OATP uptake transporters and efflux pumps as P-gp/MDR-1 or BCRP. Daridorexant also inhibited a number of drug transport proteins, in particular BCRP, P-gp, MATE2K and MATE1. The clinical relevance of putative victim or perpetrator potency was investigated through a physiology-based pharmacokinetic modelling-based predictions of DDI (see clinical assessment report). The conclusion for the clinical doses in this model are: (i) Daridorexant may be a victim of CYP3A4 inhibitors and inducers; (ii) Daridorexant may be a weak CYP3A4 inducer at clinical doses.

Relevance of CYP2C9 and CYP2C19 inhibition, inhibition of P-gp, inhibition of the BSEP transporter and whether daridorexant can be transported, or not, by the OATP1B1, OATP1B3, P-gp and BCRP at clinically relevant concentrations, were discussed in the clinical section for convenient interpretation with regard to clinical exposure.

As daridorexant and its three major metabolites were detected in milk of lactating rats, information about presence of Daridorexant and its metabolites in the milk of lactating rats is indicated in the SmPC 4.6 as there are no data about human breastmilk, the effects on the breastfed infant, or the effects on milk production. There was no available data about placental transfer.

Daridorexant treatment induced in non-clinical species some effects at the level of the central nervous system that are mainly related to the sleep-promoting activity of daridorexant around the pharmacological dose range, but also signs of exaggerated pharmacology at supra-pharmacological doses (toxicity studies have identified clinical signs of sudden muscle weakness, reminiscent of cataplexy, upon positive stimulation in dogs as the main relevant target-related toxicity; cataplexy is a known phenomenon in dogs and with DORAs given to

animals in the morning and at high doses (Mahoney 2020, Mieda 2017)). These comprised lying down, partly closed eyes, slow breathing and reduced physical activity in rats; and decubitus, lying down, loss of balance, unsteady gait, clumsy movements, unable to stand and/or immobility in dogs. Hypersalivation, vomiting and/or regurgitation may occur reflecting poor palatability of oral formulations. These clinical signs were not adverse and were reversible upon cessation of treatment, and microscopic examination of the brain did not reveal any drug related anomalies. Neurological evaluation and microscopic examination of the brain did not reveal any treatment-related anomalies. Based on the high safety margins of ≥ 45 to human exposure at 50 mg/day, cataplexy is unlikely to occur in patients.

Regarding the relationship between orexin receptor antagonism at very high doses in non-clinical species and death related to gastrointestinal dysfunction, severe hypothermia and cardiovascular impairment, this is not considered clinically relevant as findings occurred at exposures (Cmax / AUC0-24) ≥ 170/450-fold the free human exposure at clinical dose of 50mg/day.

In fertility studies, no treatment-related adverse effect was observed on male rats up to 450 mg/kg/day, and in females only the number of implantations was decreased at 300 mg/kg, causing reductions in the number of live embryos and in gravid uterine weight and an increase in the pre-implantation loss (safety margins of >30 based on free AUCs). Decrease in fetal weight was seen in rabbits at 88-fold the clinical exposure (based on free AUC levels), with developmental NOAELs of 300 mg/kg/day in rats and 60 mg/kg/day in rabbits (≥46-fold free human AUC). Given margins, these finding were not considered of concern in humans. In the pre- and post-natal development study, there was no treatment-related effect on post-weaning development of F1 rats up to exposure levels 123-fold higher than those reached in patients (based on free AUC). The changes in body weight of F1 animals at the high dose level of 300 mg/kg were considered as non-adverse notably since the reported values lied within the historical control range, and because there was no consequence on the animals' clinical condition and sexual maturation.

Daridorexant (and major human metabolites) were not considered of genotoxic potential based on in vitro (negative Ames and chromosomal aberration assays) or in vivo (no induction of micronuclei in the polychromatic erythrocytes of the bone marrow of rats up to free Cmax 47-fold higher than human exposure) studies conducting according to ICHS2 guideline. No carcinogen potential is expected in humans.

Drug Discrimination studies followed by behavioural assessment of dependence through the withdrawal syndrome and self-administration test were performed at plasma exposure compatible/superior to inhibition of orexin receptor and decrease wakefulness in rats, and target clinical exposure in humans. In the GLP-compliant studies, daridorexant had no potential for self-administration in rats with a previous history of cocaine self-administration and did not generalize to the effects of zolpidem in rats trained to discriminate zolpidem from placebo. Furthermore, there were no changes in physiological, neurobehavioral, or locomotor activity parameters associated with the withdrawal syndrome after treatment discontinuation in rats. Taken together, based on animal studies, daridorexant did not reveal any sign indicative of physical dependence or drug abuse potential. Taken together, based on animal studies, daridorexant did not reveal any sign indicative of physical dependence or drug abuse potential. These data may support a low potential for abuse and dependence in humans at 50mg Daridorexant. In humans at the therapeutic dose of 50 mg, a dose-dependent drug-liking effect was seen lower than those at supratherapeutic doses of suvorexant 150mg or zolpidem 30mg, but similar at daridorexant supratherapeutic doses of 100 and 150mg. TEAEs suggestive of euphoria such as euphoric mood and feeling abnormal were less frequent at therapeutic and supratherapeutic doses of daridorexant compared to suvorexant and zolpidem. In addition, daridorexant showed fewer perceptual alterations and less impairment of cognitive function compared to zolpidem (at all doses of daridorexant) and suvorexant (at 50mg

of daridorexant only). Such clinical pattern may support a lower abuse potential of daridorexant at the dose of 50 mg compared to higher clinical doses of zolpidem and suvorexant.

Impurities were qualified in vitro and in vivo consistently with the ICH M7/M3/S3 recommendations.

Environmental risk assessment concluded that the prescribed usage of daridorexant film-coated tablets is at low risk. One transformation product (M-1, identified as ACT-774170) was considered a major transformation product during the water/sediment (OECD 308 study) and the structure and formula were reported in the Environmental Risk Assessment report, as this information might be relevant for water suppliers and monitoring issues. In addition the following statement had been added to section 6.6 of the SmPC: "Any unused medicinal product or waste material should be disposed of in accordance with local requirements."

2.5.7. Conclusion on the non-clinical aspects

An extensive data package of non-clinical studies has been provided. The primary pharmacodynamic studies provided adequate evidence that Daridorexant exerted its activity from the brain at clinically achievable concentration. Selective and insurmountable antagonism on OX1 and OX2 receptors was the primary mode of action on OX1 and OX2 receptors from *in vitro* studies. It can be concluded that Daridorexant induced surmountable and rapid sleep-wake effects, the overall non-REM and REM sleep times being increased without the wake period did not exceed the natural sleep period, without next-day residual effect, and as animals can be awakened and able to perform normally in various motor tasks.

The safety programme provided adequate evidence that Daridorexant would not induced adverse effects in humans at clinical doses.

Daridorexant does not represent a risk for environment.

The CHMP considers the following measures necessary to address the non-clinical issues:

The Applicant is asked to submit the final reports evaluating the long-term stability of daridorexant and its metabolites (ACT-776063, ACT776537 and ACT-1016-3307) in rat (BA-17.030) and rabbit (BA-18.023) plasma by June 2022.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

2.6.2. Clinical pharmacology

Daridorexant (ACT-541468), a new chemical entity, is a potent and selective dual orexin receptor antagonist that inhibits the actions of orexin neuropeptides at both OX1 and OX2 receptors.

The clinical pharmacologic program includes 18 completed Phase 1 studies, 3 Phase 2 and 2 Phase 3 studies. The following Phase 1 studies have been conducted and are described in Table 1. Additional information was collected from studies performed in adult patients as presented in Table 2 with two pivotal Phase 3 studies (Studies **ID-078A301** and **ID-078A302**).

A Population PK analysis of daridorexant was performed and comprised PK data from 17 studies (13 Phase 1, 2 Phase 2, 2 Phase 3 studies). Therein, 412 healthy subjects (9420 plasma concentrations) and 1486 adult and elderly subjects with insomnia (3207 plasma concentrations) were included in the analysis (1898 subjects providing 12,627 plasma concentrations in total).

Table 1: Clinical Pharmacology studies

Study [Doc No.]	Study objectives
Completed Clinical Pharmacology studies	
Single-ascending dose study	
AC-078-101 [D-15.653]	Investigation of PK, PD, safety, and tolerability, biocomparison of 2 different formulations, mass balance and metabolism, and absolute bioavailability in healthy male subjects
Single and multiple-ascending dose study	
AC-078-102 [D-16.386]	Investigation of PK, PD, safety, and tolerability in healthy subjects (A: multiple-ascending dose in adults; B: single-ascending dose in elderly; C: repeated nighttime administration in adults and elderly)
Intrinsic factor PK studies	
Ethnic sensitivity studies	
AC-078-105 [D-18.155]	Investigation of PK, PD, safety, and tolerability in healthy Japanese and Caucasian subjects
ID-078-116 [ID-078-116 CSR synopsis]	Investigation of PK, PD, safety, and tolerability in healthy adult and elderly Japanese subjects
Hepatic and renal impairment studies	
ID-078-112 [D-20.146]	Investigation of PK, safety, and tolerability in patients with mild, moderate, and severe hepatic impairment compared to healthy subjects
ID-078-115 [D-20.167]	Investigation of PK, safety, and tolerability in patients with severe renal impairment compared to healthy subjects
Extrinsic factor PK studies (drug-drug interactions and food effect)	
AC-078-103 [D-16.087]	Investigation of the effect of diltiazem on the PK, safety, and tolerability of daridorexant in healthy male subjects
AC-078-104 [D-17.098]	Investigation of the effect of food on the PK of daridorexant and investigation of the effect of daridorexant on the PK, safety, and tolerability of midazolam and 1-OH midazolam in healthy male subjects
ID-078-106 [D-18.191]	Investigation of daridorexant (at steady state) on the PK of rosuvastatin in healthy male subjects
ID-078-113 [D-19.130]	Investigation of the effect of food on PK, safety, and tolerability of daridorexant in healthy male subjects
ID-078-120 [D-20.123]	Investigation of the effect of the gastric pH-modifier famotidine and the moderate CYP3A4 inducer efavirenz on the PK, safety, and tolerability of daridorexant in healthy male subjects
Human PK and PD interaction studies	
ID-078-111 [D-19.051]	Investigation of PK/PD interactions, safety, and tolerability of daridorexant and ethanol in healthy male and female subjects
ID-078-114 [D-19.250]	Investigation of PK/PD interactions, safety, and tolerability of daridorexant and citalopram in healthy male and female subjects
Safety studies	
Human abuse potential	
ID-078-107 [D-20.026]	Investigation of the abuse potential, PK, PD, safety, and tolerability in healthy subjects
Next-day driving study	
ID-078-108 [D-20.076]	Investigation of next-day driving performance, PK, safety, and tolerability in healthy subjects
Respiratory safety studies	
ID-078-109 [D-20.058]	Investigation of nighttime respiratory safety, PK, PD, and tolerability in patients with COPD
ID-078-110 [D-20.040]	Investigation of nighttime respiratory safety, PK, PD, and tolerability in patients with OSA

Thorough QT study	
ID-078-117 [D-20.174]	Investigation of the effect of therapeutic and supratherapeutic doses of daridorexant on the QT interval in healthy subjects

Table 2: Phase 2 and Phase 3 studies of daridorexant in subjects with insomnia

Study ID [Doc No]	Study objectives	Number of randomized patients	Treatment duration	Treatment/dose (mg)	Type of control/blinding
Completed Phase 2 studies					
AC-078A201 [D-17.126]	Efficacy, PK, and safety of daridorexant in adult patients with insomnia disorder	360	29 days	Daridorexant 5 mg Daridorexant 10 mg Daridorexant 25 mg Daridorexant 50 mg Zolpidem 10 mg Placebo	Placebo, double-blind
AC-078A202 [D-17.127]	Efficacy, PK, and safety of daridorexant in elderly patients with insomnia disorder	58	5 treatment periods of 2 days each, separated by wash-out periods of 5-12 days	Daridorexant 5 mg Daridorexant 10 mg Daridorexant 25 mg Daridorexant 50 mg Placebo	Placebo, double-blind
ID-078A206 [D-20.201]	Efficacy, PK and safety of daridorexant in Japanese patients with insomnia disorder (dose confirmation study)	47	4 treatment periods of 2 days each, separated by wash-out periods of 5 to 12 days	Daridorexant 10 mg Daridorexant 25 mg Daridorexant 50 mg Placebo	Placebo, double-blind
Completed Phase 3 studies					
ID-078A301 [D-20.118]	Efficacy and safety of daridorexant in adult and elderly patients with insomnia disorder	930	3 months	Daridorexant 25 mg Daridorexant 50 mg Placebo	Placebo, double-blind
ID-078A302 [D-20.183]	Efficacy and safety of daridorexant in adult and elderly patients with insomnia disorder	924	3 months	Daridorexant 10 mg Daridorexant 25 mg Placebo	Placebo, double-blind

		Ongoing Phase 3 study			
ID-078A303 [D-20.184] (extension of ID-078A301 and ID-078A302)	Long-term safety of daridorexant Efficacy of daridorexant on subjective sleep parameters and daytime functioning (exploratory)	804	40 weeks (9 months) (12 months cumulative with study 301 and 302)	Daridorexant 10 mg Daridorexant 25 mg Daridorexant 50 mg Placebo	Placebo, double-blind

2.6.2.1. Pharmacokinetics

PK data were analysed using non-compartmental analysis (NCA) and population PK modelling.

Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters.

Population pharmacokinetic analysis was performed. Population parameters were estimated using the nonlinear mixed–effects modelling approach. The Fisher information matrix and log-likelihoods were generally estimated using stochastic approximation unless specified otherwise (linear approximations were employed in case numerical convergence could not be achieved with stochastic approximation).

Absorption

Following single or multiple-dosing of daridorexant at doses between 5 mg to 200 mg in healthy volunteers, absorption was reasonably rapid with Cmax approximately achieved at median Tmax of 0.75-2.75 hours. At 25 or 50 mg, median Tmax was generally achieved at 1-2h.

Absolute bioavailability

Absolute bioavailability (F) of daridorexant has been investigated in humans. In the 100 mg dose group of study **AC-078-101**, daridorexant showed an absolute bioavailability of 62.1%, with a 95% CI ranging from 51.6 to 74.8%.

Relative bioavailability / bioequivalence

Throughout the clinical development, three formulations were used, a soft gelatine capsule (Formulation B, strength at 25 mg), a hard gelatin capsule (Formulation A, strength at 5, 10, 25 and 100 mg), and a film-coated tablet (strength at 5, 10, 25 and 50 mg) intended for commercial use. However the commercial formulation (please refer to the Quality section) have never been produced yet.

Biocomparison Formulation B vs Formulation A

Biocomparison of formulation A and B was evaluated in the 25 mg dose group of Study **AC-078-101** in a crossover design. Results of this study indicated that compared to Formulation A, Tmax was shorter with a median difference (90% CI of the median) of −0.6 h (−1.09, −0.34), and Cmax was slightly higher with a ratio of geometric means (90% CI of the means) of 1.3 (1.06–1.53), AUC and t½ were similar.

Comparability Formulation A vs Tablet formulation

The comparability of the daridorexant film coated tablets and hard gelatine capsule was investigated trough dissolution profiles comparison.

Influence of food

The effect of a standardized high fat meal on daridorexant PK was investigated in healthy subjects using the hard capsule formulation (**Study AC-078-104**) or the tablet formulation (**Study ID-078-113**).

In Study **AC-078-104**, the effect of a high fat meal on daridorexant PK was investigated in 20 healthy volunteers who were administered a single oral dose of 25 mg daridorexant (hard capsule) in the fasted and the fed states. PK results indicated that administration of a high fat meal delayed Tmax by 1.88 h decreased Cmax by 24.3% and increase AUC0-24 by 3%.

In Study **ID-078-113**, the effect of a high fat meal on daridorexant PK was investigated in 20 healthy volunteers who were administered a single oral dose of 50 mg daridorexant (film-coated tablet) in the fasted and the fed states. PK results indicated that administration of a high fat meal delayed Tmax by 1.28 h decreased Cmax by 15.6% and AUC0-24 by 8.7%.

Gastric modifier

In Study **ID-078-120**, the effect of a gastric pH modifier on daridorexant PK was investigated in 24 healthy volunteers who were administered a single oral dose of 50 mg daridorexant (film-coated tablet) in the fasted and 3h following the administration of 40 mg famotidine. PK results indicated that administration of famotidine delayed Tmax by 0.5 h, decreased Cmax by 39% and increased AUC0-48 by 3%.

Distribution

Protein Binding

From samples collected during study **AC-078-101**, (Study B-16.001) using rapid equilibrium dialysis, the binding of daridorexant to human plasma proteins ranged between 99.7 and 99.9%.

Blood Plasma ratio

B/P ratio was approximately 0.64, indicating limit penetration of daridorexant into red blood cells.

Volume of distribution

Daridorexant Vss following an IV administration was estimated at 31 L suggesting low diffusion in tissue. This results was confirmed in studies **ID-078-112** and **ID-078-115** after accounting for F (Vz/F = 59 L to 66 L).

Elimination

Across clinical studies in healthy volunteers, after single oral (morning) administration of daridorexant as film coated tablets (25 or 50 mg), median half-life ranged from 6.2 to 11.7 h, and 8.5 h following night time administration. After repeated dose of daridorexant as HCG formulation (Formulation A) median half-life ranged from 5.6 to 8.5h.

In healthy volunteers, CL was estimated at 4.97 L/h following administration of daridorexant HCG. Based on the PopPK analysis a Michaelis-Menten elimination of daridorexant was considered with a Vm of 6.94 mg/h and a Km of 2.36 ng/mL.

The main elimination route was hepatic metabolism via CYP3A4 enzyme and excretion of metabolites in both urine and feces.

- Mass balance

In study **AC-078-101**, a single oral dose of a 14C-radiolabeled daridorexant microtracer given simultaneously with a single oral dose of daridorexant as hard capsule of 50 mg was administered in 8 healthy subjects.

The total recovery of radioactivity in this mass balance study was approximately 84.5% (CI95%: 78.3-90.6%). Approximately 56.6 % and 27.9% of the radioactive dose was recovered in feces and urine respectively, unchanged daridorexant was found at trace levels in both excretas (0.3% of cumulative dose excreted).

- Metabolism

Daridorexant was extensively metabolized. 9 metabolic pathways were identified with 3 are of major importance for excretion (63% of the dose) and 6 minor pathways, none of which contributed more than 3% to total dose excreted.

A total of 77 metabolites and parent daridorexant were identified in plasma, urine and feces. Five metabolic reactions had been identified first in plasma, leading to 30 metabolites, of which 23 were found in urine as well, and 17 also found in faeces.

In plasma, M3, M1, M10 and daridorexant accounted for 28.9%, 12.7%, 9.0% and 20.9%, respectively.

Based on in vitro investigations daridorexant was found to be predominantly metabolized by CYP3A4 (89%). M3 formation is predominantly mediated by CYP3A4.

- Interconversion

Daridorexant has an asymmetric carbon (S).

- Pharmacokinetic of metabolites

M1, M3 and M10 were investigated in several clinical trials (Study **AC-078-104**, **AC-078-105**, **ID-078-112**). None of them were found to be active. Estimated half-life of these metabolites ranged from 10 to 13h.

Based on in vitro investigations all these metabolites were found to be P-gp substrate and highly bound to plasma proteins.

Dose proportionality and time dependency

Daridorexant exhibit a dose proportional increase of exposure for doses between 25 to 50 mg. Across all the available clinical studies in both healthy and adult patients, daridorexant show no or minimal accumulation. Steady state is generally reached by Day 2-3.

Population-PK modeling

Additional to formal PK investigations in healthy volunteers (phase 1 studies) and in patients with insomnia disorders (phase 2 and 3 studies), the applicant has performed one population PK analysis in order to describe and identify sources of variability of daridorexant in patients.

The population PK analysis of daridorexant used pooled data from 17 clinical studies (13 Phase 1 [**AC-078-101**, **-102**, **-104**, **-105**; **ID-078-106**, **-107**, **-108**, **-111**, **-112**, **-113**, **-114**, **-115**, **-117**], 2 Phase 2 [**AC-078A201**, **AC-078A202**], and 2 Phase 3 studies [**ID-078A301**, and **ID-078A302**]). PK samples in insomnia patients (phase 2/3 studies) were sparsely taken (1 to 3 samples each), while in healthy volunteers (phase 1

studies) 6 to 28 post-dose samples were drawn each. Overall, the Population PK dataset (**Table 3**) included 12,627 concentration measurements (3207 and 9420 from patients and HV, respectively) from 1898 subjects (1486 patients and 412 Healthy volunteers) who received single and repeated-dose administration of daridorexant 5-200 mg in healthy volunteers and 5-50 mg in patients

Table 3. Number of subjects and PK samples by study included in the Population-PK analysis

Phase 1 studies

Study	101	102	104	105	106	107	108	111	112	113	114	115	117	Total
Number of subjects	30	42	20	33	20	69	60	21	24	19	24	14	36	412
Number of concentrations	741	846	660	870	160	2567	638	315	375	741	311	252	944	9420

Phase 2 and 3 studies

Study	A201	A202	A301	A302	Total Phase 2/3	Total (all phases)
Number of subjects	239	57	597	593	1486	1898
Number of concentrations	689	223	1165	1130	3207	12627

The dose-normalized next-morning concentrations from the Phase 2 and Phase 3 studies are shown in **Figure 3**. Daridorexant concentration-time profiles per dose group for the Phase 1 studies are shown in **Figure 4**.

Figure 3. Dose-normalized next-morning concentrations 9 – 10 h after evening administration (Phase 2 and Phase 3 studies)

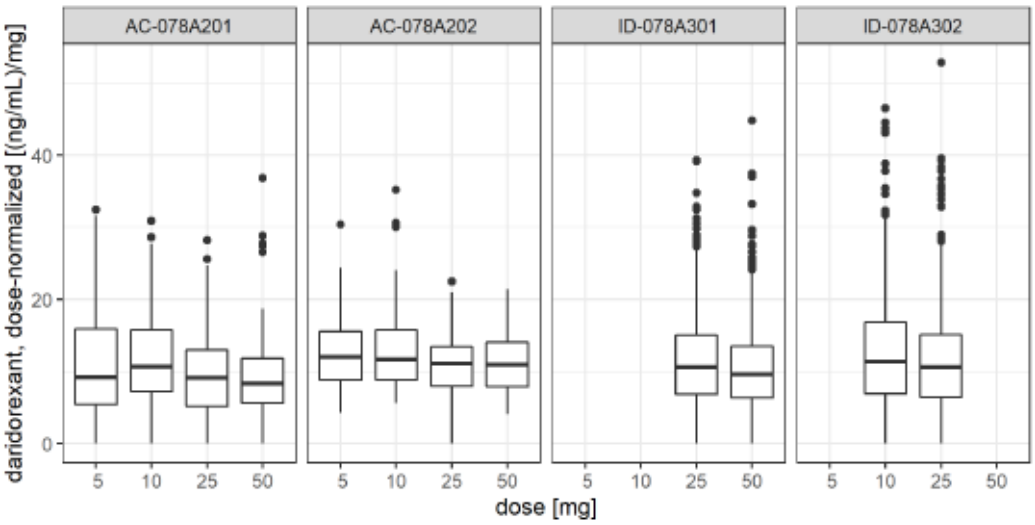
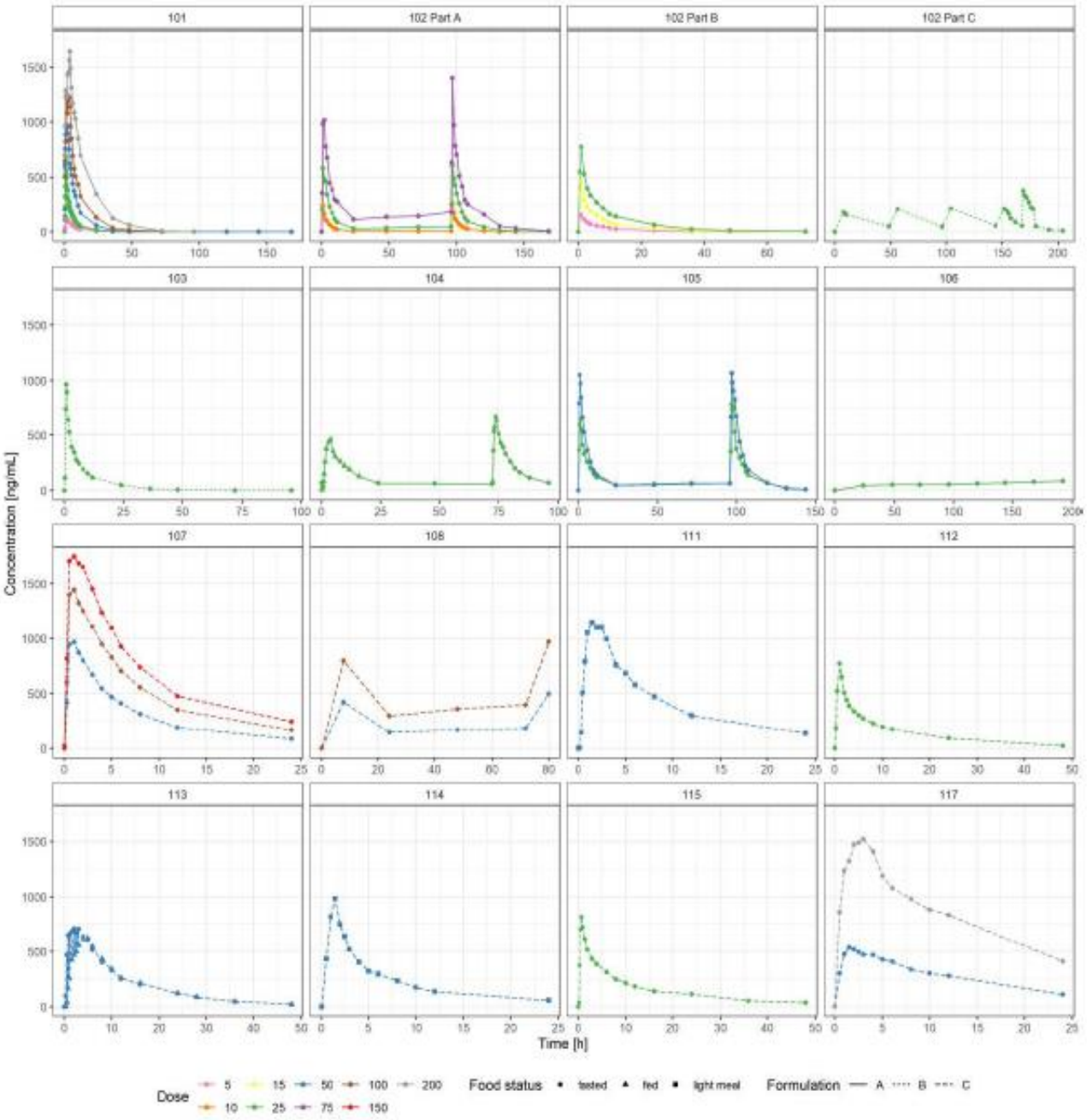


Figure 4. Average concentration vs time per dose group (Phase 1 studies)



The final population PK model was a two-compartment model with a bioavailability (F) reduced with higher doses, an absorption lag time (Tlag), a linear absorption (ka), and nonlinear elimination (Vm, Km) at high concentrations (> 800 ng/mL) reached with doses higher than 50 mg. IIV were included on all parameters. IOV was included to F and absorption parameters Tlag and ka.

Population and variability parameter estimates of the key models are presented in **Table 4** and **Table 5** respectively. The key goodness-of-fit (GOF) plots and VPC for the final model (model run 831) are shown in **Figure 5** to **Figure 8** and

Figure 9, respectively.

Table 4. PK parameter estimates of the selected models (population model parameters)

Parameter	Model 111		Model 176		Model 611		Model 615		Model 620		Model 623		Model 710		Model 831	
	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)
F	0.21	2.82	0.53	3.43	0.46	0.77	0.40	1.04	0.39	1.49	0.41	1.53	0.41		0.41	
Dose			-0.66	4.39	-0.58	2.81	-0.47	3.49	-0.48	3.92	-0.47	4.17	-0.47		-0.47	
t_{lag} (h)	0.25	3.17	0.29	0.06	0.28	2.33	0.25	2.29	0.41	7.85	0.41	7.94	0.41		0.41	
Food: fasted									-0.50	16.70	-0.51	16.50	-0.51		-0.51	
Food: fed									0.62	17.60	0.62	17.80	0.62		0.62	
k_a (1/h)	0.38	4.70	5.28	0.09	5.33	10.80	3.74	6.55	1.16	19.50	1.05	18.70	1.05		1.05	
Food: fasted									0.11	157.00	0.09	172.00	0.09		0.09	
Food: fed									-1.23	17.00	-1.19	16.90	-1.19		-1.19	
Morning admin.									0.96	12.40	1.05	11.00	1.05		1.05	
V_c (L)	1.12	10.40	24.40	2.51	21.10	2.58	16.50	1.85	14.20	1.49	14.60	1.42	14.60		14.60	
Lean body wt.											0.37	18.20	0.56	17.10	0.49	13.86
V_p (L)	11.10	3.64	19.40	4.75	16.30	3.38	12.20	2.15	13.60	2.08	13.70	1.91	13.70		13.70	
Fat mass											0.72	8.70	0.42	18.50	0.47	13.83
Q (L/h)	2.57	3.99	3.96	0.09	3.52	5.40	2.96	1.84	3.59	3.66	3.58	3.24	3.58		3.58	
Fat mass											1.21	8.57	1.39	8.76	1.47	6.48
V_m (mg/h)			4.81	6.91	4.51	2.36	5.95	0.97	5.72	1.06	6.94	1.13	6.94		6.94	
K_m (ng/mL)			0.96	0.00	1.07	2.25	1.96	2.28	1.95	2.34	2.36	2.20	2.36		2.36	
Age															0.30	6.87
ALP															0.34	10.54
Lean body weight											-0.12	79.30	-0.55	8.58	-0.20	25.95
CL (L/h)	1.57	3.61														

If no RSE value is reported, the population parameter was fixed rather than estimated.

Table 5. PK parameter estimates of the selected models (variability parameters)

Parameter	Model 111		Model 176		Model 611		Model 615		Model 620		Model 623		Model 710		Model 831	
	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)	Est.	RSE(%)
SD(F)	0.34	9.11	0.31	12.30	0.29	8.84	0.36	5.11	0.38	5.15	0.42	4.94	0.42		0.42	
SD(t_{lag})	0.28	8.55	0.23	7.38	0.25	6.80	0.35	4.62	0.28	12.80	0.26	14.40	0.26		0.26	
SD(k_a)	0.44	8.20	1.35	7.92	1.34	5.88	1.23	3.94	0.54	10.90	0.59	9.12	0.59		0.59	
SD(V_c)	1.04	7.60	0.31	9.56	0.27	7.69	0.27	5.75	0.19	6.94	0.17	7.26	0.17		0.17	
SD(V_p)	0.35	8.55	0.32	10.30	0.31	9.85	0.26	8.01	0.28	6.66	0.23	7.70	0.23		0.23	
SD(Q)	0.25	15.20	0.55	12.80	0.58	7.38	0.18	10.20	0.59	4.85	0.50	5.18	0.50		0.50	
SD(V_m)			0.27	13.00	0.24	7.94	0.06	18.50	0.08	13.20	0.09	11.90	0.09		0.09	
SD(K_m)			0.28	11.90	0.29	5.85	0.41	4.02	0.40	4.18	0.36	4.28	0.36		0.36	
SD(CL)	0.39	7.07														
IOV(F)			0.19	7.33	0.17	7.37	0.17	6.21	0.20	5.53	0.20	5.59	0.20		0.20	
IOV(t_{lag})									0.40	5.81	0.42	5.70	0.42		0.42	
IOV(k_a)									0.71	5.61	0.66	5.72	0.66		0.66	
Additive error	0.25	10.40	0.25	10.00	0.25	6.94	0.40	9.07	4.38	3.86	4.44	3.84	17.70	1.88	17.59	1.97
Multiplicative error	0.29	1.22	0.23	1.13	0.23	1.23	0.27	0.90	0.18	1.10	0.18	1.10	0.16	1.31	0.16	1.34

If no RSE value is reported, the population parameter was fixed rather than estimated.

Figure 5. Model diagnostics: observed vs predicted concentration (population and individual level)

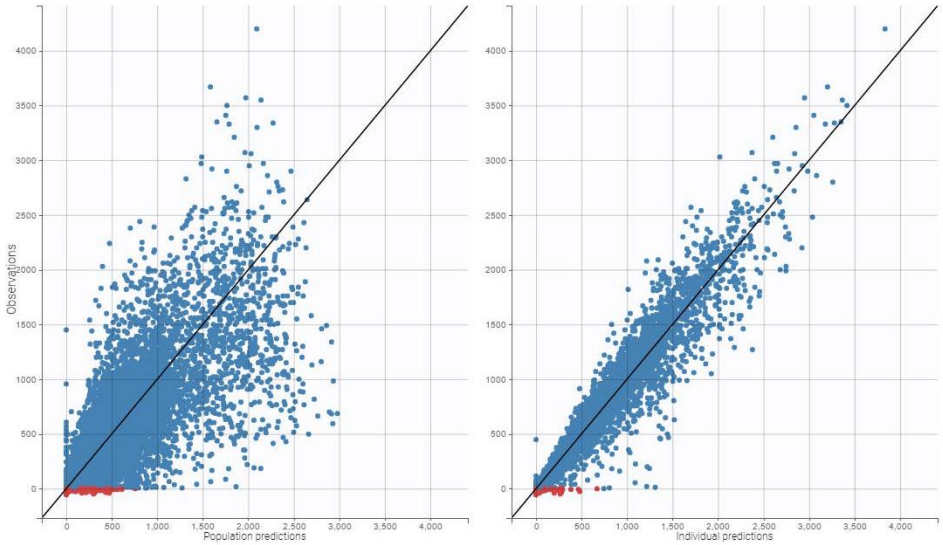
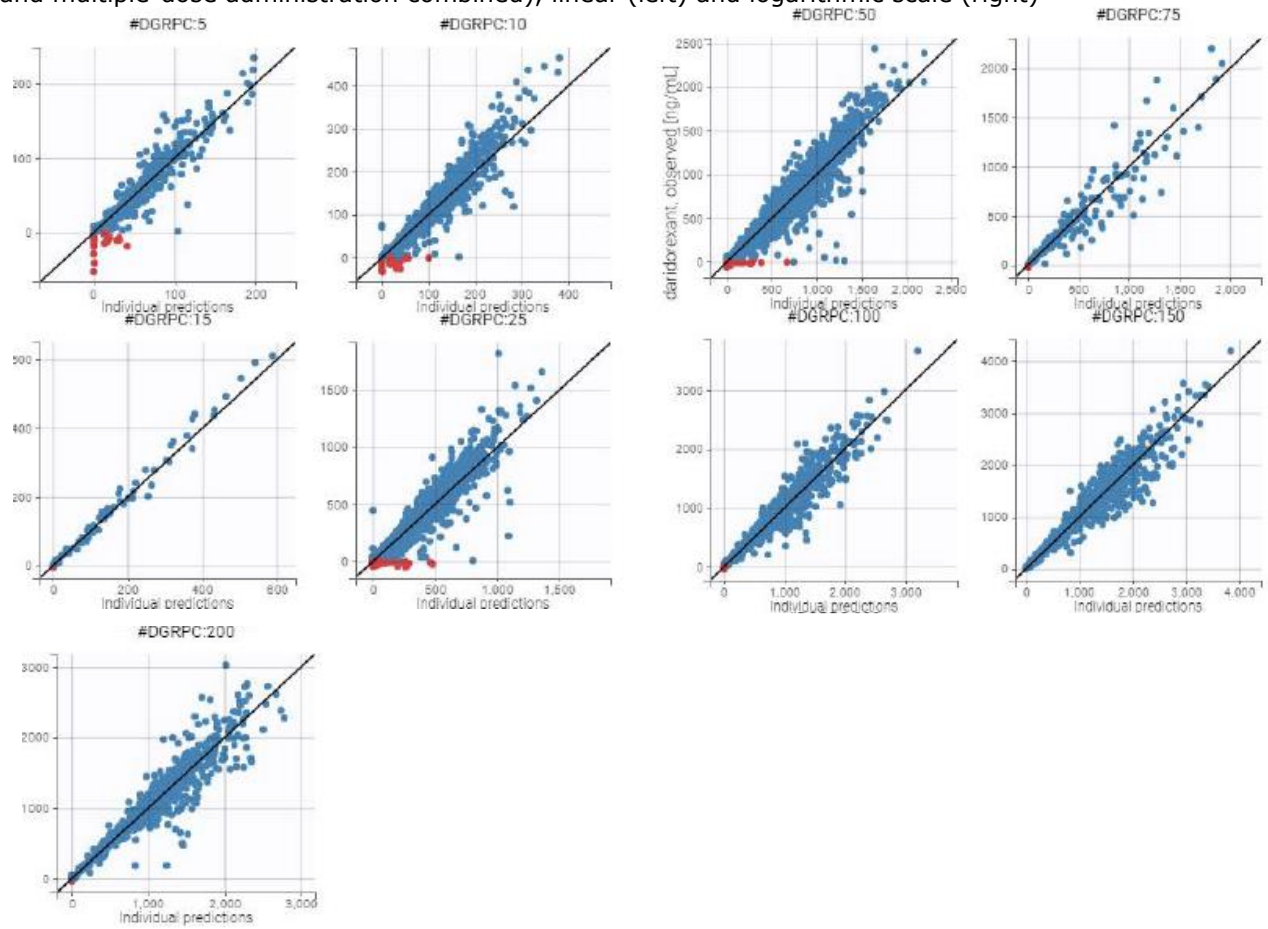


Figure 6. Model diagnostics: observed vs predicted concentration, individual level, stratified by dose (single- and multiple-dose administration combined), linear (left) and logarithmic scale (right)



Dose groups (mg) are indicated in the titles of the panels. Blue: data points, Red: censored data points, Line: line of identity. Units: ng/mL.

Figure 7. Model diagnostics: scatterplot of residuals

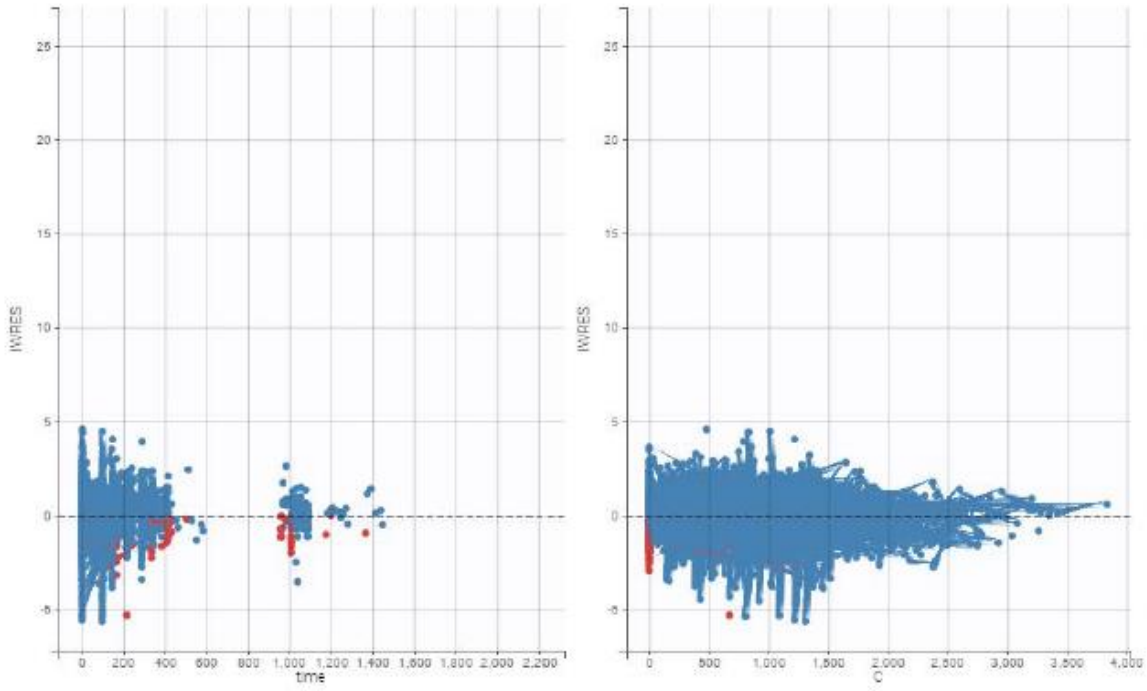


Figure 8. Model diagnostics: distribution of residuals

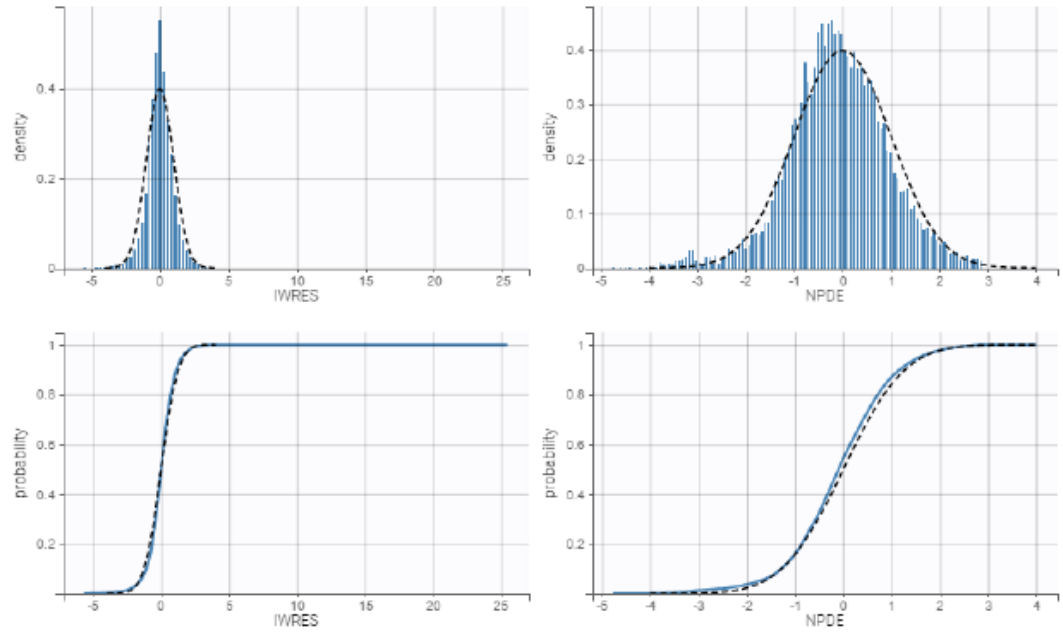
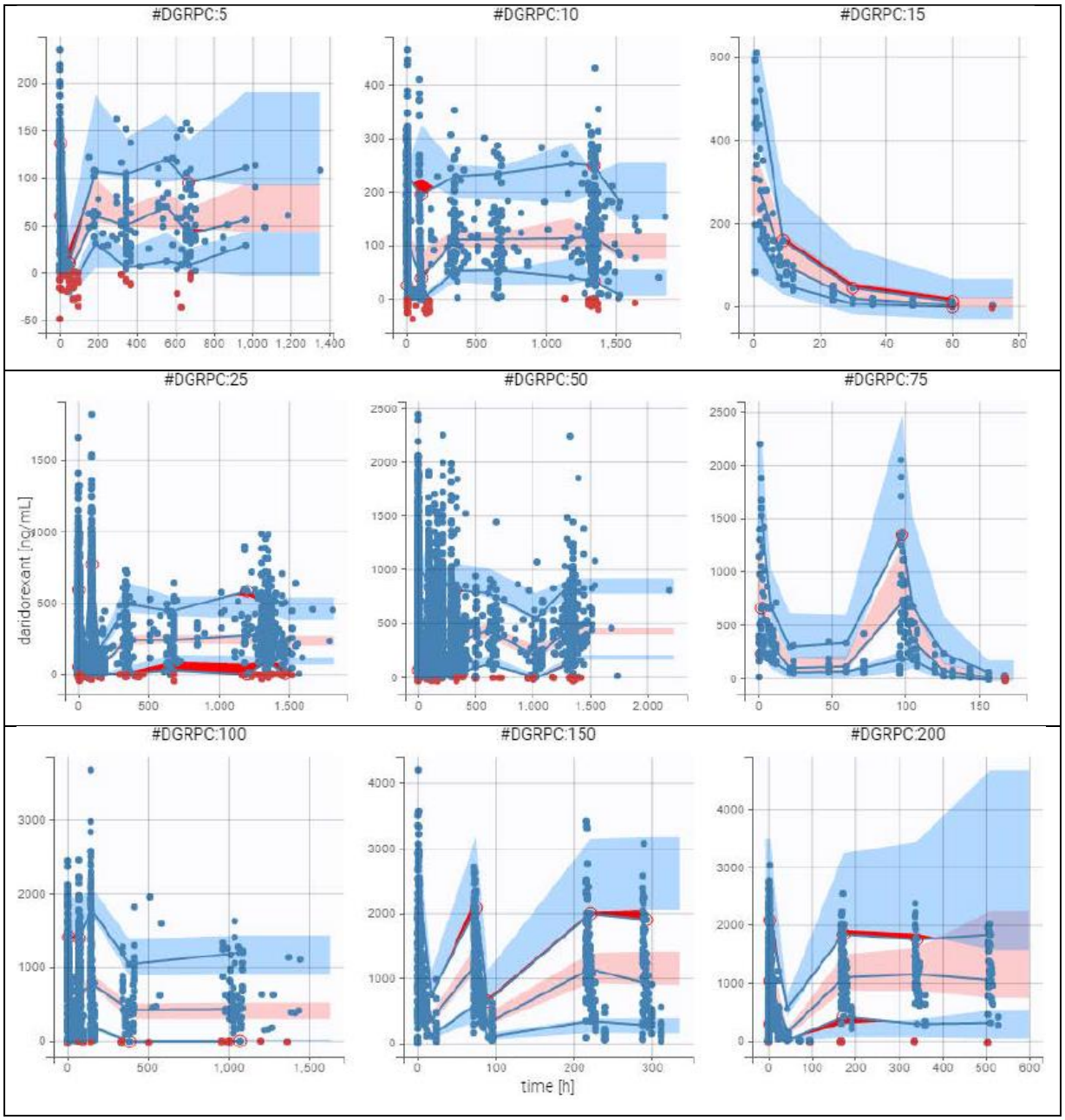


Figure 9. Visual predictive checks final structural model, stratified by dose (single- and multiple-dose studies combined)



Dose groups (mg) are indicated in the titles of the panels. Blue dots, observations; red dots, censored observations; blue lines, empirical 10th, 50th, and 90th percentiles; blue and pink areas, 90% range of simulated 10th, 50th, and 90th percentiles; red areas, empirical percentiles outside simulated percentile range.

Clinical relevance of effects of covariates / modality of use

To assess the clinical relevance of the covariates, model-based simulations were performed. Using the recommended 50 mg once daily (o.d) for 3 days, concentration-time profiles were derived from model predictions for a typical subject 60 years of age, with 20 kg fat mass, 55 kg lean body weight, and 60 U/L ALP. Covariates were varied to include different ages (23 and 74 years), fat masses (13.1 and 39.1 kg), lean body weights (36.2 and 69.1 kg), and ALP (38 and 99 U/L), corresponding to the 5th and 95th percentiles of the

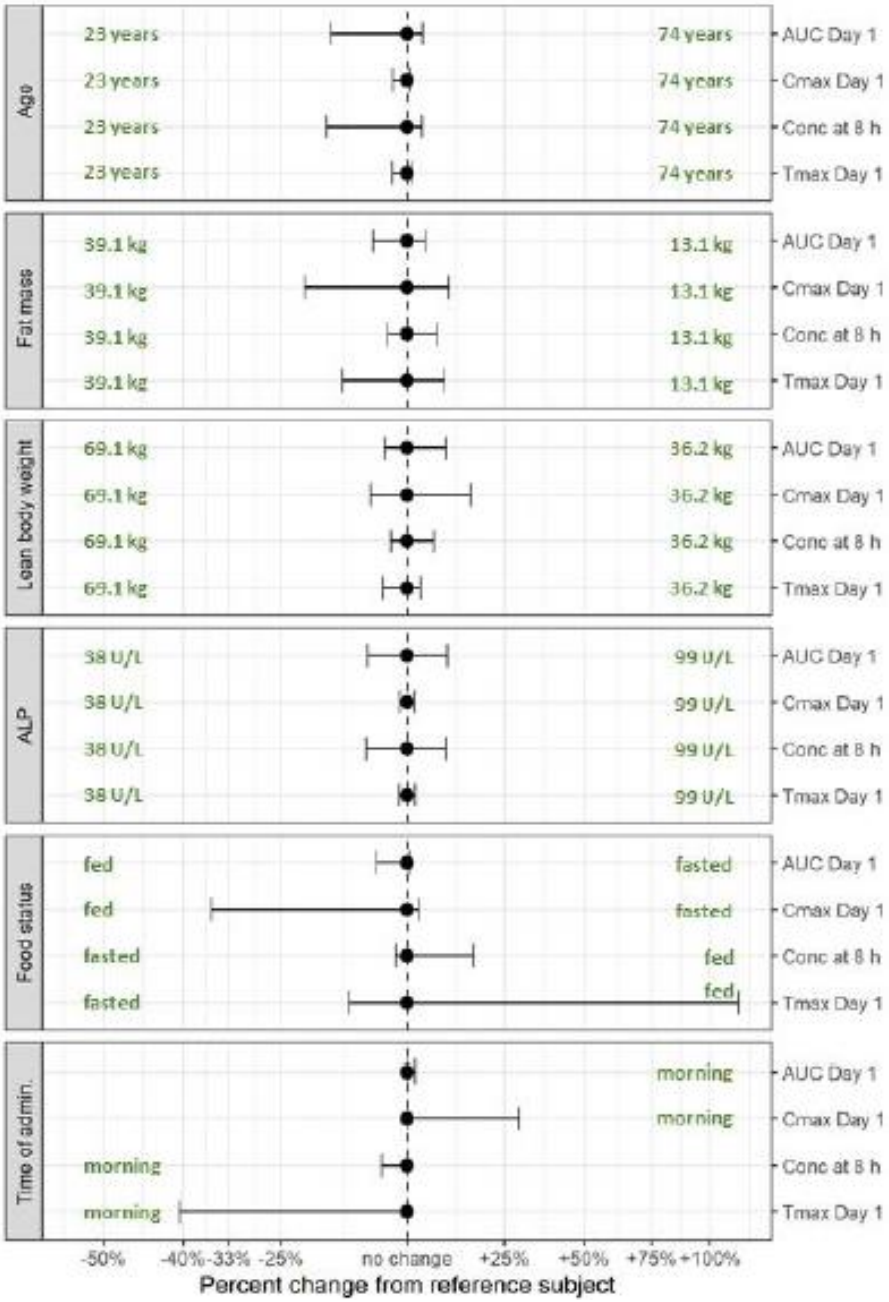
data. The model-based simulations were subsequently used to derive the exposure parameters C_{max}, t_{max}, AUC_{0-24h}, and C_{8h} summarised in **Table 6** and

Figure 10.

Table 6. Covariate effects on daridorexant exposure parameters on Day 1.

Covariate	Exposure metric	Covariate values			Absolute exposure			Relative exposure change (%)	
		Low (5th percentile)	Reference	High (95th percentile)	Low	Reference	High	Low	High
Age (years)	AUC_{0-24h}	23	60	74	6665.34	7930.70	8216.12	-15.95	3.60
Age (years)	C_{max}	23	60	74	790.44	817.00	822.43	-3.25	0.67
Age (years)	C_{8h}	23	60	74	317.44	381.10	394.70	-16.71	3.56
Age (years)	t_{max}	23	60	74	2.03	2.10	2.12	-3.33	0.95
Fat mass (kg)	AUC_{0-24h}	39.1	20	13.1	7339.46	7930.70	8266.69	-7.45	4.24
Fat mass (kg)	C_{max}	39.1	20	13.1	646.72	817.00	898.10	-20.84	9.93
Fat mass (kg)	C_{8h}	39.1	20	13.1	364.75	381.10	408.98	-4.30	7.31
Fat mass (kg)	t_{max}	39.1	20	13.1	1.81	2.10	2.29	-13.81	9.05
Lean body weight (kg)	AUC_{0-24h}	69.1	55	36.2	7535.79	7930.70	8678.55	-4.98	9.43
Lean body weight (kg)	C_{max}	69.1	55	36.2	752.13	817.00	946.72	-7.94	15.88
Lean body weight (kg)	C_{8h}	69.1	55	36.2	367.56	381.10	405.26	-3.56	6.33
Lean body weight (kg)	t_{max}	36.2	55	69.1	1.99	2.10	2.17	-5.24	3.33
ALP (U/L)	AUC_{0-24h}	38	60	99	7239.24	7930.70	8704.22	-8.72	9.75
ALP (U/L)	C_{max}	38	60	99	803.01	817.00	831.37	-1.71	1.76
ALP (U/L)	C_{8h}	38	60	99	347.10	381.10	417.32	-8.93	9.49
ALP (U/L)	t_{max}	38	60	99	2.06	2.10	2.14	-1.90	1.91
Food status	AUC_{0-24h}	fed	fasted	light meal/ uncontrolled	7398.71	7930.70	7969.83	-6.71	0.49
Food status	C_{max}	fed	fasted	light meal/ uncontrolled	523.15	817.00	839.62	-35.97	2.77
Food status	C_{8h}	light meal/ uncontrolled	fasted	fed	371.94	381.10	443.60	-2.41	16.39
Food status	t_{max}	light meal/ uncontrolled	fasted	fed	1.84	2.10	4.48	-12.38	113.33
Time of administration	AUC_{0-24h}	evening	evening	morning	7930.66	7930.70	8085.55		1.95
Time of administration	C_{max}	evening	evening	morning	816.98	817.00	1053.60		28.96
Time of administration	C_{8h}	morning	evening	evening	360.12	381.10	381.13	-5.51	
Time of administration	t_{max}	morning	evening	evening	1.25	2.10	2.10	-40.48	

Figure 10. Covariate effects on daridorexant exposure parameters with a dose of 50 mg (percent change)



Simulations indicated that the largest effects on daridorexant exposures were seen in food status, time of administration and fat mass composition. Food status fed results in a decrease of C_{max} by 36%, a prolongation of t_{max} more than twice (4.48 h vs 2.1 h), a 16% higher C_{8h}, and 7% lower AUC_{0-24h} compared to light meal/ uncontrolled. Morning administration compared to evening administration showed an increase of C_{max} by 29% and a shortening of 40% in t_{max} (0.85 h). In subject with a fat mass, C_{max} was 21% lower, while T_{max} was slightly shortened by about 14% and AUC_{0-24h} only reduced by about 7.5% compared to that observed for a typical subject of 20 kg fat mass.

All others subject-specific characteristics, including age, food status fasted, lean body weight and ALP, showed no relevant difference (i.e., <20%) in exposure parameters AUC, t_{max}, C_{max}, and C_{8h} compared to a typical subject.

Overall, given the fact that morning administration is not relevant clinically (with regards to the indication) and that high-fat high-calorie food is an extreme-case scenario unlikely to occur in clinical practice, the applicant's recommendation that daridorexant is to be taken in the evening / night (within 30 minutes before going to bed) is endorsed.

Special populations

- Hepatic impairment

A formal dedicated PK study (**ID-078-112**) was performed in subjects with impaired hepatic function compared to matched-control healthy subjects to investigate the effect of mild and moderate hepatic impairment on the PK of a single 25-mg dose of daridorexant.

Results of the formal dedicated PK study indicated that the daridorexant Cmax decreased by 50% and 58% in mild and moderate hepatic impaired subjects compared to healthy subjects. Similarly, daridorexant AUC0-inf decreased by 50% and 26%, in mild and moderate hepatic impaired subjects. In contrast, half-life was found 1.6-fold (11h) in mild and 2-fold increased (19h) in moderate compared to healthy subjects.

The unbound fraction of daridorexant appears to be affected by increasing hepatic impairment with approximately an increase of Cu/C by 2-fold in moderate hepatic impaired subjects compared to healthy subjects. Therefore for moderate hepatic impairment subjects a dose of 25 mg is recommended.

Daridorexant has not been studied and is not recommended in subjects with severe hepatic impairment. (Child-Pugh score ≥ 10).

- Renal impairment

A formal dedicated PK study (**ID-078-115**) was performed in subjects with impaired renal function compared to matched-control healthy subjects to investigate the effect of severe renal impairment on the PK of a single 25-mg dose of daridorexant. PK results show that renal impairment have no effect on daridorexant PK, this was expected, provided the results from the mass balance study.

Therefore no dose adjustment are recommended in patients with any level of renal impairment.

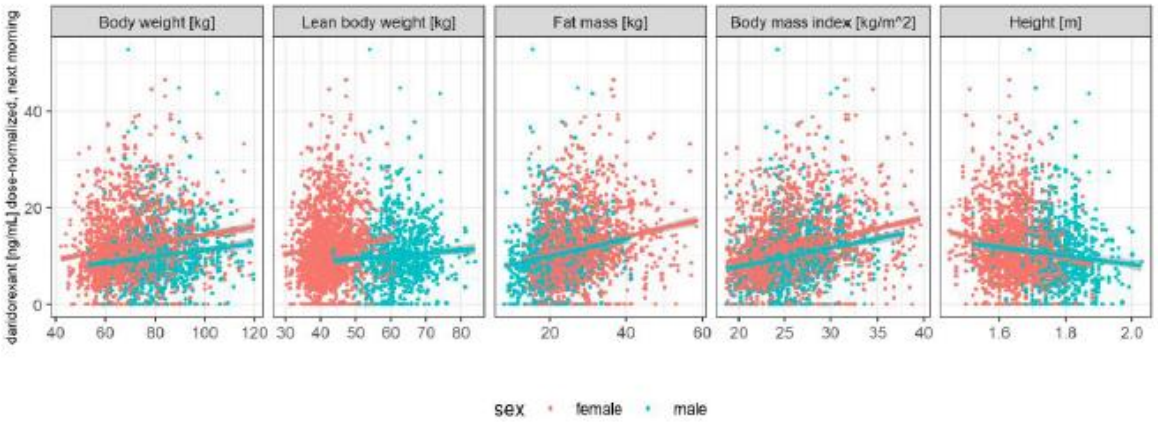
- Gender

No formal PK study to investigate the effect of gender on the PKs of daridorexant has been performed. Besides, the effect of gender on the PKs of daridorexant was investigated in patients based on the Population-PK approach. Among the 1898 included in the dataset, both sexes were represented with more female (n= 1155; 60.9%) than male (n = 743; 39.1%).

In Phase 3 studies in patients with insomnia disorders, next-morning plasma concentrations tended to be slightly higher in females than in males. However, these differences disappeared once body composition (lean body weight and fat mass) was accounted for, which suggest that these two body size descriptors capture the sex difference (

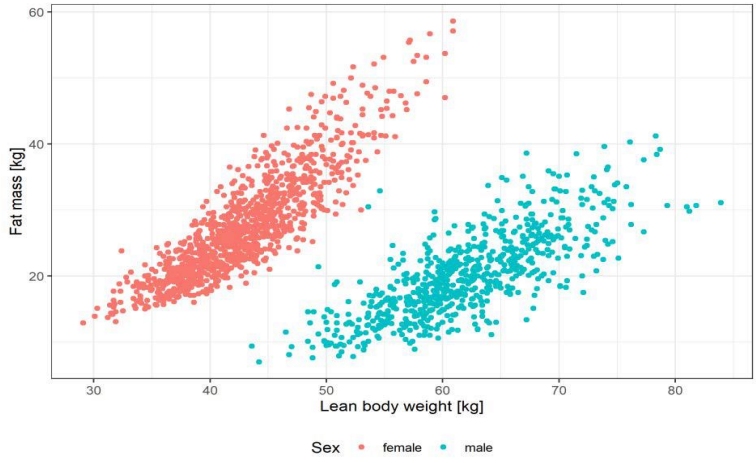
Figure 11). The relationship, i.e., the slope of the linear regression fit, appears strongest in fat mass and BMI. Most relationships show a difference between the sexes (red and turquoise lines) while fat mass shows very similar regression fits for the sexes.

Figure 11. Morning concentrations (dose-normalized) after evening administration vs body size descriptors in patients with insomnia disorder



Assessing body composition, the graphical display of individual fat mass vs lean body weight shows a complete separation of sexes, suggesting that these two body size descriptors capture the sex difference (**Figure 12**).

Figure 12. Fat mass vs lean body weight by sex in patients with insomnia disorder



Based on the Population-PK analysis, when body composition is included in the model (lean body mass was found to be significant covariate on Vc and elimination parameter Km; while body fat mass was associated to Vp and Q), gender was no more identified as a significant covariate influencing PK parameters of daridorexant. Overall, based on these results, the applicant concluded that no adjustment dosing regimen is warranted based on sex. This conclusion is agreed.

- Race

Race effect was investigated in several clinical studies (**AC-078-105**, **ID-078-116**, **ID-078A206**).

A formal dedicated From Study **AC-078-105**, in Japanese subjects, Cmax and AUC0-24h exposure (at 50 mg) were higher by 1.4- and 1.3-fold, respectively compared to Caucasian subjects. However, in a subsequent study (**ID-078-116**, please refer to next section), the daridorexant PK in Japanese subjects were similar to the PK observed in Caucasian subjects in previous studies. In the Japanese Phase 2 study in subjects with insomnia (**ID-078A206**), mean residual morning concentrations at 9−10 h post dose were slightly lower than those observed in the global Phase 2 and Phase 3 program, with no indication of next-day residual effects at any dose.

Therefore there are no evidence that race have a clear effect on daridorexant PK at the 25 mg or the 50 mg dose.

Among the 1898 subjects included in the dataset, a majority of patients n= 1646 (86.7%) are White Caucasian, n= 175 (9.2%) are Black or African American, n= 36 (0.02%) are Asian, n=17 (0.009%) are Japanese and 24 are other race or not classified.

Based on the Population-PK approach, the effect of race/ethnicity on daridorexant PK was investigated and found not to be a statistically significant covariate influencing PK parameters of daridorexant. Given the PK data available, this conclusion could only be endorsed for Black or African American (compared to the reference Caucasian race). For other races, very limited data are available to allow for valid conclusions. Overall, the recommendation to no adjust the dose for Black or African American patients (compared to Caucasian) could be agreed. Dosing recommendations in other races (Asian, Japanese) should be rather based on NCA results from formal studies.

- Weight

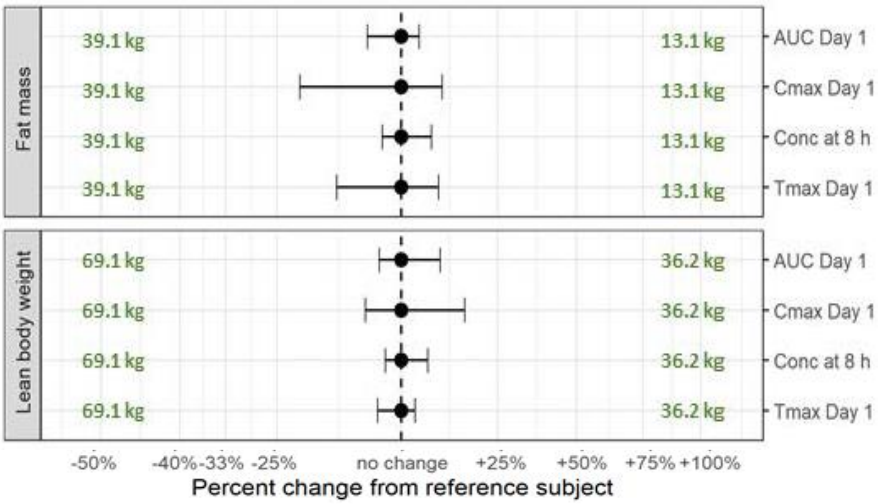
No formal studies were conducted to investigate the effect of BW on daridorexant PK.

Based upon the Population-PK analysis, the effect of BMI and body weight as well as lean body weight (LBM) and fat mass (FM) were explored. LBM and FM were found to be a statistically significant covariates on volumes of distribution (Vc and Vp), inter-compartmental drug transfer Q, and elimination: Vc and Vp increase with higher LBM and FM, respectively, while Km decrease (increase on elimination) with higher LBM. Despites this statistically significance of LBM and FM on PK parameters, this does not result on a clinically significant impact on the exposure parameters of daridorexant. Indeed, model-based simulations (50-mg once daily regimen) for a typical subject [60 years of age, 20 kg FM, 55 kg LBM, and 60 U/L ALP] using different LBM (from 36.2 to 69.1 kg) and FM (13.1 and 39.1 kg) values corresponding to the 5th and 95th percentiles of the data, show that all LBM and FM effects on C_{max}, AUC, t_{max}, and residual next-morning concentrations C_{8h} metrics were <20% difference from the reference, excepted for the upper limit of FM (39.1 kg) which was associated to a decrease on C_{max} of 21% (border line influence) compared to that observed for a typical subject (**Table 6** and

Figure 13). It should be noted also that subsequent add of BW and BMI as covariates (assessed by graphical analyses and statistical criteria) did not result on additional relevant significance.

Based on these findings, a flat dosing regimen (irrespective to BW) is proposed for daridorexant. This conclusion could be endorsed.

Figure 13. Lean body mass and fat mass effects on exposure parameters with a dose of 50 mg (percent change)



- Age / Elderly

PK of daridorexant in elderly (> 65 years) was evaluated after single and repeated administration in healthy subjects during two phase 1 studies (MAD and SAD parts of **AC-078-102** and dedicated study **ID-078-116** in elderly Japanese subjects), but also in patients with insomnia in Phase 2 and 3 studies. The impact of age was further investigated as a covariate in the Population-PK analysis of daridorexant.

From Study **AC-078-102**, at a 25 mg dose, half-life was increased by 60%, and both Cmax and AUC increased by 30% in elderly subjects compared to young subjects.

From Study **ID-078-116**, the PK parameters (Cmax and AUC) were generally similar except half-life which was approximately 2-fold greater in elderly subjects compared to non-elderly subjects.

From Phase 2 and 3 studies, in line with observations from Phase 1 study (AC-078-102) in healthy volunteers, next-morning plasma concentrations ($C_{8\text{-}9h}$) in patients with insomnia disorders which received the recommended 50 mg dose were found 28% (557 /433 ng/mL =1.28;) and 27% (591 /465 ng/mL =1.27) higher elderly patients compared to those observed in younger adults in Phase 2 and Phase 3, respectively.

Population-PK approach

- The median age (min; max) of subjects included in the population dataset was 54 years (18; 88). However, among the 1898 subjects included, the number of elderly subjects and PK samples included in the different subgroups of age: [65 to 74 years], [75 to 84 years] and >85 years old is not known.

Age was investigated as a continuous covariate in the context of the population-PK analysis, wherein it was identified as a statistically significant covariate and retained in the final model for daridorexant on elimination parameter Km $[(Age/60)^{0.3}]$ with exponent estimated to 0.3 (RSE =6.87%). This suggests that patients with higher age are expected to have higher Km (i.e., drug elimination decreases). However, based on model-based simulations, this finding did not result on a clinically significant difference on the exposure parameters of daridorexant (C_{max}, $AUC_{0\text{-}24h}$, t_{max}, and $C_{8\text{-}9h}$). Indeed, when varying age from 23 to 74 years (corresponding to the 5th and 95th percentiles of the data), all effects are found <20% difference from a typical subject (aged 60 years-old). The more pronounced difference is predicted in subject aged 23 years, with $AUC_{0\text{-}24h}$ and C_{8h} to be 16% and 16.7% lower than those in a typical subject of 60 years. Further, when taking extremes 5th and 95th

percentiles of age values, the Population-PK model predicted that, after taking 50 mg daridorexant at bedtime, a 74-year-old subject would have a residual $C_{8\text{-}9h}$ morning 20% higher than a 23-year-old subject.

Based on all the above, the applicant concluded that dose adjustments in elderly patients are not warranted. Further investigations regarding PKs of daridorexant in elderly were requested and provided by the applicant during the responses to the D120 and D180 LoQ. These data overall support that no significant PK change is to be expected in the elderly population. Therefore, the applicant's dosing recommendation in elderly patients can be supported although it should be emphasized that limited PK data are available in patients > 75 years of age. A specific statement reflecting this point has been included in section 5.2. of the SmPC.

Interactions

Effects of other drugs on daridorexant

Daridorexant was not identified as BCRP or P-gp substrates. Only metabolites M1 and M10 transports were mediated by P-gp.

Daridorexant clearance is mostly dependent on CYP3A4, accounting for 89% of metabolic turnover based on nonclinical experiments [B-15.073]. CYP3A4 inhibitors and inducers are expected to modify daridorexant PK.

CYP Daridorexant administered at 25 mg induced a 1.4- and 2.4-fold increase in Cmax and AUC0-∞ respectively when co-administered with the moderate CYP3A4 inhibitor diltiazem (240 mg, at steady state). It is expected an even more marked inhibition of CYP3A4 following strong CYP3A4 administration at the therapeutic dose of 50 mg.

Co-administration with the moderate CYP3A4 inducer efavirenz (600 mg) at steady state, daridorexant 50 mg Cmax and AUC0-∞ decreased by 35% and 61%, respectively.

Based on in vitro results, daridorexant induction potential for CYP2C9 and CYP2B6 could not be excluded. No in vivo study to assess daridorexant induction potency for CYP2C9, and CYP2B6 has been provided.

The main metabolites M1 and M3 induction potential was only evaluated for CYP2B6 and 1A2. Both metabolites were inducers of CYP2B6 but not of CYP1A2. No investigation was conducted for CYP2C9 (e.g. warfarin or tolbutamide as probe substrate).

SSRI Coadministration of citalopram 20 mg, a SSRI, did not affect daridorexant PK at 50 mg (study ID-078-114).

Alcohol Co-administration of daridorexant 50 mg and ethanol as an i.v. infusion led to a prolonged tmax of daridorexant of 1.25 h. The other PK parameters, Cmax, AUC0-∞, and t½, were unchanged (study ID-078-111).

Effect of daridorexant on other drugs

CYPs Daridorexant and its metabolites M1, M3, and M10 inhibition potential for CYPs isoforms recommended per EMA guideline was, in general, adequately conducted. In vitro, daridorexant was identified as potential inhibitor of CYP2C9, CYP2C19 and CYP3A4 which latter inhibition was time-dependent. Only daridorexant inhibition for CYP3A4 was investigated in vivo in study AC-078-104 with midazolam following a two fold-lower dose than the recommended (i.e. 25 mg versus 50 mg). Inferences of expected inhibition of CYP3A4 by daridorexant following 50 mg oral dosing was assessed by PBPK model, which is not endorsed due to unsufficient qualification.

The PK results showed no significant impact on midazolam exposure (GMR = 1.1 and 90% CI 1.03 - 1.19) but a trend toward an increase in Cmax (GMR = 1.2 and 90% CI 1.07 – 1.34). Inferences of expected inhibition of CYP3A4 by daridorexant following 50 mg oral dosing addressed by a PBPK model is not endorsed. The clinical results with midazolam should be reflected in SmPC, in particular the trend toward a Cmax increase following 25 mg daridorexant. Effect on CYP3A4 substrate following 50 mg daridorexant is thus uncertain.

In vitro, daridorexant induced CYP3A4 and CYP2C9. It may be inducer of CYP enzyme regulated by PXR pathway including CYP2C9 in vivo. No clinical study with CYP2C9 was submitted to assess the clinical relevance of the in vitro results.

Transporters In vitro investigations on daridorexant potential inhibition for transporters were conducted in agreement with EMA interactions guideline. Daridorexant inhibition for P-gp or BCRP in vivo cannot be excluded with estimated IC50 of 24 µM (digoxin as substrate) for P-gp and 3 µM for BCRP.

Only daridorexant inhibition potential for BCRP was further investigated in the clinical DDI (study 78-106) where co-administration of 25 mg daridorexant with rosuvastatin, BCRP probe substrate. The result of this study show daridorexant following 25 mg oral dosing did not affect rosuvastatin PK. The impact of daridorexant at the 50 mg therapeutic dose was addressed by PBPK which model is not considered sufficiently qualified.

No in vivo investigation was performed for P-gp inhibition with adequate probe substrate (e.g. dabigatran).

Alcohol Co-administration of daridorexant 50 mg and ethanol as an i.v. infusion led to a prolonged tmax of daridorexant of 1.25 h. The other PK parameters, Cmax, AUC0-∞, and t½, were unchanged (study ID-078-111).

2.6.2.2. Pharmacodynamics

Mechanism of action

Daridorexant, also known as ACT-541468, is a specific and potent DORA acting on both orexin 1 (OX1) and orexin 2 (OX2) receptors. The orexin neuropeptides (orexin A and orexin B) act on orexin receptors to promote wakefulness. It could therefore be hypothesized that daridorexant will act on sleep maintenance and on sleep latency in contrast with hypnotics such as benzodiazepines and z-drugs which act mainly on sleep latency.

Exposure-response analysis for efficacy

Data from the two pivotal B/R Phase 3 studies **ID-078A301** and **ID-078A302** were used.

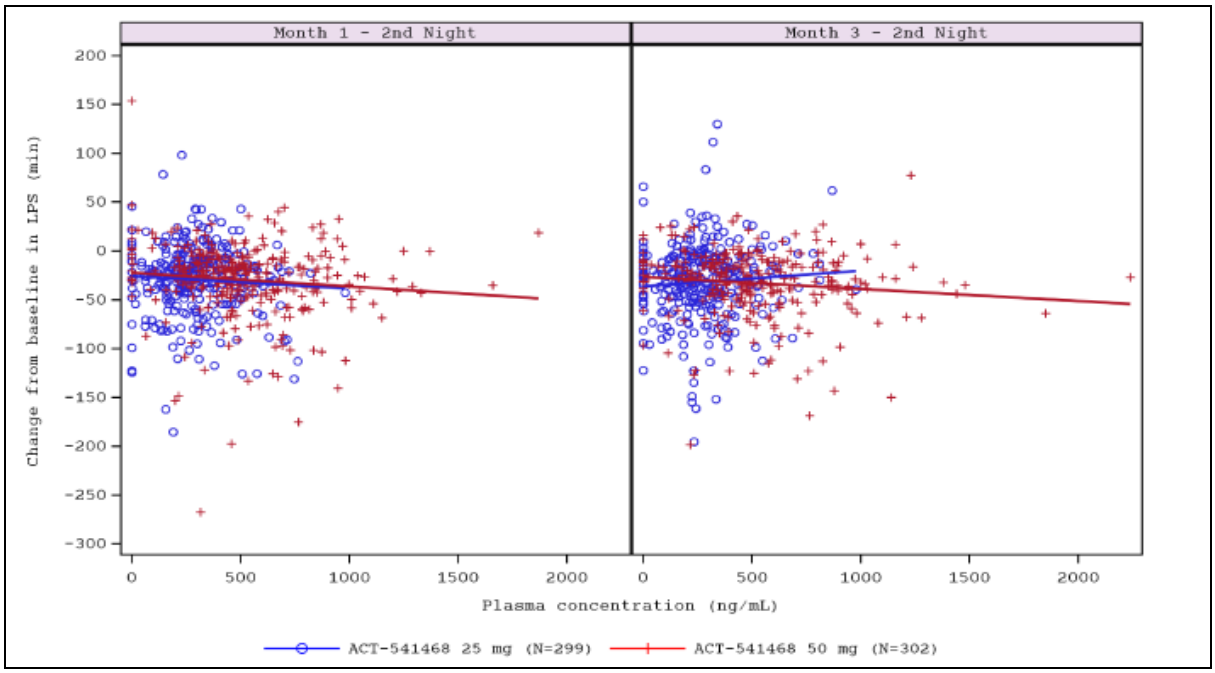
The observed steady state (Month 1 and Month 3) daridorexant plasma concentrations measured in the morning 9-10 h ($C_{9\text{-}10h}$) was the exposure PK metric. To assess efficacy, the changes from baseline to month 1 and month 3 for the primary [Latency to persistent sleep (LPS and Wake after sleep onset (WASO)], secondary [Total sleep time (sTST) and Insomnia Daytime Symptoms and Impacts Questionnaire (IDSiq) sleepiness/tiredness domain score] efficacy endpoints (determined by PSG), with additional clinical endpoints [Visual analog scale (VAS) for quality of sleep, depth of sleep, daytime alertness and daily ability to function] were analyzed. These clinical endpoints are qualified as clinically valid / pertinent for the purpose (please refer to clinical efficacy report).

No population PKPD modelling was developed. Graphical scatter plots with a linear regression were provided to link exposure parameter $C_{9\text{-}10h}$ to the efficacy endpoints (LPS and WASO, sTST, and IDSIQ sleepiness/tiredness domain score). From the provided plots (

Figure 14 and

Figure 15), no correlation between the change from baseline in the selected efficacy variables and daridorexant C9-10h from both 25 and 50 mg (study ID-078A301) or 10 and 25 mg (study ID-078A302) was observed. However, it should be noted that the estimated regression coefficients β and error terms ε for the different relationships were not provided or could not be found.

Figure 14. Change from baseline of LPS [min] at each time point vs plasma concentration of daridorexant [ng/mL] in study ID-078A301 (25 and 50 mg) and ID-078A302 (10 and 25 mg)



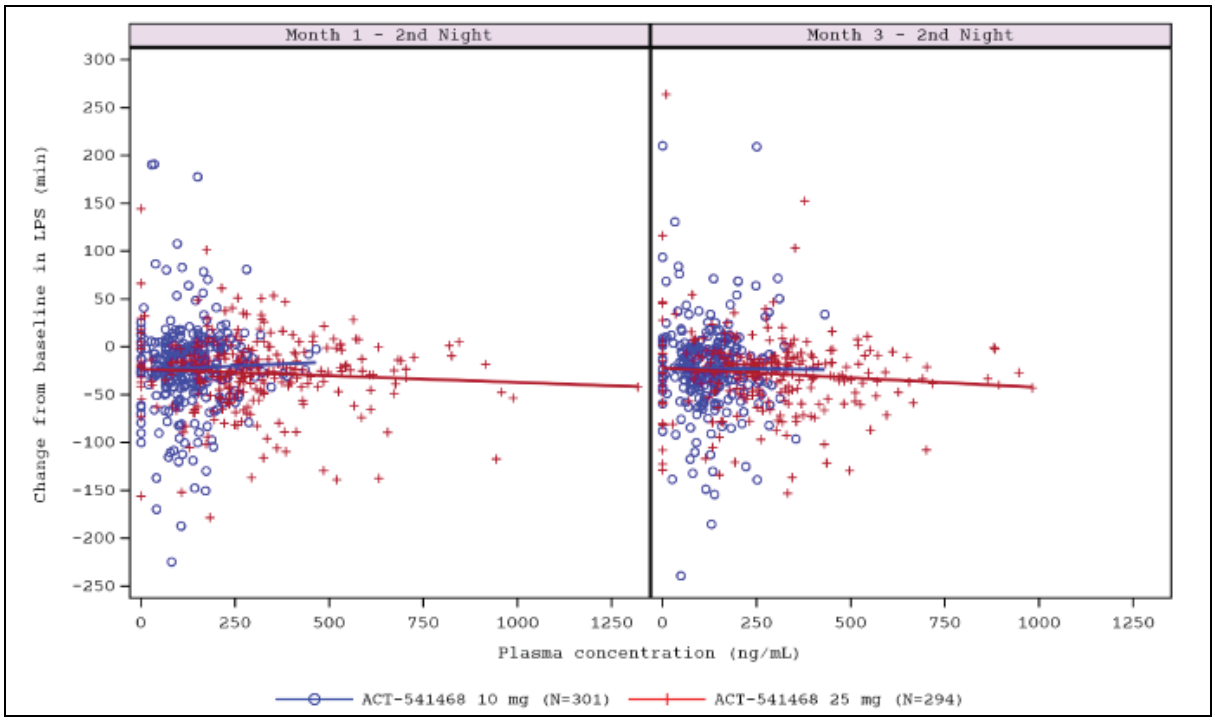
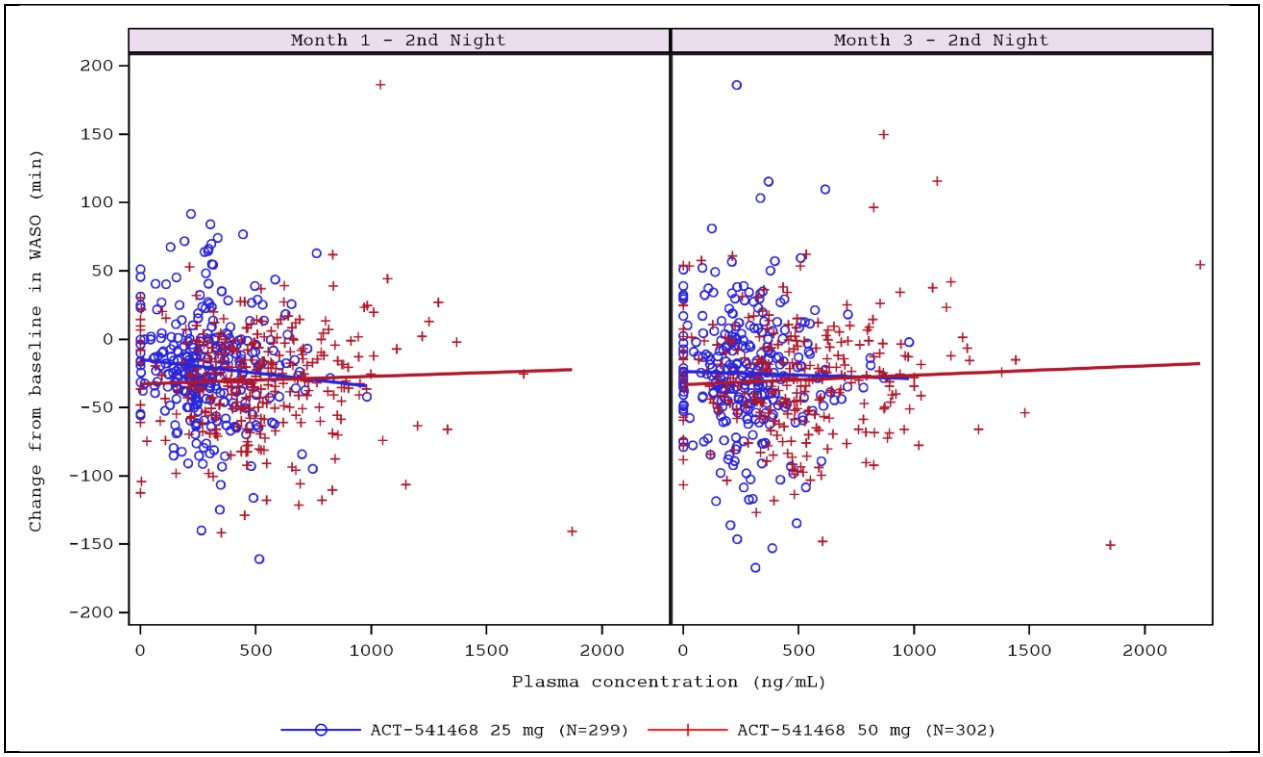
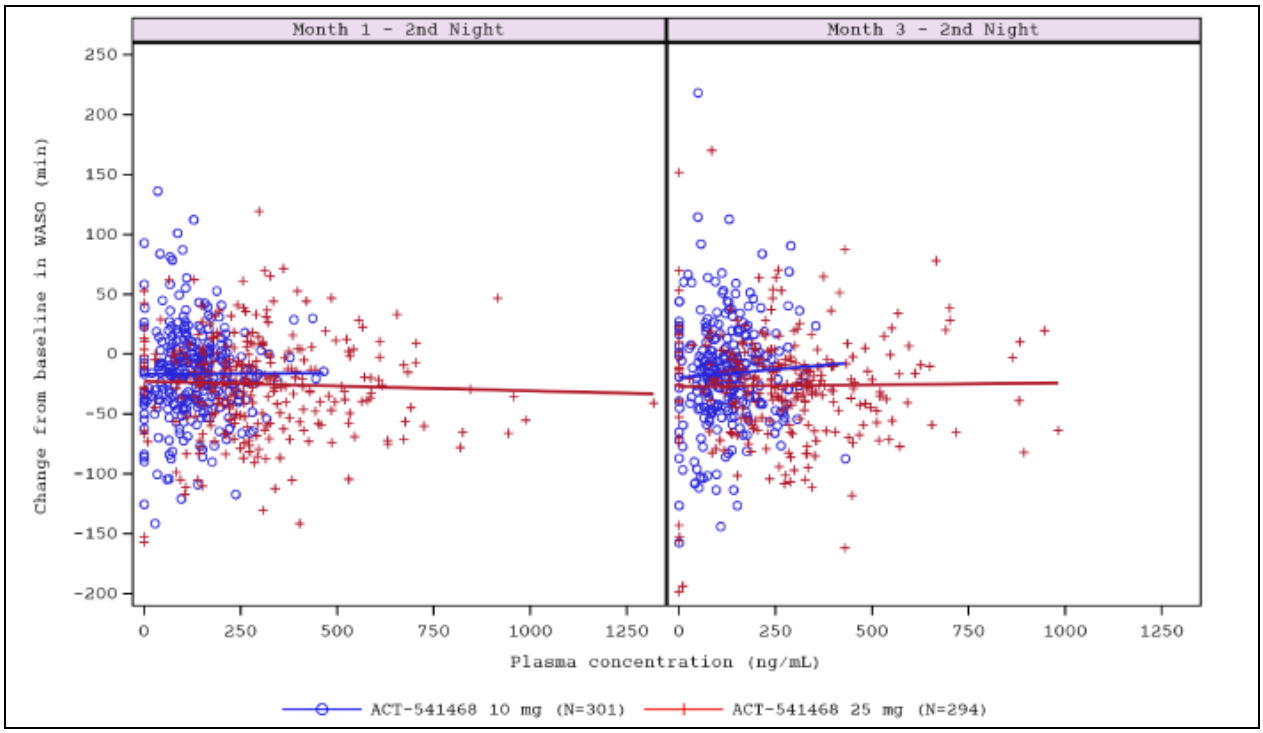


Figure 15. Change from baseline of WASO [min] at each time point vs plasma concentration of daridorexant [ng/mL] in study ID-078A301 (25 and 50 mg) and ID-078A302 (10 and 25 mg)





Based on these findings, the applicant concluded that daridorexant concentrations measured the next morning do not have an obvious correlation to the efficacy assessed during the previous night. Even this conclusion could be agreed (based on the shape of provided exposure/clinical endpoints relationships), the provided analyses do not appear relevant to draw valid conclusions regarding the purpose of dosing recommendations; and this at least for two points:

- The targeted response (changes from baseline) that should at least be reached to inform success of treatment is neither stated / clear nor its achievement (or not) was investigated and compared between doses levels to allow more robust comparison of dose/exposure effectiveness,

- From a PK perspective, the probabilities of distributions of the PK endpoint ($C_{9\text{-}10h}$) observed at both 25 and 50 mg doses (**Figure 16**) on one hand or those from 10 and 25 mg doses (

Figure 17 on the other hand show substantial overlaps that preclude a clear separation / distinction between dose levels.

Figure 16. Phase 3 study ID-078A301. Probability density function of the plasma concentration of daridorexant at month 1.

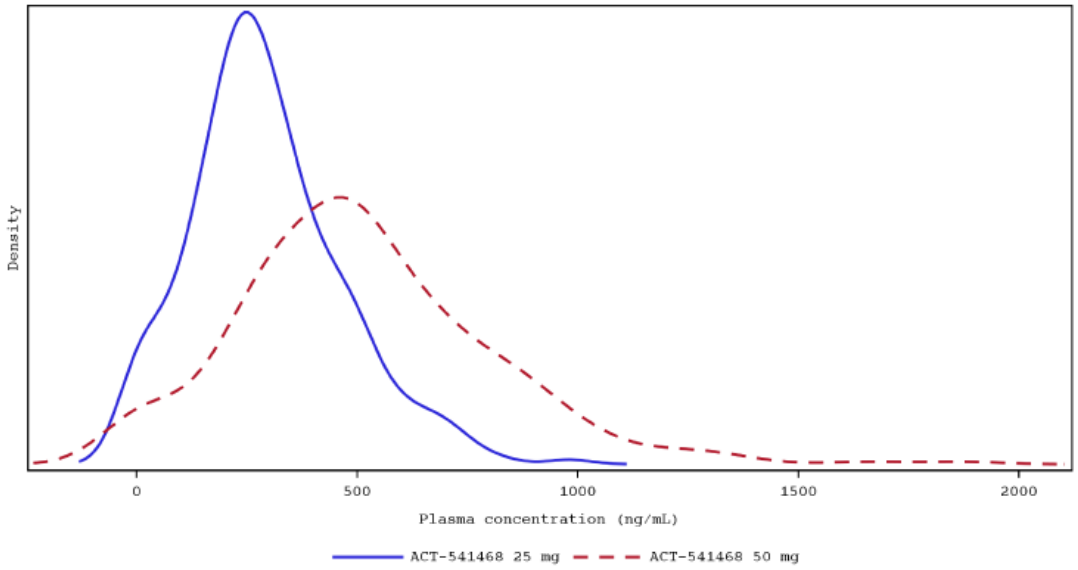
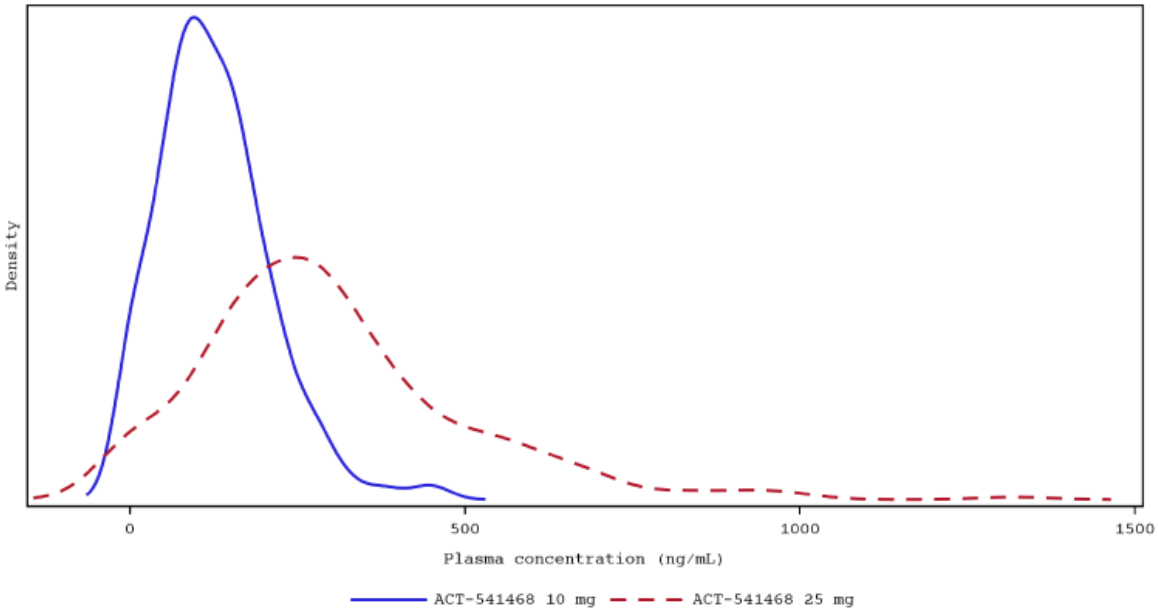


Figure 17. Phase 3 study ID-078A302. Probability density function of the plasma concentration of daridorexant at month 2



Overall, the provided exposure-efficacy analysis should only be considered as exploratory and not be used to support dosing recommendations, that should be based on formal clinical efficacy and safety evidence at the doses of interest.

Exposure-response analysis for safety

Data from the two pivotal B/R Phase 3 studies **ID-078A301** and **ID-078A302** were used. Exposure PK metric is the same that for the E-R analysis for efficacy (morning C9-10h concentrations at Month 1 and 3). To assess the safety, the changes from baseline to month 1 and month 3 for the related parameters on next-morning residual effect: coding sub-test© and morning sleepiness score on the visual analog scale were selected.

No population PKPD modeling was developed. Graphical scatter plots with a linear regression were provided to link steady state exposure parameter (C9-10h) to the safety endpoints (coding sub-test© and morning sleepiness score on the visual analog scale). No correlation between the change from baseline in the selected efficacy variables and daridorexant exposure parameter (C9-10h) issued from both 25 and 50 mg (study ID-078A301) or 10 and 25 mg (study ID-078A302) was observed.

Based on this finding, the applicant concluded that the exposure to daridorexant measured the next morning does not have an obvious correlation to the safety next-morning residual effect.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

ADME

Relative Bioavailability/Bioequivalence

Across the clinical development, three oral formulations were developed (Formulation B, Formulation A and film coated tablets). Importantly, no PK data are available for the commercial formulation which differs slightly compared to the film coated tablets used in phase 1 and pivotal B/R phase 3 studies.

Bridging Capsule formulation A versus Tablet formulation

The capsule formulation A (used in early phase 1 and phase 2 studies) and the tablet product (used in phase 1 to pivotal B/R studies) have different qualitative composition and different manufacturing process. No formal dedicated comparative bioavailability study was performed to confirm the comparability of the biopharmaceutical performance between the two formulations and allow extrapolation of PK properties / findings collected with capsule A to the tablet formulation. Instead, in vitro investigations (comparison of dissolution profiles) and food effects comparison have been performed.

Both formulations have a pH-dependent dissolution profiles, and except at, the dissolution profiles are different between formulations. Moreover, indirect comparison between studies (with different subjects, design, doses, experimental conditions, uncontrolled variability etc..) is not considered to provide adequate /appropriate data to draw valid conclusions regarding the PK/ bioavailability comparability between the two formulations neither for the fasted nor for the fed state. In conclusion, bioavailability comparative data between the capsule formulation A and the tablet product are lacking. The applicant was requested to provide such data or explain why not doing so. No bioavailability comparative data between the two formulations (hard capsule vs tablet) was provided. According to the applicant, a bio comparison study was not considered necessary before starting Phase 3 studies, provided the *in vitro* dissolution profiles and a claimed near complete absorption of daridorexant as no parent drug was observed in feces. Nevertheless based on the PopPK analysis the formulation effect, tested as a covariate was not found to have a significant effect on daridorexant PK.

Bridging to-be marketed product versus phase 3 B/R tablet formulation

No PK/ clinical data is available with the product intended for commercial use that was never used throughout the clinical development. However, this product version is identical to tablet formulation used in phase 1 and in the pivotal phase 3 studies, except for the colour of coating (light orange during clinical studies for blinding purpose versus different colours for commercial formulation). From a PK point of view, it's agreed that this small /minor difference is not expected to have a significant impact on the biopharmaceutical performances of the product. Additional in vitro investigations (comparison of dissolution profiles) were requested to ensure quality pharmaceutical comparability and submitted with satisfactory results.

Distribution volume

Daridorexant Vss following an IV administration was estimated at 31 L suggesting low diffusion in tissue. This results was confirmed in studies ID-078-112 and ID-078-115 after accounting for F (Vz/F = 59 L to 66 L).

However these NCA estimates of the volume of distribution appears to be not consistent with that estimated based on the Population-PK model (V/F = 28.3 L with Vp and Vc of 14.6 and 13.7 L, respectively). The applicant was asked to explain such discrepancy, however no conclusive explanation was provided, the issue was not further pursued.

Dose proportionality

Dose proportionality was assessed in several studies:

From 5 to 200 mg or 5 to 50 mg a less than dose proportional increase of PK parameters was observed (Study **AC-078-101**), or from 10 to 75 mg (single dose or at steady-state, Study **AC-078-102-Part A***),* or from 25 to 50 mg (Study **AC-078-105**) or from 50 mg to 150 mg (**AC-078-107**). In these studies daridorexant was administered as hard capsule. Such dose non-linearity was to note handled in the PopPK analysis by using a MM elimination.

Only in study **ID-078-116**, from 10 to 50 mg, where daridorexant was administered as tablet, both PK parameters increased with increasing dose. In contrast in the multiple dose study **ID-078A206** performed in Japenese subjects, no dose proportionality assessment was performed, nevertheless, as stated by the applicant, the C9h-10h increase after increasing dose, this is agreed, however in a less than dose proportional manner.

In addition, based on the structure of the PopPK model (please refer to section 2.1.8), the non-linear behaviour of daridorexant has been handled at two levels with the parameterization of a less than dose proportional bioavailability (dose as covariate on F), and by using a MM elimination.

All together the statement in the SmPC that "Daridorexant plasma exposure is dose proportional at doses up to 50 mg" is not endorsed, as available PK data suggests a less than dose proportional increase for the entire tested range of doses up to 50 mg. The applicant was asked to discuss this issue and to propose a rewording of this statement. To this end, throughout the clinical development program, the applicant summarized all the observed exposure AUC0-24h, Cmax and C9-10h ratios compared to the theoretical expected ones using the different dose levels tested. Currently, the focus is met on the recommended dose interval 25 to 50mg and the statement of an approximately dose proportional increase of exposure of daridorexant between 25 and 50 mg could be agreed. Over the course of the assessmenthe Applicant shared this statement and updated the SmPC accordingly.

Population PK analysis

In response to D120 question, the applicant has clarified that models 611 and 623 in the Pop-PK model (report D-20.188) used exclusively dense PK sampling from Phase 1 studies. The structural model as well as PK parameters estimates were subsequently fixed in the further models (710 and the final one 831) that integrated sparse PK data from phase 2 and 3 studies (providing only next - morning C9-10 samples i.e., single measurements over a dosing interval) As such samples cannot robustly estimate absorption and elimination parameters and may lead to unreliable parameter estimates and large RSE, the adopted sequential approach of parameter estimation is acceptable.

Overall, population typical values, associated variabilities and covariate effects were in general fixed for the final model (run 831) except for covariate effects on volumes, Q and Km who were precisely estimated (low RSE% <20%, except for the effect of lean body weight on km: RSE 25.95%). The magnitude of the proportional errors was low (16%) and the additive error was estimated at 17.6 ng/L (acceptable when compared to geometric mean steady state C_{max} around 800 ng/L with the recommended 50 mg dose and taking into account that no correlation between low concentrations neither with efficacy nor safety endpoints was demonstrated). A high variability was observed for absorption-related parameters: CV% of 51% and 76.8% for Tlag and ka, respectively, 64.8% for F; while moderate IIV was observed for remaining parameters: 41.2 and 47.9% $V_{central}$ and $V_{peripheral,}$ respectively and 30% and 60% for Vm and Km, respectively.

No major deficiencies could be noted for the diagnostic plots. Furthermore, pcVPCs suggests that the model describe well the observed data across the dose range from 5 to 200 mg in healthy subjects and 5 to 50 mg in patients with insomnia disorder (despite some over-prediction and high predicted variability for the higher doses of 150 and 200 mg, which will have no clinical consequences, given the recommended doses of 25 to 50 mg in clinic). The model seems to show acceptable descriptive and predictive performance across the recommended dose range from 25 to 50 mg in patients with insomnia disorder.

Based on the findings of the Pop-PK model, the typical absolute bioavailability (F) was estimated to 0.41 for the reference dose 50 mg. F was found to decrease with higher doses: at 100 mg dose, F is estimated to be

around 0.33. However, using the NCA approach, daridorexant showed an average F estimate of 0.62 for the 100 mg dose based on results of the ADME study AC-078-101. At D120, the applicant was asked to provide a clear estimate of F at the recommended dose of 50 mg. Based on the relative bioavailability of daridorexant for the 50 mg versus 100 mg calculated based on the modelling approach (0.41/0.33 =1.23), an estimate of F = 0.75 is proposed at 50 mg for the NCA approach. This estimate (0.75) is not consistent with that from the Population approach (0.41). Overall, estimation of F daridorexant after oral administration appears not consistent from both methods (NCA versus population modeling). The applicant was again asked to justify this discrepancy. In the responses to Day180 LoQ, the Applicant explain that the population PK model did not utilise the i.v. data and that the most robust estimate of F should be derived by the NCA method applied to the dedicated study AC-078-101 with oral and intravenous administration of daridorexant to the same subjects. This statement is agreed. Therefore, data from the Population PK model (neither F estimate = 0.41 nor the relation of F for 2 different doses based on which F estimate is calculated: F = 62.1%*1.23 = 75% with a dose of 50 mg.) should not be used to estimate F. Overall, the only reliable estimate of F is available with the 100 mg dose and no data could be provided with the 50 mg dose level. This was reflected in the SmPC and the issue was considered as solved.

The apparent typical volume of distribution was estimated to 28.3 L (Vp and Vc of 14.6 and 13.7 L, respectively) which appears far from that estimated by NCA analysis (see above). In response to D120 question, the requested daridorexant half-life elimination (t½) estimate from the Pop-PK model is provided. Based on model parameters estimates, this gives a t½ = 8.1 h and 7.4 h, in line with NCA analyses (t½ = 6-8 h).

Food status (fasted, light meal/ uncontrolled, fed) and time of drug administration (morning, evening) were identified as significant covariates on absorption parameters (ka and or Tlag). The Vc was associated with lean body mass and the Vp and Q were associated with body fat mass. The elimination parameter Km was found to be related to lean body weight, age, and alkaline phosphatase (ALP). To assess the clinical relevance of the covariates, model-based simulations were performed using the recommended 50 mg once daily (o.d) for 3 days and a typical subject (60 years of age, 20 kg fat mass, 55 kg lean body weight and 60 U/L ALP). Covariates were varied to include different ages (23 and 74 years), fat masses (13.1 and 39.1 kg), lean body weights (36.2 and 69.1 kg), and ALP (38 and 99 U/L), corresponding to the 5th and 95th percentiles of the data.

Simulations of exposure parameters C_{max}, t_{max}, AUC_{0-24h}, and C_{8h} indicated that the largest effects on daridorexant exposures were seen in food status, time of administration. Food status fed results in a decrease of C_{max} by 36%, a prolongation of t_{max} more than twice (4.48 h vs 2.1 h), a 16% higher C8h, and 7% lower AUC0-24h compared to light meal/ uncontrolled. Morning administration compared to evening administration showed an increase of C_{max} by 29% and a shortening of 40% in t_{max} (0.85 h). All others subject-specific characteristics, including age, Food status fasted, lean body weight and ALP, showed no relevant difference (i.e., <20%) in exposure parameters AUC, tmax, Cmax, and C8h compared to a typical subject.

Overall, given the fact that morning administration is not relevant clinically (with regards to the indication) and that high-fat high-calorie food is an extreme-case scenario unlikely to occur in clinical practice, the applicant's recommendation that daridorexant is to be taken in the evening / night (within 30 minutes before going to bed) is endorsed.

Special populations

Age/Elderly

For completeness of the data and in order to endorse the proposed flat dosing recommendations in the elderly population, the applicant was asked to specify the number of patients with PK observations included in the following subgroups of age: [65 to 74 years], [75 to 84 years] and >85 years. For each class of age, PK

exposure metrics at steady state (AUC_{0-24h}, C_{max}, C_{8h} and C_{min}) after repeated administration of the recommended 50 mg OD should be derived from the final Pop-PK model to provide dosing recommendations. If no clinical / PK data were available or insufficient for one of the subgroups, this should be clearly implemented (warnings for inclusion) in the SmPC. The requested data was provided over the course of the assessment. Overall, data from 495 and 85 subjects were available in the age ranges 65-74 years and 75-84 years, respectively. However, only 4 subjects with age 85 and higher were included in the study population.

Overall, the model-predicted concentrations did not indicate any significant (>20%) PK change in elderly patients (C8h ranging from 512 to 548 ng/mL in comparison to a reference C8h value of 491 ng/mL in subjects ≤65 years old). Therefore, the applicant conclusion that no dose adjustment in elderly patients is warranted could be endorsed. A statement reflecting the limited extent of PK data available in patients > 75 years of age has been included in section 5.2. of the SmPC.

Interactions

The PBPK model submitted is considered insufficiently qualified for its intended purpose. Therefore extrapolations on DDI outcomes based on PBPK simulations is not considered acceptable. In general, because of the large target population with high probabilities of various co-morbidities, the drug-drug interactions study mentioned below needs to be addressed in vivo as post-approval measure.

Effects of other drugs on daridorexant

CYPs Daridorexant administered at 25 mg induced a 1.4- and 2.4-fold increase in Cmax and AUC0-∞ respectively when co-administered with the moderate CYP3A4 inhibitor diltiazem (240 mg, at steady state). It is expected an even more marked daridorexant exposure following strong CYP3A4 administration at the therapeutic dose of 50 mg. Given the large target population which includes the elderly, and the SNC-related AEs (e.g. dizziness, somnolence), an increase in these AE's along with the increase in exposure resulting from association with strong CYP3A4 inhibitor is probable. Daridorexant is contraindicated with strong CYP3A4 inhibitor.

Effect of daridorexant on other drugs

CYPs:

The conducted DDI study to assess daridorexant effect on midazolam PK, CYP3A4 probe substrate, was not conducted at the therapeutic dose of 50 mg but two-fold lower (i.e. 25 mg). These results could thus not be extrapolated to PK interactions between midazolam and daridorexant administered at the therapeutic dose of 50 mg, in particular when considering the trend toward a Cmax increase following 25 mg daridorexant. Daridorexant as CYP3A4 both time-dependent inhibitor and inducer, the net effect following 50 mg daridorexant is thus uncertain, and this is reflected in SmPC by caution of use with CYP3A4 substrates and avoidance of concomitant use with CYP3A4 substrates with NTI. To document this interaction potential, following D195 response, the Applicant has committed to conduct interaction study with midazolam as PAM.

Based on in vitro results, daridorexant induction potential for CYP2C9 could not be excluded. Cautions of use in case of association of daridorexant with CYP2C9 substrates with close monitoring in case of NTI drugs co-administration has been specified in SmPC. To document the interaction potential with CYP2C9 substrates, I the Applicant has committed to conduct n vivo study to assess daridorexant induction potency for CYP2C9 should be provided as PAM.

In vitro investigations showed daridorexant inhibition for P-gp or BCRP in vivo cannot be excluded with estimated IC50 of 24 µM (digoxin as substrate) for P-gp and 3 µM for BCRP.

Only daridorexant inhibition potential for BCRP was further investigated in the clinical DDI (study 78-106) where co-administration of 25 mg daridorexant with rosuvastatin, BCRP probe substrate. The result of this study show daridorexant following 25 mg oral dosing did not affect rosuvastatin PK. The impact of daridorexant at the 50 mg therapeutic dose was addressed by PBPK which model is not endorsed. As a results, the impact of co-administration of BCRP substrate with daridorexant at 50 mg, on BCRP substrate PK is uncertain. Caution should be use in case of concomitant treatment of daridorexant with BCRP substrates has been specified in SmPC. The Applicant has committed to conduct clinical DDI study with rosuvastatin at therapeutic dose as PAM.

No in vivo investigation was performed for P-gp inhibition with adequate probe substrate (e.g. dabigatran). Consequently, following 50 mg daridorexant, clinically significant inhibition of P-gp cannot be excluded. As a result, SmPC 4.5 section has specified caution of use in case of concomitant treatment of daridorexant with P-gp drug substrates with cross reference to 5.2 section where in vitro interaction results should be reported. The Applicant has committed to conduct the clinical drug-drug interactions with 50 mg daridorexant and P-gp drug substrates as PAM.

PKPD relationships

No PKPD modelling were provided to link daridorexant exposure parameters with relevant PD parameters that would be associated to clinical efficacy and safety. For the purpose, only graphical scatter plots with linear regressions were provided. Based on the pivotal B/R Phase 3 studies ID-078A301 and ID-078A302, no evident correlation between the available exposure parameter (morning $C_{9\text{-}10h}$ measured at Month 1 and 3) neither with the selected efficacy (changes from baseline to month 1 and month 3 of treatment for LPS, WASO, sTST, and IDSIQ sleepiness/tiredness domain score) nor with and safety endpoints (changes from baseline to month 1 and month 3 for coding sub-test© and morning sleepiness score on the visual analog scale) was observed for both 25 and 50 mg (study ID-078A301) or 10 and 25 mg doses (study ID-078A302). Even these conclusions could be agreed (based on the shape of provided exposure/clinical endpoints relationships), it should be emphasized that the provided analyses do not appear relevant to draw valid conclusions on dosing recommendations. Indeed, a) the targeted response (changes from baseline) that should at least be reached to inform success / safety of treatment is neither clear nor its achievement (or not) was compared between the dose levels; and b) the substantial overlap for the probabilities of distributions on $C_{9\text{-}10h}$ observed for the 25 and 50 mg doses on one hand and for the 10 and 25 mg doses on the other hand preclude a clear distinction between dose levels.

To conclude from a PKPD perspective, the provided analyses for exposure-efficacy and exposure-safety should only be considered as exploratory and not be used to support dosing recommendations, that should be based on formal clinical efficacy and safety evidence at the doses of interest.

CLINICAL PHARMACOLOGY SAFETY STUDIES

In a specific phase 1 study (111), the concomitant administration of daridorexant 50 mg and ethanol (5 h intravenous infusion at 0.6 g/L) was assessed and led to reinforced drug actions indicative of an additive effect on PD markers without any evidence of a synergic effect of daridorexant and ethanol on any of the defined PD variables. Somnolence is the main reported AE with a higher frequency in the daridorexant group with or without alcohol compared to the placebo group with or without alcohol. Alcohol consumption is

therefore not recommended during treatment with daridorexant in the SmPC. For this matter, a precaution for concomitant use is stated in section 4.4 of the SmPC. This kind of precaution is in accordance with CNS-depressant effect, which reflects the expected pharmacological effect.

In a specific phase 1 study (108), a driving study was performed with a simulator in healthy subjects without sleep disorder, at therapeutic (50 mg) and supratherapeutic (100 mg) doses, compared to placebo and zopiclone. The results showed a dose-dependent impairment of driving performance 9 hours after first dose administration with daridorexant, but that effect disappeared after repeated doses (4 consecutive nights), even at the supratherapeutic dose of 100 mg. The incidence of AEs i.e. fatigue or somnolence was rather high at Day 2 and considerably decreased at Day 5. Thus the driving performance seems not significantly impaired after a few days of treatment. However, some clarifications need to be provided regarding this study. Concerning the SmPC, a special warning and precaution for use is stated in sections 4.4 and 4.7.

In two specific phase 1 studies (109 and 110), the effect of daridorexant 50 mg on night-time respiratory and sleep parameters in subjects with moderate COPD and in subjects with mild or moderate OSA was investigated. For study 109, patients with COPD received 50 mg daridorexant and the treatment did not cause oxygen desaturation after single-dose administration and at steady state compared to placebo. Overall, there seems to be no deleterious effect of daridorexant in subjects with moderate COPD. A statement related to the absence of data in patients with severe COPD is added in the SmPC. The statement for subjects with moderate COPD was deleted from the SmPC as no safety signal has been observed (see SmPC). For study 110, patients with mild or with moderate OSA received 50 mg daridorexant and the treatment had no effect on AHI after single-dose administration and at steady state compared to placebo. Overall, there seems to be no deleterious effect of daridorexant in subjects with mild-to-moderate OSA. A statement related to the absence of data in patients with severe OSA is added in the SmPC. The statement for subjects with mild to moderate OSA was deleted from the SmPC as no safety signal has been observed.

In a specific phase 1 study (117), patients received daridorexant to evaluate the effect of single therapeutic (50 mg) and supratherapeutic (200 mg) single doses of daridorexant on the QT/QTc interval duration in ECGs within the first 24 hours of administration vs placebo and the active comparator moxifloxacine 400 mg. It fulfilled the requirements to conclude that daridorexant meets the ICH E14 criteria of a negative TQT study. Thus, daridorexant doses up to 200 mg did not prolong the QT interval. The statement related to the cardiac electrophysiology was deleted from section 5.1 of the SmPC as no safety signal has been observed.

In a specific study assessing the human abuse potential of daridorexant (107), patients received daridorexant at therapeutic and supratherapeutic single oral doses compared to the control drugs suvorexant and zolpidem in healthy recreational drug users. Daridorexant (50 mg, 100, mg and 150 mg) drug-liking was observed as compared to placebo in healthy current sedative recreational users and seems comparable to that of suvorexant (150 mg), and zolpidem (30 mg) at supratherapeutic doses (100 mg and 150 mg). The analysis of TEAES suggestive of drug abuse potential from phase 3 studies did not permit to confirm the abuse risk of daridorexant for the target population of patient with insomnia under experimental conditions (exclusion of patients with a history of abuse or addiction to alcohol or other drugs). The Applicant’s proposal to add “Abuse potential” safety concern as important potential risk on the RMP, and a warning in section 4.4 of the SmPC was endorsed.

Considering the risk of withdrawal syndrome, no AEs indicating a withdrawal syndrome were observed in 301, 303 and pool safety data while significant higher proportion of subjects with at least one risk symptom BWSQ item scored as severe (>20) at the end of treatment withdrawal period in the daridorexant group was observed as compared to placebo.

2.6.4. Conclusions on clinical pharmacology

The PK of daridorexant was thoroughly investigated using the non-compartmental and nonlinear-mixed effects modelling approaches. Overall, the PK properties of daridorexant product to be administered by oral route are considered as sufficiently characterized.

There are concerns on the clinical relevance of the in vitro induction of CYP2C9 and the inhibition of BCRP and P-gp, and most importantly on the clinical outcome of daridorexant at 50 mg as perpetrator on CYP3A4 substrates in absence of clinical data. These interactions should be investigated *in vivo* considering the large target population with various co-morbidities and/or co-medications, and daridorexant being a first in class in Europe. As a consequence, in absence of clinical data 4.5 section of SmPC was amended to cover potential interactions which may affect efficacy, and or safety of the drug products.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

The DDI studies have been requested and will be conducted by February 2023:

Clinical interaction study with midazolam, clinical interaction study with P-gp drug substrate (dabigatran) clinical interaction study with BCRP drug substrate (rosuvastatin), clinical interaction study with CYP2C9 drug substrate (warfarin).

2.6.5. Clinical efficacy

The clinical evidence of the efficacy and safety of daridorexant in the treatment of patients with insomnia is primarily derived from 2 pivotal Phase 3 studies, ID-078A301 (named study 301 in this AR) and ID-078A302 (study 302), supported by the interim results from one ongoing DB Phase 3 extension study, ID-078A303 (study 303), and two Phase 2 dose-finding studies, AC-078A201 (study 201 in adult subjects) and AC-078A202 (study 202 in elderly subjects).

Dose-response studies

Dose finding was performed in phase 2 studies in adults (study 201) and elderly patients (study 202) with moderate to severe insomnia. The following doses were assessed: 5 mg, 10 mg, 25 mg, 50 mg compared to placebo. Study 201 includes zolpidem arm as an active reference. No statistical comparison between daridorexant and zolpidem was performed.

Study 201

The primary efficacy objective parameter is Wake after sleep onset (WASO) and secondary endpoints are latency to persistent sleep (LPS), subjective latency to sleep onset (sLSO) and subjective WASO (sWASO).

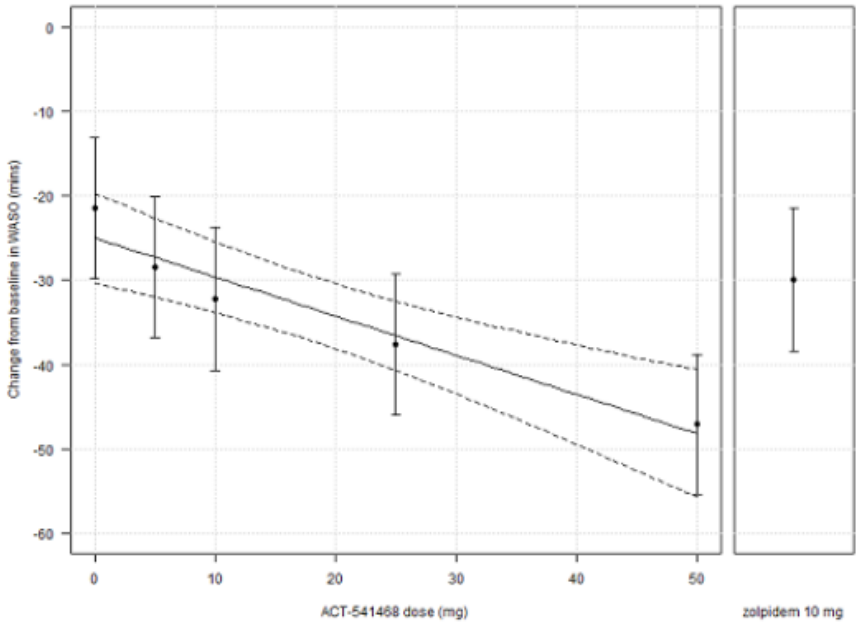
WASO represents duration in minutes of awakenings. LPS measures the time in minutes to sleep onset. Both are assessed objectively by polysomnography. sLSO and sWASO are reported by the patient with sleep diary questionnaire (SDQ).

Table 4-1 Between-treatment analysis for change from baseline in WASO (min) to Days 1 and 2 (study 201), mFAS

	Baseline**		Difference to placebo	
	Mean (SD)	LS Means [95% CL]	LS Means [95% CL]	P-value (two-sided)
5 mg (N = 60)	97.4 (47.1)	–28.4 [–36.8, –20.1]	–7.0 [–18.7, 4.7]	0.241
10 mg (N = 58)	98.8 (36.3)	–32.3 [–40.8, –23.8]	–10.8 [–22.6, 1.0]	0.072
25 mg (N = 60)	99.6 (40.9)	–37.7 [–46.0, –29.3]	–16.2 [–27.9, –4.5]	0.007
50 mg (N = 61)	94.0 (31.9)	–47.1 [–55.3, –38.8]	–25.6 [–37.3, –13.9]	<.001
Placebo (N = 60)	95.8 (34.7)	–21.4 [–29.8, –13.1]	-	-

ANCOVA = analysis of covariance; CL = confidence limit; mFAS = modified Full analysis set; LS = least squares; N = number of subjects in the mFAS by treatment group; SD = standard deviation; WASO = wake after sleep onset.
** Observed baseline value.
ANCOVA model: Change from baseline in WASO = treatment + baseline WASO + gender.
Source: Compiled from D-17.126 table 11-4 and table 11-6.

Figure 4-1 Predicted mean (95% CL) dose-response profile and LS means (95% CL) for change from baseline to Days 1/2 in WASO, mFAS (study 201)



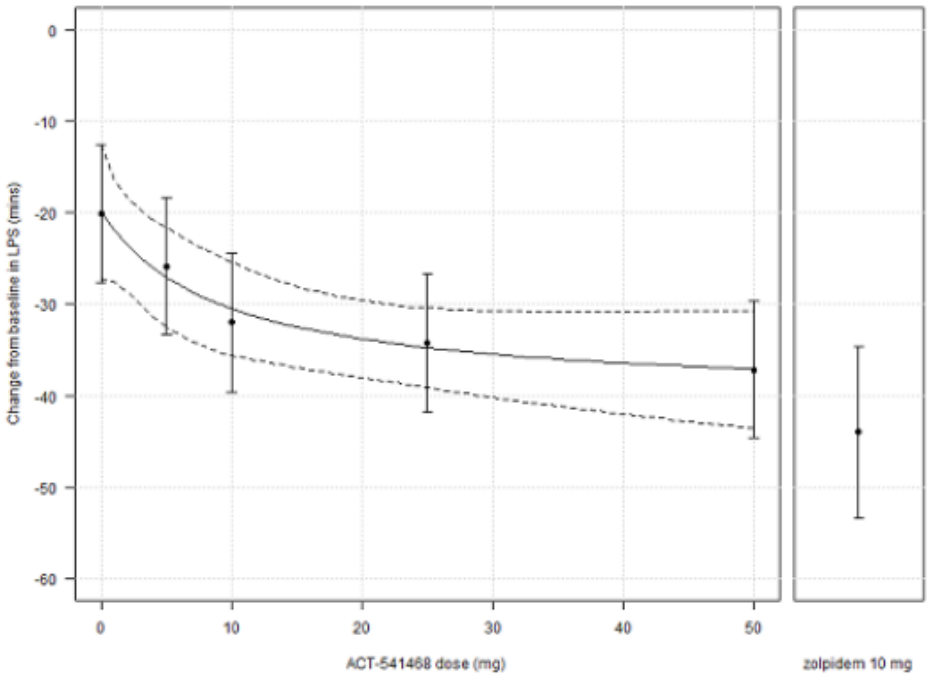
CL = confidence limit; LS mean = least squares mean; mFAS = modified full analysis set; WASO = wake after sleep onset.
Source: D-17.126 figure 11-1.

Table 4-2 Between-treatment analysis for change from baseline in LPS (min) to Days 1 and 2 (study 201), FAS

	Baseline** Mean (SD)	LS Means [95% CL]	Difference to placebo LS Means [95% CL]	Difference to placebo P-value (two-sided)
5 mg (N = 60)	72.7 (51.9)	–25.9 [–33.4, –18.4]	–5.8 [–16.3, 4.8)]	0.282
10 mg (N = 58)	66.1 (31.8)	–32.0 [–39.7, –24.4]	–11.9 [–22.5, –1.3]	0.028
25 mg (N = 60)	74.3 (43.5)	–34.2 [–41.7, –26.7]	–14.1 [–24.6, –3.6]	0.009
50 mg (N = 61)	69.6 (30.2)	–37.2 [–44.6, –29.7]	–17.0 [–27.5, –6.6]	0.002
Placebo (N = 60)	74.3 (39.3)	–20.1 [–27.6, –12.6]	-	-

ANCOVA = analysis of covariance; CL = confidence limit; FAS = Full analysis set; LPS = latency to persistent sleep; LS = least squares; N = number of subjects by treatment group; SD = standard deviation.
** Observed baseline value.
ANCOVA model: Change from baseline in LPS = treatment + baseline LPS + gender.
Source: Compiled from D-17.126 table 11-9 and table 11-10.

Figure 4-2 Predicted mean (95% CL) dose-response profile and LS means (95% CL) for change from baseline to Days 1/2 in LPS, FAS (study 201)



CL = confidence limit; FAS = Full analysis set; LPS = latency to persistent sleep; LS mean = least squares mean.
Source: D-17.126 figure 11-4.

In study 201, statistically significant superiority over placebo is shown at the 25 mg and 50 mg doses for the primary efficacy objective parameter (WASO) and first objective secondary endpoint (LPS). No statistically significant superiority over placebo at the 10 mg dose is observed for the primary endpoint. Statistically significant superiority over placebo at the 10 mg dose is observed for first secondary endpoint (LPS). Subjective endpoint (sWASO and sLSO) did not show a statistically significant difference over placebo for all doses. No statistically significant effect of zolpidem compared to placebo is observed for WASO. A Statistically significant superiority of zolpidem over placebo is observed for LPS. This might be explained by zolpidem mechanism of action.

Study 202

Study 202 performed in elderly patients provided dose finding data compared to placebo with a crossover design.

Table 4-3 Between-treatment analysis for change from baseline in WASO (min) to Days 1 and 2 (study 202), mFAS

	Baseline**		Difference to placebo	
	Mean (SD)	LS Means [95% CL]	LS Means [95% CL]	P-value (two-sided)
5 mg (N = 56)	116.7 (40.7)	–18.9 [–27.7, –10.2]	–5.4 [–14.7, 4.0]	0.258
10 mg (N = 54)	117.7 (39.6)	–32.0 [–40.8, –23.1]	–18.4 [–27.8, –9.0]	<.001
25 mg (N = 55)	116.1 (40.9)	–45.1 [–53.9, –36.2]	–31.5 [–40.9, –22.2]	<.001
50 mg (N = 56)	116.3 (39.9)	–61.4 [–70.1, –52.6]	–47.8 [–57.2, –38.5]	<.001
Placebo (N = 54)	117.7 (39.6)	–13.6 [–22.4, –4.7]	-	-

CL = confidence limit; LS = least squares; mFAS = modified full analysis set; N = number of subjects in the mFAS by treatment group; SD = standard deviation; WASO = wake after sleep onset.
** Observed baseline value; FAS is displayed for baseline values.
Note: the FAS and the mFAS were identical in study 202.
Linear mixed effects model: Change from baseline in WASO = dose group + baseline WASO + period + subject (random).
Covariance structure: Compound symmetry
Source: Compiled from D-17.127 table 11-3 and table 11-5.

Statistically significant superiority over placebo is shown at the 10 mg, 25 mg and 50 mg doses for the primary efficacy objective parameter (WASO) and first objective secondary endpoint (LPS). No statistic comparison is made on sWASO and sLSO but the effect on these secondary endpoints is higher with daridorexant than placebo and increase with the dose.

The dose selected for phase 3 studies are 10 mg, 25 mg and 50 mg. These doses are well justified based on the two phase 2 dose ranging study results.

Main Pivotal studies (Study 301 and study 302)

Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety of ACT-541468 at 25 mg and 50 mg in adult and elderly subjects with insomnia disorder (study 301)

Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety of ACT-541468 at 10 mg and 25 mg in adult and elderly subjects with insomnia disorder (study 302)

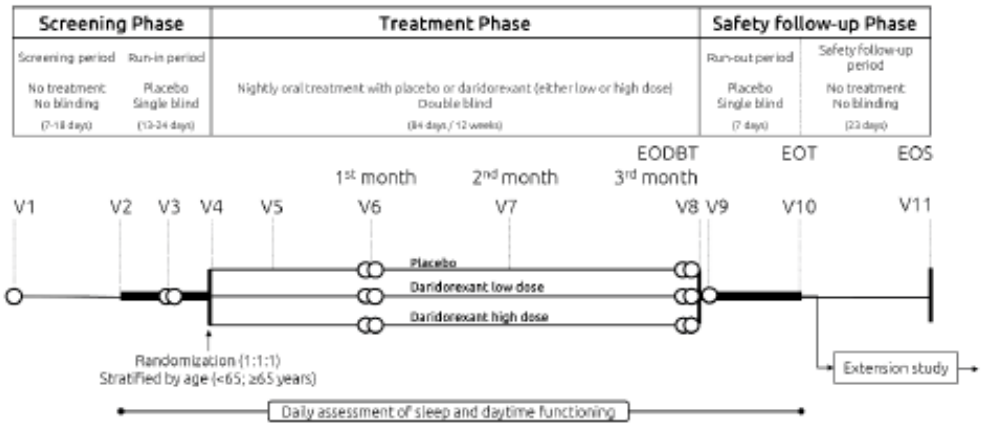
As only doses differ between study 301 and studies 302, they are described together in this report.

Methods

After a screening period of 7-18 days followed by a single-blind placebo run-in period of 13-24 days, subjects were randomized (1:1:1; stratified by age < 65 and ≥ 65 years) to receive one tablet of daridorexant 25 mg, 50 mg or placebo (study 301) or daridorexant 10 mg, 25 mg or placebo (study 302), orally once daily in the

evening, for 12 weeks. The 12-week treatment period was followed by a 7-day single-blind placebo run-out, after which subjects could enter the 9-month extension study 303.

Figure 2-1 Design of the confirmatory Phase 3 studies



V5 and V11 were telephone calls; all other visits were at the site.
Study 302: low dose = 10 mg, high dose = 25 mg; Study 301: low dose = 25 mg, high dose = 50 mg.
V = Visit; ○ = polysomnography nights; EODBT = end-of-double-blind-treatment; EOS = end-of-study; EOT = end-of-treatment.

Study Participants

Inclusion and exclusion criteria were identical in study 301 and 302.

Main inclusion criteria

Eligible patients in study 301 and 302 were adult (18-64 years) and elderly (≥ 65 years) subjects with insomnia disorder according to the Diagnostic and Statistical Manual of Mental Disorders® (5th edition; DSM-5®) criteria. Self-reported insomnia should be of at least moderate severity (Insomnia Severity Index© score ≥15) at screening. Sleep disturbance induce clinically significant distress or impairment in social, occupational, educational, academic, behavioural, or other important areas of functioning.

Patient should report insufficient sleep quantity (≥30minutes to fall asleep, wake time during sleep ≥ 30 minutes, and subjective total sleep time [sTST] ≤6.5hours during the night) for at least 3 nights per week during at least 3 months prior to the screening visit, and for at least 3 out of 7 nights on the SDQ completed during the placebo run-in period prior to the placebo run-in PSG nights.

Objective sleep quantity parameters assessed at 2 consecutive PSG nights during the placebo run-in period should report a mean latency to persistent sleep (LPS) ≥ 20 minutes, with neither of the 2 nights < 15 minutes; mean wake after sleep onset (WASO) ≥ 30minutes, with neither of the 2 nights <20 minutes; and mean total sleep time (TST)< 420 minutes.

Main exclusion criteria:

The main exclusion criteria are: subjects self-reporting daytime napping ≥ 1 hour per day and ≥ 3 days per week, subjects with a body mass index (BMI) <18.5 or > 40.0 kg/m2, subjects with acute or unstable psychiatric conditions, suicidal ideation, alcohol or drug abuse, sleep-related breathing disorders, periodic

limb movement disorder, restless legs syndrome, circadian rhythm disorder, rapid eye movement (REM) behaviour disorder, narcolepsy, subjects with MMSE score <25, caffeine consumption ≥ 600 mg per day or any caffeine consumption after 4 pm and heavy tobacco use.

Subject treated with central nervous system-active drugs were excluded; cognitive behavioural therapy was allowed if started at least 1 month prior to the run-in PSG nights and continued throughout the study.

Treatments

In study 301, daridorexant tablets were provided at strengths of 25 mg and 50 mg. In study 302, daridorexant tablets strengths was 10 mg and 25 mg. The treatment was administered orally, once daily in the evening during the DB treatment period (12 weeks). At the site, 1 tablet of study treatment was taken at least 2 h after the last meal and 30±5min before lights off, in the evening of each PSG night. At home, study treatment was taken at bedtime to mimic real life drug intake habits.

Daridorexant matching placebo was administered in the evening during the single-blind run-in period (13–24 days), the DB treatment period (84 ± 2 days) and the single-blind run-out period (7+ 2 days).

Objectives

The primary objective was to evaluate the efficacy of daridorexant, at 25 mg and 50 mg in study 301 and at 10 mg and 25 mg in study 302, on objective sleep parameters in subjects with insomnia disorder. Secondary objectives were also the same in both pivotal studies and were to evaluate the efficacy daridorexant on subjective sleep parameters and daytime functioning in subjects with insomnia disorder.

Safety objectives were to assess the safety and tolerability of daridorexant in subjects with insomnia disorder during treatment and upon treatment discontinuation.

Outcomes/endpoints

EFFICACY

Primary efficacy endpoints

- Change from baseline to Month 1 in WASO (sleep maintenance).
- Change from baseline to Month 3 in WASO.
- Change from baseline to Month 1 in LPS (sleep onset).
- Change from baseline to Month 3 in LPS.

Secondary efficacy endpoints

- Change from baseline to Month 1 and Month 3 in sTST (sleep duration)
- Change from baseline to Month 1 and Month 3 in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score.

Other efficacy and exploratory endpoints

- Change from baseline to Month 1 and Month 3 in TST, sLSO, sWASO, and morning VAS for depth and quality of sleep,

- Change from baseline to Month 1 and Month 3 in the IDSIQ mood and alert/cognition domain scores, IDSIQ total score, evening VAS for ability to function and daytime alertness, to further characterize daytime functioning,
- Change from baseline to Month 1 and Month 3 in ISI© score.

PHARMACOKINETICS: Daridorexant plasma concentrations, measured 9–10 h post-dose (morning after the second PSG night at Visits 6 and 8), or in the event of excessive sleepiness based on the investigator's opinion.

Randomisation and blinding (masking)

Subject were randomized in a 1:1:1 ratio to daridorexant 25 mg, 50 mg, and placebo in study 301 and in a 1:1:1 ratio to daridorexant 10 mg, 25 mg, and placebo in study 302. In both studies, treatment allocation was stratified by age into 2 categories: < 65 and ≥ 65 years. It was planned that approximately 40% of subjects would be elderly (≥ 65 years old), with approximately 5% of these elderly subjects above 75 years old.

During placebo run-in and run-out periods, placebo treatment was administered in a single-blind fashion. Subjects remained blinded to their study treatment until the unblinding of the ID-078A303 extension study. From randomization until EODBT, the study was performed in a DB fashion.

Statistical methods

The analysis were performed using the Full analysis set.

For WASO, LPS, and sTST, the difference compared to placebo in the mean change from baseline to Month 1 and Month 3 (± the assumed standard deviation [SD]per treatment group), was assumed to be 15 (±40) min, 15 (±40) min, and 20 (±54) min, respectively (based on Phase 2 data from studies AC-078A201 and AC-078A202). The corresponding effect size (mean/SD) was approximately 0.37.

For IDSIQ sleepiness domain score, the difference compared to placebo in the mean change from baseline to Month 1 and Month 3 (± the assumed SD per treatment group) was assumed to be 5 (±5) (based on data from study AC-078A203). The corresponding effect size (mean/SD) was approximately 1.

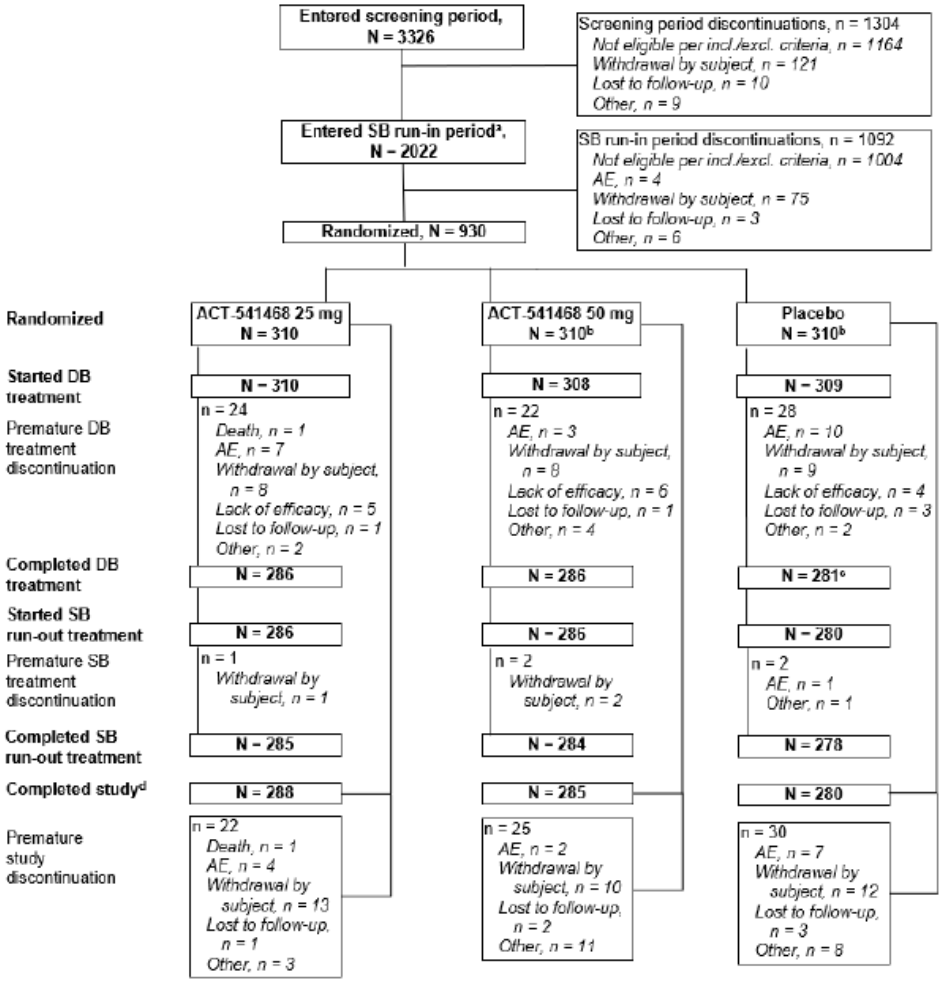
For study 301, based on a two-sample z-test, at least 900 subjects randomized to 50 mg daridorexant, 25 mg daridorexant, and placebo in a 1:1:1 ratio (i.e., 300 per group) provided at least 90% power to detect an effect size of 0.37 for testing 9 independent null hypotheses. This accounts for the Bonferroni correction.

For study 302, based on a two-sample z-test, at least 900 subjects randomized to 25 mg daridorexant, 10 mg daridorexant, and placebo in a 1:1:1 ratio (i.e., 300 per group) provided at least 90% power to detect an effect size of 0.37 for testing 9 independent null hypotheses. This accounts for the Bonferroni correction.

Results

Participant flow

Figure 10-1 Disposition of subjects in study ID-078A301



AE = adverse event; DB = double-blind; SB = single-blind.
Subjects are displayed by randomized treatment group.
[a] Subject received at least one dose of SB run-in treatment.
[b] 3 subjects (Subject 1600051 and Subject 3505068 [daridorexant 50 mg] and Subject 1903136 [placebo]) were discontinued from the study before receiving DB treatment as they did not meet eligibility criteria and had been randomized in error.
[c] Subject 1906070 completed DB treatment but did not start run-out treatment; the subject completed the study.
[d] Subject completed the 30-day follow-up telephone call.
Source: Compiled from Table 15.1.1-1.1, Table 15.1.1-2.1, Table 15.1.1-3.1, Table 15.1.1-4.1, Table 15.1.1-5.1, Listing 16.2.1-3.1, Listing 16.2.5-1.1.

Figure 10-1 Disposition of subjects in study ID-078A302

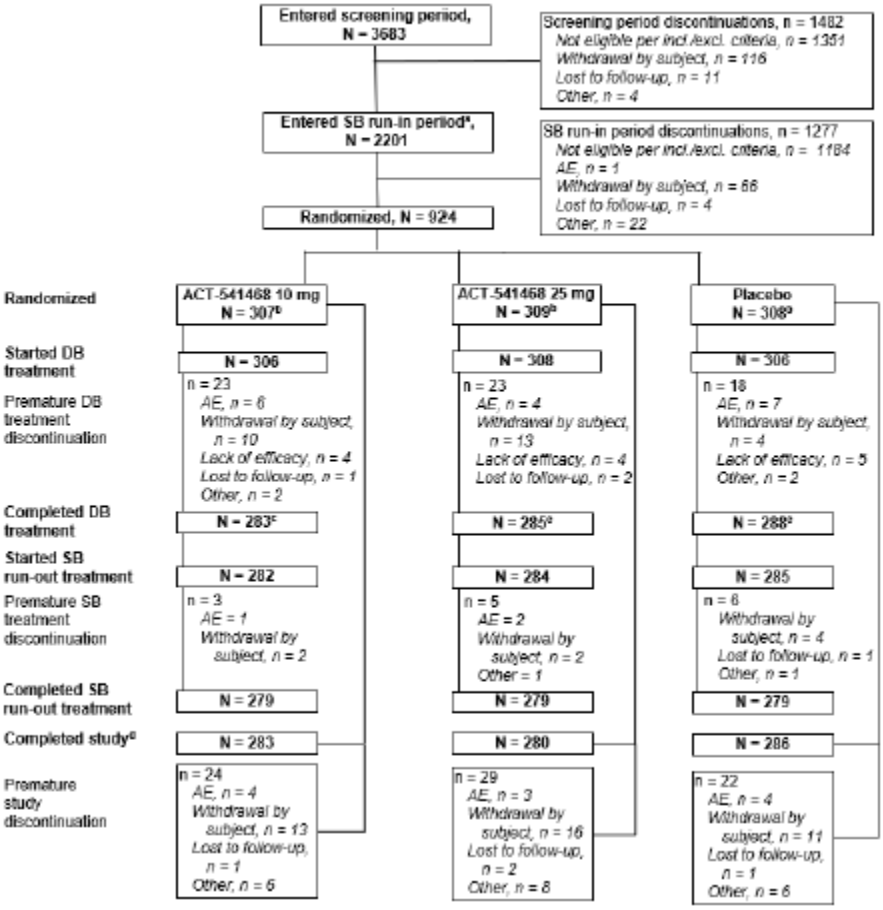


Table 3-2 Disposition of subjects and reasons for premature discontinuation of double-blind treatment in the individual confirmatory Phase 3 studies (Screened analysis set and FAS)

Disposition	Study 301 n (%)			Study 302 n (%)		
Screened analysis set						
Number of countries	10			11		
Number of centers	75			81		
Screened	3326			3683		
Screen failed (overall)	2396 (72.0)			2759 (74.9)		
Run-in period failed	1092 (32.8)			1277 (34.7)		
FAS	**25 mg (N = 310)**	**50 mg (N = 310)**	**Placebo (N = 310)**	**10 mg (N = 307)**	**25 mg (N = 309)**	**Placebo (N = 308)**
Randomized	310	310	310	307	309	308
Started double-blind treatment [a]	310 (100)	308 (99.4)	309 (99.7)	306 (99.7)	308 (99.7)	306 (99.4)
Completed double-blind treatment [a]	286 (92.3)	286 (92.3)	281 (90.6)	283 (92.2)	285 (92.2)	288 (93.5)
Started single-blind run-out treatment [b]	286 (100)	286 (100)	280 (99.6)	282 (99.6)	284 (99.6)	285 (99.0)
Completed single-blind run-out treatment [c]	285 (99.7)	284 (99.3)	278 (99.3)	279 (98.9)	279 (98.2)	279 (97.9)
Completed study [a]	288 (92.9)	285 (91.9)	280 (90.3)	283 (92.2)	280 (90.6)	286 (92.9)
Prematurely discontinued double-blind treatment [a]	24 (7.7)	22 (7.1)	28 (9.0)	23 (7.5)	23 (7.4)	18 (5.8)
Reason for premature discontinuation fr om double-blind treatment [a]						
Adverse event	7 (2.3)	3 (1.0)	10 (3.2)	6 (2.0)	4 (1.3)	7 (2.3)
Lack of efficacy	5 (1.6)	6 (1.9)	4 (1.3)	4 (1.3)	4 (1.3)	5 (1.6)
Withdrawal by subject	8 (2.6)	8 (2.6)	9 (2.9)	10 (3.3)	13 (4.2)	4 (1.3)
Lost to follow-up	1 (0.3)	1 (0.3)	3 (1.0)	1 (0.3)	2 (0.6)	0
Death	1 (0.3)	0	0	0	0	0
Other	2 (0.6)	4 (1.3)	2 (0.6)	2 (0.7)	0	2 (0.6)
Completed study and consented to:						
Participate in extension study [d] [e]	132 (45.8)	137 (48.1)	123 (43.9)	143 (50.5)	138 (49.3)	133 (46.5)
Not participate in extension study [d]	156 (54.2)	148 (51.9)	157 (56.1)	140 (49.5)	142 (50.7)	153 (53.5)

Baseline data

Table 3-4 Demographic characteristics in the individual Phase 3 studies (FAS) and the pooled FAS

Variable	Study 301			Study 302			Pooled data[a]	
Statistic	**25 mg (N = 310)**	**50 mg (N = 310)**	**Placebo (N = 310)**	**10 mg (N = 307)**	**25 mg (N = 309)**	**Placebo (N = 308)**	**25 mg (N = 619)**	**Placebo (N = 618)**
Mean (SD) age at screening [years]	55.8 (15.3)	55.5 (15.3)	55.1 (15.4)	57.1 (14.0)	56.3 (14.4)	56.7 (14.1)	56.0 (14.9)	55.9 (14.8)
Age stratification group 1 (years) [n(%)]								
≥ 65	121 (39.0)	121 (39.0)	122 (39.4)	121 (39.4)	121 (39.2)	121 (39.3)	242 (39.1)	243 (39.3)
Sex [n(%)]								
Female	215 (69.4)	199 (64.2)	210 (67.7)	215 (70.0)	218 (70.6)	205 (66.6)	433 (70.0)	415 (67.2)
Race[b] [n(%)]								
Black or African American	19 (6.1)	30 (9.7)	28 (9.0)	16 (5.2)	26 (8.4)	29 (9.4)	45 (7.3)	57 (9.2)
Asian	3 (1.0)	4 (1.3)	2 (0.6)	14 (4.6)	11 (3.6)	10 (3.2)	14 (2.3)	12 (1.9)
White	287 (92.6)	274 (88.4)	278 (89.7)	273 (88.9)	271 (87.7)	267 (86.7)	558 (90.1)	545 (88.2)
Ethnicity [n (%)]								
Hispanic or Latino	51 (16.5)	44 (14.2)	51 (16.5)	17 (5.5)	14 (4.5)	16 (5.2)	65 (10.5)	67 (10.8)
Region								
US	99 (31.9)	97 (31.3)	104 (33.5)	103 (33.6)	108 (35.0)	114 (37.0)	207 (33.4)	218 (35.3)
BMI at screening (kg/m²) Mean (SD)	26.6 (4.4)	26.3 (4.3)	26.4 (4.1)	26.0 (4.3)	26.1 (4.2)	26.2 (4.3)	26.4 (4.3)	26.3 (4.2)
BMI at screening (kg/m²) [n(%)]								
< 25.0	122 (39.4)	127 (41.0)	118 (38.1)	146 (47.6)	135 (43.7)	135 (43.8)	257 (41.5)	253 (40.9)
25.0 – ≤ 30.0	125 (40.3)	128 (41.3)	135 (43.5)	114 (37.1)	120 (38.8)	119 (38.6)	245 (39.6)	254 (41.1)
> 30.0	63 (20.3)	55 (17.7)	57 (18.4)	47 (15.3)	54 (17.5)	54 (17.5)	117 (18.9)	111 (18.0)

BMI = body mass index; FAS = Full analysis set; SD= standard deviation.
[a] Pooled daridorexant 25 mg and pooled placebo from studies 301 and 302.
[b] Race groups representing > 1% of subjects in any treatment group are presented.
Source: Compiled from D-20.118 table 15.1.4-1.1, D-20.183 table 15.1.4-1.1, and table ise-1.6.

Baseline insomnia characteristics

Table 3-5 Baseline insomnia characteristics (mean [SD]) in the individual Phase 3 studies (FAS)

	Study 301			Study 302		
Parameter	25 mg N = 310	50 mg N = 310	Placebo N = 310	10 mg N = 307	25 mg N = 309	Placebo N = 310
Time since insomnia diagnosis (years)						
Mean (SD)	10.17 (10.10)	10.73 (10.66)	10.96 (10.46)	12.12 (11.96)	11.73 (11.86)	10.54 (10.52)
Median (Q1, Q3)	6.9 (2.6, 14.3)	6.6 (3.2, 15.2)	8.2 (3.5, 15.2)	8.3 (3.2, 18.8)	8.2 (3.3, 15.7)	7.4 (2.7, 15.0)
WASO (min)	97.9 (38.8)	95.5 (37.8)	102.5 (40.8)	104.6 (46.2)	106.0 (49.1)	108.1 (48.7)
LPS (min)	67.3 (38.6)	63.6 (37.4)	66.5 (39.8)	67.4 (41.7)	68.9 (40.5)	71.8 (46.1)
sTST (min)	309.8 (60.1)	313.2 (57.6)	315.9 (53.1)	308.4 (51.4)	308.5 (52.8)	307.6 (51.5)
IDSIQ sleepiness domain score	22.1 (6.9)	22.5 (7.2)	22.3 (6.9)	22.7 (6.3)	22.2 (6.2)	22.6 (5.8)
IDSIQ alert/ cognition domain score	31.7 (10.1)	32.3 (10.6)	32.2 (10.2)	32.5 (8.9)	31.7 (8.8)	32.2 (8.4)
IDSIQ mood domain score	19.2 (8.7)	19.8 (8.6)	19.1 (8.8)	19.8 (7.8)	19.2 (7.7)	19.7 (7.6)
IDSIQ total score	73.1 (24.6)	74.5 (25.2)	73.6 (24.6)	75.1 (21.5)	73.1 (21.2)	74.5 (20.3)
ISI© score	19.0 (4.3)	19.3 (4.0)	19.2 (4.0)	19.9 (3.8)	19.5 (4.0)	19.6 (4.1)
ISI© ≥ 22 (% of N)	81 (26%)	90 (29%)	89 (29%)	106 (35%)	92 (30%)	103 (33%)

FAS = Full analysis set, IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; ISI© = Insomnia Severity Index©; LPS = latency to persistent sleep; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; sTST = subjective total sleep time; WASO = wake after sleep onset.
Higher IDSIQ sleepiness domain score represents greater daytime impairment.
Source: Compiled from D-20.118 table 15.1.4-3.1, table 15.2.9-1.1, table 15.2.9-2.1, table 15.2.9-3.1, table 15.2.9-4.1, table 15.2.9-8.1, table 15.2.9-9.1, table 15.2.9-10.1, table 15.2.9-29.1 and listing 16.2.6-13.1; and D-20.183 table 15.1.4-3.1, table 15.2.9-1.1, table 15.2.9-2.1, table 15.2.9-3.1, table 15.2.9-4.1, table 15.2.9-8.1, table 15.2.9-9.1, table 15.2.9-10.1, table 15.2.9-29.1 and listing 16.2.6-13.1.

Previous and concomitant diseases at baseline

In study 301, previous psychiatric disorders were reported for 54 subjects (5.8%), of which the most common was depression (24 subjects, 2.6%); additionally, major depression was reported for 7 subjects (0.8%) and anxiety for 4 subjects (0.4%).

In study 302, previous psychiatric disorders were reported for 63 subjects (6.8%), of which the most common was depression (38 subjects, 4.1%), followed by major depression (8 subjects; 0.9%) and anxiety (7 subjects; 0.8%).

Previous and concomitant therapy at baseline

In study 301, previous therapies discontinued less than 30 days prior to signing of the ICF were reported for 43 subjects (4.6%) in the Safety set; use of previous therapies was balanced across the treatment groups. ATC classes most commonly reported were benzodiazepine-related drugs (8 subjects, 0.9%), other antidepressants (8 subjects, 0.9%), benzodiazepine derivatives (6 subjects, 0.6%), and other hypnotics and sedatives (6 subjects, 0.6%).

Concomitant therapies ongoing at baseline

In study 302, previous therapies discontinued less than 30 days prior to signing of the ICF were reported for 60 subjects (6.5%) in the Safety set; use of previous therapies was balanced across the treatment groups.

ATC classes most commonly reported were benzodiazepine-related drugs (13 subjects, 1.4%), other hypnotics and sedatives (8 subjects, 0.9%), benzodiazepine derivatives (5 subjects, 0.5%), and melatonin receptor agonists (5 subjects, 0.5%).

Concomitant therapies ongoing at baseline

Numbers analysed

Table 3-3 Overview of analysis sets according to treatment randomized in the confirmatory Phase 3 studies 301 and 302 (FAS) and for pooled data (pooled FAS)

	Daridorexant			Placebo	Total
	10 mg n (%)	25 mg n (%)	50 mg n (%)	n (%)	n (%)
Study 301	-	**N = 310**	**N = 310**	**N = 310**	**N = 930**
Full analysis set (FAS)	-	310 (100)	310 (100)	310 (100)	930 (100)
Study 302	**N = 307**	**N = 309**	-	**N = 308**	**N = 924**
Full analysis set (FAS)	307 (100)	309 (100)	-	308 (100)	924 (100)
Pooled data		**N = 619**		**N = 618**	
Pooled Full analysis set (FAS)	-	619 (100)	-	618 (100)	-
Study 301	-	310 (50.1)	-	310 (50.2)	-
Study 302	-	309 (49.9)	-	308 (49.8)	-

FAS = Full analysis set.
Source: Compiled from D-20.118 table 15.1.2-1.1, D-20.183 table 15.1.2-1.1, and table ise-1.5.

Outcomes and estimation

Primary endpoint: Wake after sleep onset (WASO) at month 1 and month 3

Table 3-10 Between-treatment analysis for change from baseline in WASO (min) to Month 1 and Month 3 in the individual confirmatory Phase 3 studies and the pooled FAS

	Baseline** Mean (SD)	LS Means [95% CL]	Difference to placebo LS Means [95% CL]	Difference to placebo P-value (two-sided)
Study 302 (FAS)				
Change from baseline to Month 1				
10 mg (N = 307)	104.6 (46.2)	–15.3 [–19.5, –11.1]	–2.7 [–8.7, 3.2]	0.3669
25 mg (N = 309)	106.0 (49.1)	–24.2 [–28.5, –19.9]	–11.6 [–17.6, –5.6]	0.0001*
Placebo (N = 308)	108.1 (48.7)	–12.6 [–16.8, –8.3]	-	-
Change from baseline to Month 3				
10 mg (N = 307)	104.6 (46.2)	–16.0 [–20.7, –11.2]	–2.0 [–8.7, 4.8]	0.5686
25 mg (N = 309)	106.0 (49.1)	–24.3 [–29.0, –19.5]	–10.3 [–17.0, –3.5]	0.0028*
Placebo (N = 308)	108.1 (48.7)	–14.0 [–18.8, –9.2]	-	-
Study 301 (FAS)				
Change from baseline to Month 1				
25 mg (N = 310)	97.9 (38.8)	–18.4 [–22.1, –14.7]	–12.2 [–17.4, –7.0]	< .0001*
50 mg (N = 310)	95.5 (37.8)	–29.0 [–32.7, –25.3]	–22.8 [–28.0, –17.6]	< .0001*
Placebo (N = 310)	102.5 (40.8)	–6.2 [–9.9, –2.5]	-	-
Change from baseline to Month 3				
25 mg (N = 310)	97.9 (38.8)	–23.0 [–27.0, –19.0]	–11.9 [–17.5, –6.2]	< .0001*
50 mg (N = 310)	95.5 (37.8)	–29.4 [–33.4, –25.4]	–18.3 [–23.9, –12.7]	< .0001*
Placebo (N = 310)	102.5 (40.8)	–11.1 [–15.1, –7.1]	-	-
Pooled analysis (Pooled FAS)				
Change from baseline to Month 1				
25 mg (N = 619)	101.9 (44.4)	–22.0 [–24.9, –19.0]	–11.9 [–15.9, –7.8]	<.0001
Placebo (N = 618)	105.3 (45.0)	–10.1 [–13.0, –7.2]	-	-
Change from baseline to Month 3				
25 mg (N = 619)	101.9 (44.4)	–24.5 [–27.7, –21.3]	–11.1 [–15.6, –6.6]	<.0001
Placebo (N = 618)	105.3 (45.0)	–13.4 [–16.6, –10.2]	-	-
Study effect 301 vs 302		–0.4 [–4.0, 3.1]	-	-

Primary endpoint: Latency to persistent sleep (LPS) at month 1 and month 3

Table 3-11 Between-treatment analysis for change from baseline in LPS (min) to Month 1 and Month 3 in the individual confirmatory Phase 3 studies and the pooled FAS

	Baseline** Mean (SD)	LS Means [95% CL]	Difference to placebo LS Means [95% CL]	Difference to placebo P-value (two-sided)
Study 302 (FAS)				
Change from baseline to Month 1				
10 mg (N = 307)	67.4 (41.7)	–22.6 [–26.7, –18.5]	–2.6 [–8.4, 3.2]	0.3782
25 mg (N = 309)	68.9 (40.5)	–26.5 [–30.6, –22.3]	–6.5 [–12.3, –0.6]	0.0303
Placebo (N = 308)	71.8 (46.1)	–20.0 [–24.1, –15.9]	-	-
Change from baseline to Month 3				
10 mg (N = 307)	67.4 (41.7)	–23.1 [–27.6, –18.6]	–3.2 [–9.5, 3.1]	0.3233
25 mg (N = 309)	68.9 (40.5)	–28.9 [–33.4, –24.4]	–9.0 [–15.3, –2.7]	0.0053
Placebo (N = 308)	71.8 (46.1)	–19.9 [–24.4, –15.4]	-	-
Study 301 (FAS)				
Change from baseline to Month 1				
25 mg (N = 310)	67.3 (38.6)	–28.2 [–31.5, –24.8]	–8.3 [–13.0, –3.6]	0.0005*
50 mg (N = 310)	63.6 (37.4)	–31.2 [–34.5, –27.9]	–11.4 [–16.0, –6.7]	< .0001*
Placebo (N = 310)	66.5 (39.8)	–19.9 [–23.2, –16.5]	-	-
Change from baseline to Month 3				
25 mg (N = 310)	67.3 (38.6)	–30.7 [–34.0, –27.4]	–7.6 [–12.3, –2.9]	0.0015*
50 mg (N = 310)	63.6 (37.4)	–34.8 [–38.1, –31.5]	–11.7 [–16.3, –7.0]	< .0001*
Placebo (N = 310)	66.5 (39.8)	–23.1 [–26.5, –19.8]	-	-
Pooled analysis (Pooled FAS)				
Change from baseline to Month 1				
25 mg (N = 619)	68.1 (39.5)	–28.0 [–30.6, –25.4]	–7.3 [–11.0, –3.7]	<.0001
Placebo (N = 618)	69.2 (43.1)	–20.6 [–23.2, –18.0]	-	-
Change from baseline to Month 3				
25 mg (N = 619)	68.1 (39.5)	–30.5 [–33.4, –27.6]	–8.3 [–12.4, –4.3]	<.0001
Placebo (N = 618)	69.2 (43.1)	–22.2 [–25.1, –19.3]	-	-
Study effect 301 vs 302		–3.2 [–6.4, 0.0]		

Secondary endpoint: Subjective total sleep time (sTST) at month 1 and month 3

Table 3-13 Between-treatment analysis for change from baseline in sTST (min) to Month 1 and Month 3 in the individual confirmatory Phase 3 studies and the pooled FAS

			Difference to placebo	
	Baseline** Mean (SD)	LS Means [95% CL]	LS Means [95% CL]	P-value (two-sided)
Study 302 (FAS)				
Change from baseline to Month 1				
10 mg (N = 307)	308.4 (51.4)	41.0 [35.4, 46.6]	13.4 [5.5, 21.2]	0.0009
25 mg (N = 309)	308.5 (52.8)	43.8 [38.1, 49.4]	16.1 [8.2, 24.0]	<.0001*
Placebo (N = 308)	307.6 (51.5)	27.6 [22.0, 33.3]	-	-
Change from baseline to Month 3				
10 mg (N = 307)	308.4 (51.4)	50.7 [44.4, 57.0]	13.6 [4.7, 22.5]	0.0028
25 mg (N = 309)	308.5 (52.8)	56.2 [49.8, 62.5]	19.1 [10.1, 28.0]	<.0001*
Placebo (N = 308)	307.6 (51.5)	37.1 [30.8, 43.5]	-	-
Study 301 (FAS)				
Change from baseline to Month 1				
25 mg (N = 310)	309.8 (60.1)	34.2 [28.7, 39.6]	12.6 [5.0, 20.3]	0.0013*
50 mg (N = 310)	313.2 (57.6)	43.6 [38.2, 49.1]	22.1 [14.4, 29.7]	< .0001*
Placebo (N = 310)	315.9 (53.1)	21.6 [16.1, 27.0]	-	-
Change from baseline to Month 3				
25 mg (N = 310)	309.8 (60.1)	47.8 [41.3, 54.3]	9.9 [0.8, 19.1]	0.0334*
50 mg (N = 310)	313.2 (57.6)	57.7 [51.2, 64.2]	19.8 [10.6, 28.9]	< .0001*
Placebo (N = 310)	315.9 (53.1)	37.9 [31.4, 44.4]	-	-
Pooled analysis (Pooled FAS)				
Change from baseline to Month 1				
25 mg (N = 619)	309.2 (56.6)	38.9 [35.1, 42.7]	14.3 [9.0, 19.6]	<.0001
Placebo (N = 618)	311.7 (52.5)	24.6 [20.8, 28.4]	-	-
Change from baseline to Month 3				
25 mg (N = 619)	309.2 (56.6)	51.9 [47.5, 56.4]	14.4 [8.2, 20.7]	<.0001
Placebo (N = 618)	311.7 (52.5)	37.5 [33.0, 41.9]	-	-
Study effect 301 vs 302		–5.9 [–11.1, –0.7]		

Responders analysis on sTST

Minimum change in sTST of clinical importance at an individual level of 55 minutes was determined. The percentage of subjects showing an improvement of at least 55 minutes from baseline at Month 3 was 48.4% in the daridorexant 50 mg group, 41.1% in the 25 mg group and 36.7% in the placebo group in study 301.

In study 302, 47.4% 46.0% and 34.5% of subjects achieved an improvement of at least 55 minutes from baseline at Month 3 in the 25 mg, 10 mg and placebo groups.

Secondary endpoint: IDSIQ – sleepiness domain score at month 1 and month 3

Table 3-14 Between-treatment analysis for change from baseline in IDSIQ sleepiness domain score to Month 1 and Month 3 in the individual confirmatory Phase 3 studies and the pooled FAS

	Baseline** Mean (SD)	LS Means [95% CL]	Difference to placebo LS Means [95% CL]	Difference to placebo P-value (two-sided)
Study 302 (FAS)				
Change from baseline to Month 1				
10 mg (N = 307)	22.7 (6.3)	–3.2 [–3.8, –2.6]	–0.4 [–1.3, 0.4]	0.3048
25 mg (N = 309)	22.2 (6.2)	–3.5 [–4.1, –2.9]	–0.8 [–1.6, 0.1]	0.0733
Placebo (N = 308)	22.6 (5.8)	–2.8 [–3.3, –2.2]	-	-
Change from baseline to Month 3				
10 mg (N = 307)	22.7 (6.3)	–4.8 [–5.4, –4.1]	–0.7 [–1.7, 0.2]	0.1393
25 mg (N = 309)	22.2 (6.2)	–5.3 [–6.0, –4.6]	–1.3 [–2.2, –0.3]	0.0120
Placebo (N = 308)	22.6 (5.8)	–4.0 [–4.7, –3.3]	-	-
Study 301 (FAS)				
Change from baseline to Month 1				
25 mg (N = 310)	22.1 (6.9)	–2.8 [–3.3, –2.2]	–0.8 [–1.5, 0.0]	0.0547
50 mg (N = 310)	22.5 (7.2)	–3.8 [–4.3, –3.2]	–1.8 [–2.5, –1.0]	< .0001*
Placebo (N = 310)	22.3 (6.9)	–2.0 [–2.6, –1.5]	-	-
Change from baseline to Month 3				
25 mg (N = 310)	22.1 (6.9)	–4.8 [–5.5, –4.1]	–1.0 [–2.0, 0.0]	0.0534
50 mg (N = 310)	22.5 (7.2)	–5.7 [–6.4, –5.0]	–1.9 [–2.9, –0.9]	0.0002*
Placebo (N = 310)	22.3 (6.9)	–3.8 [–4.5, –3.1]	-	–
Pooled analysis (Pooled FAS)				
Change from baseline to Month 1				
25 mg (N = 619)	22.2 (6.5)	–3.1 [–3.5, –2.7]	–0.8 [–1.3, –0.2]	0.0053
Placebo (N = 618)	22.4 (6.4)	–2.4 [–2.7, –2.0]	-	-
Change from baseline to Month 3				
25 mg (N = 619)	22.2 (6.5)	–5.0 [–5.5, –4.5]	–1.1 [–1.8, –0.4]	0.0013
Placebo (N = 618)	22.4 (6.4)	–3.9 [–4.3, –3.4]	-	-
Study effect 301 vs 302		0.7 [0.1, 1.2]		

Responders analysis on IDSIQ sleepiness domain score

Minimum improvement of clinical importance on the IDSIQ sleepiness domain of 4 points, at the individual level, was determined. In study 301, the percentage of subjects showing a decrease from baseline at Month 3 in the IDSIQ sleepiness domain score of at least 4 points was 52.9% in the daridorexant 50 mg group, 50.0% in the 25 mg group and 44.4% in the placebo group. In study 302, 49.1, 47.6 and 43.9% of subjects achieved a decrease from baseline at Month 3 in IDSIQ sleepiness domain score of at least 4 points in the 25 mg, 10 mg and placebo groups.

A decrease of at least 8 points (corresponding to a Patient Global Impression of Change score "moderately better" or to 2 point decrease in Patient Global Impression of Severity) was achieved by 37.1% of subjects in the 50 mg group, 25.5% in the 25 mg group and 24.0% in the placebo group.

Other efficacy endpoints

Objective total sleep time (TST)

Table 3-15 Between-treatment analysis for change from baseline in TST (min) to Month 1 and Month 3 in the individual confirmatory Phase 3 studies and the pooled FAS

	Baseline** Mean (SD)	LS Means [95% CL]	Difference to placebo LS Means [95% CL]	Difference to placebo P-value (two-sided)
Study 302 (FAS)				
Change from baseline to Month 1				
10 mg (N = 307)	316.2 (63.5)	36.6 [31.3, 41.9]	6.2 [–1.3, 13.7]	0.1050
25 mg (N = 309)	312.6 (68.8)	48.1 [42.7, 53.5]	17.7 [10.2, 25.2]	<.0001
Placebo (N = 308)	307.4 (69.0)	30.4 [25.1, 35.7]	-	-
Change from baseline to Month 3				
10 mg (N = 307)	316.2 (63.5)	35.7 [29.8, 41.5]	4.6 [–3.6, 12.8]	0.2736
25 mg (N = 309)	312.6 (68.8)	48.5 [42.6, 54.3]	17.4 [9.2, 25.5]	<.0001
Placebo (N = 308)	307.4 (69.0)	31.1 [25.3, 36.9]	-	-
Study 301 (FAS)				
Change from baseline to Month 1				
25 mg (N = 310)	322.5 (55.1)	45.3 [40.2, 50.3]	20.6 [13.5, 27.7]	< .0001
50 mg (N = 310)	328.3 (50.2)	58.0 [53.0, 63.0]	33.4 [26.3, 40.4]	< .0001
Placebo (N = 310)	318.6 (54.4)	24.7 [19.6, 29.7]	-	-
Change from baseline to Month 3				
25 mg (N = 310)	322.5 (55.1)	51.4 [46.3, 56.4]	18.4 [11.2, 25.5]	< .0001
50 mg (N = 310)	328.3 (50.2)	61.7 [56.6, 66.7]	28.6 [21.5 35.8]	< .0001
Placebo (N = 310)	318.6 (54.4)	33.1 [28.0, 38.1]	-	-
Pooled analysis (Pooled FAS)				
Change from baseline to Month 1				
25 mg (N = 619)	317.6 (62.5)	48.1 [44.4, 51.8]	19.1 [13.9, 24.2]	<.0001
Placebo (N = 618)	313.0 (62.3)	29.1 [25.4, 32.7]	-	-
Change from baseline to Month 3				
25 mg (N = 619)	317.6 (62.5)	51.6 [47.6, 55.5]	17.8 [12.3, 23.3]	<.0001
Placebo (N = 618)	313.0 (62.3)	33.7 [29.8, 37.7]	-	-
Study effect 301 vs 302		4.5 [–0.0, 9.1]		

Subjective sleep maintenance (sWASO)

Table 3-16 Between-treatment analysis for change from baseline in sWASO (min) to Month 1 and Month 3 in the individual confirmatory Phase 3 studies and the pooled FAS

	Baseline** Mean (SD)	LS Means [95% CL]	Difference to placebo LS Means [95% CL]	Difference to placebo P-value (two-sided)
Study 302 (FAS)				
Change from baseline to Month 1				
10 mg (N = 307)	79.1 (45.3)	–22.8 [–27.3, –18.3]	–4.3 [–10.6, 2.0]	0.1837
25 mg (N = 309)	78.3 (43.6)	–19.9 [–24.4, –15.3]	–1.4 [–7.8, 5.0]	0.6687
Placebo (N = 308)	79.6 (46.1)	–18.5 [–23.0, –13.9]	-	-
Change from baseline to Month 3				
10 mg (N = 307)	79.1 (45.3)	-26.9 [–31.3, –22.5]	–4.9 [–11.1, 1.3]	0.1219
25 mg (N = 309)	78.3 (43.6)	-27.1 [–31.5, –22.7]	–5.1 [–11.3, 1.2]	0.1114
Placebo (N = 308)	79.6 (46.1)	-22.0 [–26.5, –17.6]	-	-
Study 301 (FAS)				
Change from baseline to Month 1				
25 mg (N = 310)	88.5 (60.1)	–24.3 [–28.8, –19.7]	–8.3 [–14.8, –1.9]	0.0111
50 mg (N = 310)	79.7 (53.3)	–23.1 [–27.6, –18.5]	–7.1 [–13.5, –0.7]	0.0294
Placebo (N = 310)	81.6 (52.6)	–15.9 [–20.5, –11.3]	-	-
Change from baseline to Month 3				
25 mg (N = 310)	88.5 (60.1)	–30.8 [–35.9, –25.8]	–6.9 [–14.0, 0.3]	0.0604
50 mg (N = 310)	79.7 (53.3)	–28.8 [–33.9, –23.7]	–4.8 [–11.9, 2.4]	0.1892
Placebo (N = 310)	81.6 (52.6)	–24.0 [–29.1, –18.9]	-	-
Pooled analysis (Pooled FAS)				
Change from baseline to Month 1				
25 mg (N = 619)	83.4 (52.7)	–22.2 [–25.4, –19.0]	–4.7 [–9.2, –0.2]	0.0404
Placebo (N = 618)	80.6 (49.4)	–17.5[–20.7, –14.3]	-	-
Change from baseline to Month 3				
25 mg (N = 619)	83.4 (52.7)	–29.2 [–32.6, –25.7]	–5.8 [–10.7, –1.0]	0.0179
Placebo (N = 618)	80.6 (49.4)	–23.3 [–26.8, –19.9]	-	-
Study effect 301 vs 302		0.7 [–3.4, 4.9]		

Subjective sleep onset (sLSO)

Table 3-17 Between-treatment analysis for change from baseline in sLSO (min) to Month 1 and Month 3 in the individual confirmatory Phase 3 studies and the pooled FAS

	Baseline** Mean (SD)	LS Means [95% CL]	Difference to placebo LS Means [95% CL]	Difference to placebo P-value (two-sided)
Study 302 (FAS)				
Change from baseline to Month 1				
10 mg (N = 307)	66.4 (36.6)	−18.6 [−21.88, −15.4]	−4.6 [−9.1, −0.0]	0.0488
25 mg (N = 309)	62.5 (35.0)	−20.2 [−23.5, −16.9]	−6.2 [−10.8, −1.6]	0.0085
Placebo (N = 308)	67.3 (38.3)	−14.0 [−17.3, −10.8]	-	-
Change from baseline to Month 3				
10 mg (N = 307)	66.4 (36.6)	−23.7 [−26.9, −20.4]	−7.1 [−11.7, −2.5]	0.0026
25 mg (N = 309)	62.5 (35.0)	−24.8 [−28.1, −21.5]	−8.3 [−12.9, −3.6]	0.0005
Placebo (N = 308)	67.3 (38.3)	−16.5 [−19.8, −13.2]	-	-
Study 301 (FAS)				
Change from baseline to Month 1				
25 mg (N = 310)	64.5 (41.1)	−14.9 [−18.1, −11.6]	−7.3 [−11.8, −2.8]	0.0015
50 mg (N = 310)	60.6 (34.3)	−15.3 [−18.5, −12.1]	−7.8 [−12.3, −3.3]	0.0008
Placebo (N = 310)	58.5 (32.1)	−7.5 [−10.8, −4.3]	-	-
Change from baseline to Month 3				
25 mg (N = 310)	64.5 (41.1)	−20.1 [−23.7, −16.5]	−8.4 [−13.4, −3.3]	0.0012
50 mg (N = 310)	60.6 (34.3)	−18.3 [−21.8, −14.6]	−6.5 [−11.6, −1.4]	0.0121
Placebo (N = 310)	58.5 (32.1)	−11.8 [−15.4, −8.2]	-	-
Pooled analysis (Pooled FAS)				
Change from baseline to Month 1				
25 mg (N = 619)	63.5 (38.1)	−17.3 [−19.6, −14.9]	−6.6 [−9.9, −3.3]	<.0001
Placebo (N = 618)	62.9 (35.5)	−10.7 [−13.0, −8.3]	-	-
Change from baseline to Month 3				
25 mg (N = 619)	63.5 (38.1)	−22.2 [−24.6, −19.7]	−8.1 [−11.6, −4.6]	<.0001
Placebo (N = 618)	62.9 (35.5)	−14.1 [−16.5, −11.6]	-	-
Study effect 301 vs 302		3.4 [0.3, 6.5]		

IDSIQ scores

IDSIQ total score ranging from 0 to 140 include sleepiness domain (ranging from 0 to 40) alert/cognition domain score (ranging from 0 to 60), and mood domain score (ranging from 0 to 40).

At baseline, mean IDSIQ total scores ranged between 73.1 and 75.1 across treatment groups of both studies, approximately at the mid-point of the 140-point scale. Both at Month 1 and Month 3, differences to placebo were in favor of daridorexant at all doses. The LS mean difference to placebo at month 1 and month 3 are higher in the daridorexant 50 mg arm (-7.2 [-10.5; -3.9] at month 3) compared to the 25 mg arm (-3.5 [-6.8; -0.1] at month 3 in study 301).

At baseline, mean IDSIQ alert /cognition domain ranged between 31.7 and 32.5 across treatment groups of both studies, approximately at the mid-point of the 60-point scale. Both at Month 1 and Month 3, differences to placebo were in favor of daridorexant at all doses. The LS mean difference to placebo at month 1 and month 3 are higher in the daridorexant 50 mg arm (-2.5 [-3.9; -1.1] at month 3) compared to the 25 mg arm (-0.9 [-2.3; 0.5] at month 3 in study 301).

At baseline, mean IDSIQ mood domain ranged between 19.1 and 19.8 across treatment groups of both studies, approximately at the mid-point of the 40-point scale. Both at Month 1 and Month 3, differences to placebo were in favor of daridorexant at all doses. The LS mean difference to placebo at month 1 and month

3 is higher in the daridorexant 50 mg arm (-2.8 [-3.8; -1.7] at month 3) compared to the 25 mg arm (-1.6 [-2.6; -0.5] at month 3 in study 301).

Exploratory endpoints

Visual analog scales

As part of the SDQ, 5 VAS scores collected daily information on the quality of sleep, depth of sleep, morning sleepiness (all assessed in the morning: morning VAS), as well as daytime alertness and daily ability to function (both assessed in the evening: evening VAS). The VAS scores were answered on a continuous bipolar scale ranging from 0–100 points, with a higher score reflecting a better outcome.

Observed results on VAS scores are consistent with the effects observed on the other endpoints. An improvement of sleep quality and daytime functioning is observed with daridorexant 50 mg but also at 25 mg compared to placebo. The LS mean difference to placebo is higher with the 50 mg dose compared to the 25 mg dose.

Insomnia Severity Index© score

Table 3-23 ISI© score in the individual confirmatory Phase 3 studies, FAS

Endpoint - Baseline and change from baseline to Month 1 (M1) and Month 3 (M3)		Study 302			Study 301		
		10 mg (N = 307)	25 mg (N = 309)	Placebo (N = 308)	25 mg (N = 310)	50 mg (N = 310)	Placebo (N = 310)
ISI© score[1]							
Baseline:	n	305	308	306	310	308	309
	Mean (SD)	19.9 (3.8)	19.5 (4.0)	19.6 (4.1)	19.0 (4.3)	19.3 (4.0)	19.2 (4.0)
Change to M1:	n	297	287	294	292	299	297
	Mean (SD)	–4.7 (5.1)	–5.1 (5.2)	–3.8 (4.6)	–4.1 (4.7)	–4.9 (5.5)	–3.1 (4.7)
Change to M3:	n	272	280	277	286	283	281
	Mean (SD)	–6.9 (6.2)	–6.9 (6.0)	–5.4 (5.5)	–6.0 (5.8)	–7.2 (6.5)	–5.4 (5.7)
ISI© score < 10[2]							
Baseline:	Nn (%)	1 (0.3)	3 (1.0)	1 (0.3)	5 (1.6)	5 (1.6)	2 (0.6)
M1:	Nn (%)	49 (16.4)[3]	60 (20.9)	40 (13.6)	56 (19.2)	61 (20.4)	33 (11.1)
M3:	Nn (%)	91 (33.3)[3]	95 (33.9)	64 (23.1)	98 (34.3)	100 (35.3)	71 (25.3)
ISI© decrease ≥ 6 points from baseline[2]							
M1:	Nn (%)	112 (37.7)	109 (38.0)	87 (29.6)	103 (35.3)	120 (40.1)	85 (28.6)
M3:	Nn (%)	149 (54.8)	154 (55.0)	127 (45.8)	145 (50.7)	160 (56.5)	131 (46.6)

The proportion of subjects with an ISI© score < 10 at the end of the study was higher in daridorexant 50mg group (about 35% at month 3) compared to the placebo groups (about 24% at month 3). The proportion of subjects with an ISI© score < 10 in daridorexant 25 mg was about 20%.

The proportion of subjects with a decrease in ISI© score of ≥ 6 points from baseline was higher in daridorexant 50 mg group (56.5% at month 3) compared to the placebo groups (46% at month 3). The proportion of subjects with an ISI© score of ≥ 6 points from baseline in daridorexant 25 mg was about 50% at month 3. Difference between daridorexant doses is low with a slight higher proportion with the 50 mg dose. Effect on ISI score observed at month 1 is increased at month 3.

Sleep architecture

PSG assessments done at baseline, Month 1 and Month 3 evaluated the effect of treatment on sleep architecture in the pivotal Phase 3 studies.

The percentage of rapid eye movement in relation to TST did not change with daridorexant treatment when compared to baseline.

Ancillary analyses

In the individual studies, subgroup analyses were performed by age (< 65; ≥ 65 years), sex (male; female), and region (US; other).

An additional post-hoc subgroup analysis by region (Europe; other) at Month 1 and Month 3 was performed for the 2 studies separately. "Europe" included subjects enrolled in sites from Denmark, Germany, Poland, Spain and Switzerland (study 301) and Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Hungary, and Sweden (study 302).

There is no apparent difference of the results depending on the sex, age or region observed in study 301 or in study 302.

For the pooled FAS, pre-planned subgroups of interest included age (< 65 years vs ≥ 65 years, and < 75 years vs ≥ 75 years), sex (male/female), region (US vs other), ethnicity (White vs Black/African American vs others), and BMI (> 30 kg/m2 vs ≤ 30 kg/m2). No difference is observed.

Summary of main efficacy results

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

Table I Summary of efficacy for trial 301

Title: Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety of ACT-541468 in adult and elderly subjects with insomnia disorder.	
Study identifier	ID-078A301
Design	Multi-center, double-blind (DB), randomized, placebo-controlled, parallel-group The study protocol comprised a core study, and a patient preferences sub-study (PAUSe). The core study consisted of a Screening phase with a screening period and placebo run-in period (20-31 days), a DB treatment phase (84 days), and a safety follow-up phase (30 days). Subjects who completed study treatment (DB treatment and placebo run-out treatment) in the core study were eligible to enter an extension study, ID-078A303 that was conducted at all study sites in the USA and Germany. At site visits (prior to PSG nights), study treatment (placebo run-in, DB, or placebo run-out treatment) was administered at least 2 h after the evening meal and approximately 30 min before lights off. At home, study treatment was taken at bedtime.

	Duration of Run-in phase: Duration of main phase: Duration of Run out: Duration of extension phase		13-24 days 84 days 7 weeks 40 weeks
Hypothesis	Superiority over placebo		
Treatments groups	Daridorexant (ACT-541468) 25 mg		84 ± 2 days
	Daridorexant (ACT-541468) 50 mg		84 ± 2 days
	Placebo (PBO)		Double blind phase: 84 ± 2 days
Endpoints and definitions	Co-Primary endpoints	WASO at M1	WASO was the time spent awake after onset of persistent sleep until lights on, as determined by PSG (sleep maintenance). Change from baseline to Month 1
		WASO at M3	Change from baseline to Month 3
		LPS at M1	LPS was the time from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 min) scored as non-awake, i.e., epochs scored as either S1, S2, SWS or REM, as determined by PSG (sleep onset). Change from baseline to Month 1 in LPS
		LPS at M3	Change from baseline to Month 3 in LPS.
	Key Secondary endpoints	sTST at M1	sTST was the time reported by the subject in answer to the SDQ question "In total, how long did you sleep last night?" Change from baseline to Month 1
		IDSIQ sleepiness domain score at M1	The IDSIQ is a patient-reported outcome measure structured in 3 domains (alert/cognition; mood; sleepiness). The IDSIQ sleepiness domain score, based on the subject's responses for 4 items, could range from 0 to 40 (whole numbers only) with higher scores indicating greater burden of illness during the daytime. Change from baseline to Month 1
	Key other endpoint	TST at M1	TST is the time recorded by PSG from non-awake. Change from baseline to Month 1
Database lock	31 March 2020.		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	The analysis of primary and secondary efficacy endpoints described below were performed using the Full analysis set, which included all randomized subjects. All available data were included in the analysis as per the intention-to-treat principle.			
Descriptive statistics and effect estimate per comparison vs placebo Co-primary endpoints	Treatment group	Daridorexant 25 mg	Daridorexant 50 mg	Placebo
	Number of subject	310	310	310
	Change in **WASO** from baseline to **M1** LS mean [95% CL]	−18.4 [−22.1, −14.7]	−29.0 [−32.7, −25.3]	−6.2 [−9.9, −2.5]
	LS Mean Difference to placebo [95% CL]	−12.2 [−17.4, −7.0]	−22.8 [−28.0, −17.6]	NA
	P-value	< .0001*	< .0001*	NA
	Change in **WASO** from baseline to **M3** LS mean [95% CL]	−23.0 [−27.0, −19.0]	−29.4 [−33.4, −25.4]	−11.1 [−15.1, -7.1]
	LS Mean Difference to placebo [95% CL]	−11.9 [−17.5, −6.2]	−18.3 [-23.9, -12.7]	NA
	P-value	< .0001*	< .0001*	NA
	Change in **LPS** from baseline to **M1** LS mean [95% CL]	−28.2 [−31.5, −24.8]	−31.2 [−34.5, −27.9]	−19.9 [−23.2, -16.5]
	LS Mean Difference to placebo [95% CL]	−8.3 [−13.0, −3.6]	−11.4 [−16.0, −6.7]	NA
	P-value	0.0005*	< .0001*	NA
	Change in **LPS** from baseline to **M3** LS mean [95% CL]	−30.7 [−34.0, −27.4]	−34.8 [−38.1, −31.5]	−23.1 [−26.5, −19.8]
	LS Mean Difference to placebo [95% CL]	−7.6 [−12.3, −2.9]	−11.7 [−16.3, −7.0]	NA
	P-value	0.0015*	< .0001*	NA
Key secondary endpoint	Change in **sTST** from baseline to **M1** LS mean [95% CL]	34.2 [28.7, 39.6]	43.6 [38.2, 49.1]	21.6 [16.1, 27.0]
	LS Mean Difference to placebo [95% CL]	12.6 [5.0, 20.3]	22.1 [14.4, 29.7]	NA

	P-value	0.0013*	< .0001*	NA
	Change in **IDSIQ sleepiness domain** from baseline to **M1** LS mean [95% CL]	−2.8 [−3.3, −2.2]	−3.8 [−4.3, −3.2]	−2.0 [−2.6, −1.5]
	LS Mean Difference to placebo [95% CL]	−0.8 [−1.5, 0.0]	−1.8 [−2.5, −1.0]	NA
	P-value	0.0547	< .0001*	NA
Key other endpoint	Change in **TST** from baseline to **M1** LS mean [95% CL]	45.3 [40.2, 50.3]	58.0 [53.0, 63.0]	24.7 [19.6, 29.7]
	LS Mean Difference to placebo [95% CL]	20.6 [13.5, 27.7]	33.4 [26.3, 40.4]	NA
	P-value	< .0001	< .0001	NA
Notes	After multiplicity comparison adjustment, the effects comparing daridorexant vs PBO in ITT population at 25 mg and 50 mg are statistically significant for all endpoints presented above except for IDSIQ sleepiness domain at 25 mg.			
Analysis description	**Secondary analysis** Please refer to respective sections in the AR			

Table II. Summary of efficacy for trial 302

Title: Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety of ACT-541468 in adult and elderly subjects with insomnia disorder		
Study identifier	ID-078A302	
Design	Multi-center, double-blind (DB), randomized, placebo-controlled, parallel-group The study protocol comprised a core study, and a patient preferences sub-study (PAUSe). The core study consisted of a Screening phase with a screening period and placebo run-in period (20-31 days), a DB treatment phase (84 days), and a safety follow-up phase (30 days). Subjects who completed study treatment (DB treatment and placebo run-out treatment) in the core study were eligible to enter an extension study, ID-078A303 that was conducted at all study sites in the USA and Germany. At site visits (prior to PSG nights), study treatment (placebo run-in, DB, or placebo run-out treatment) was administered at least 2 h after the evening meal and approximately 30 min before lights off. At home, study treatment was taken at bedtime.	
	Duration of Run-in phase:	13-24 days
	Duration of main phase:	84 days
	Duration of Run out:	7 weeks
	Duration of extension phase	40 weeks

Hypothesis	Superiority over placebo		
Treatments groups	Daridorexant (ACT-541468) 10 mg		84 ± 2 days
	Daridorexant (ACT-541468) 25 mg		84 ± 2 days
	Placebo (PBO)		Double blind phase: 84 ± 2 days
Endpoints and definitions	Co-Primary endpoints	WASO at M1	WASO was the time spent awake after onset of persistent sleep until lights on, as determined by PSG (sleep maintenance). Change from baseline to Month 1
		WASO at M3	Change from baseline to Month 3
		LPS at M1	LPS was the time from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 min) scored as non-awake, i.e., epochs scored as either S1, S2, SWS or REM, as determined by PSG (sleep onset). Change from baseline to Month 1 in LPS
		LPS at M3	Change from baseline to Month 3 in LPS.
	Key Secondary endpoints	sTST at M1	sTST was the time reported by the subject in answer to the SDQ question "In total, how long did you sleep last night?" Change from baseline to Month 1
		IDSIQ sleepiness domain score at M1	The IDSIQ is a patient-reported outcome measure structured in 3 domains (alert/cognition; mood; sleepiness). The IDSIQ sleepiness domain score, based on the subject's responses for 4 items, could range from 0 to 40 (whole numbers only) with higher scores indicating greater burden of illness during the daytime. Change from baseline to Month 1
	Key other endpoint	TST at M1	TST is the time recorded by PSG from non-awake. Change from baseline to Month 1
Database lock	18 June 2020.		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The analysis of primary and secondary efficacy endpoints described below were performed using the Full analysis set, which included all randomized subjects. All available data were included in the analysis as per the intention-to-treat principle.			
Descriptive statistics and effect estimate per comparison vs placebo	Treatment group	Daridorexant 10 mg	Daridorexant 25 mg	Placebo
	Number of subject	307	309	308

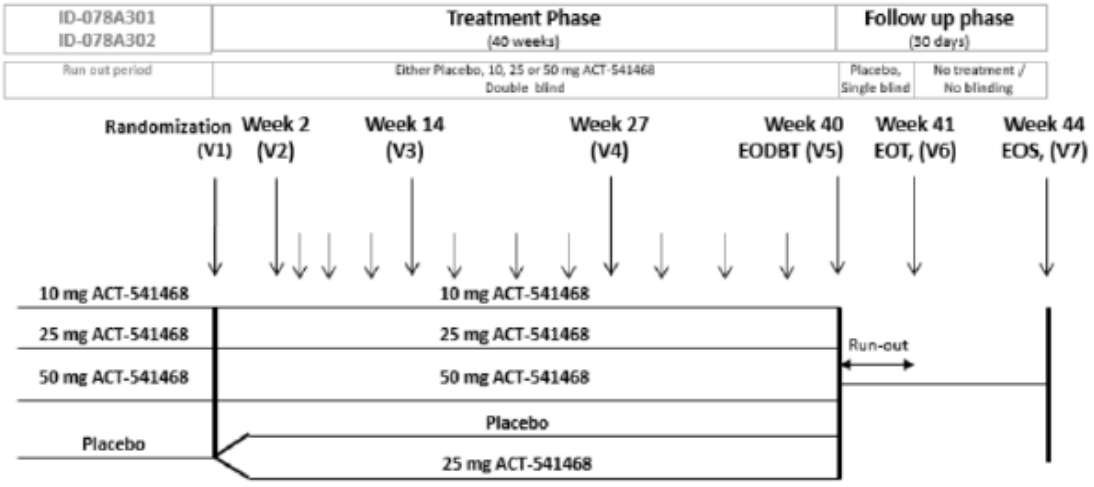
Co-primary endpoints	Change in **WASO** from baseline to **M1** LS mean [95% CL]	−15.3 [−19.5, −11.1]	−24.2 [−28.5, −19.9]	−12.6 [−16.8, −8.3]
	LS Mean Difference to placebo [95% CL]	−2.7 [−8.7, 3.2]	−11.6 [−17.6, −5.6]	NA
	P-value	0.3669	0.0001*	NA
	Change in **WASO** from baseline to **M3** LS mean [95% CL]	−16.0 [−20.7, −11.2]	−24.3 [−29.0, −19.5]	−14.0 [−18.8, −9.2]
	LS Mean Difference to placebo [95% CL]	−2.0 [−8.7, 4.8]	−10.3 [−17.0, −3.5]	NA
	P-value	0.5686	0.0028*	NA
	Change in **LPS** from baseline to **M1** LS mean [95% CL]	−22.6 [−26.7, −18.5]	−26.5 [−30.6, −22.3]	−20.0 [−24.1, −15.9]
	LS Mean Difference to placebo [95% CL]	−2.6 [−8.4, 3.2]	−6.5 [−12.3, −0.6]	NA
	P-value	0.3782	0.0303	NA
	Change in **LPS** from baseline to **M3** LS mean [95% CL]	−23.1 [−27.6, −18.6]	−28.9 [−33.4, −24.4]	−19.9 [−24.4, −15.4]
	LS Mean Difference to placebo [95% CL]	−3.2 [−9.5, 3.1]	−9.0 [−15.3, −2.7]	NA
	P-value	0.3233	0.0053	NA
Key secondary endpoint	Change in **sTST** from baseline to **M1** LS mean [95% CL]	41.0 [35.4, 46.6]	43.8 [38.1, 49.4]	27.6 [22.0, 33.3]
	LS Mean Difference to placebo [95% CL]	13.4 [5.5, 21.2]	16.1 [8.2, 24.0]	NA
	P-value	0.0009	<.0001*	NA
	Change in **IDSIQ sleepiness domain** from baseline to **M1** LS mean [95% CL]	−3.2 [−3.8, −2.6]	−3.5 [−4.1, −2.9]	−2.8 [−3.3, −2.2]
	LS Mean Difference to placebo [95% CL]	−0.4 [−1.3, 0.4]	−0.8 [−1.6, 0.1]	NA

	P-value	0.3048	0.0733	NA
Key other endpoint	Change in **TST** from baseline to **M1** LS mean [95% CL]	36.6 [31.3, 41.9]	48.1 [42.7, 53.5]	30.4 [25.1, 35.7]
	LS Mean Difference to placebo [95% CL]	6.2 [−1.3, 13.7]	17.7 [10.2, 25.2]	NA
	P-value	0.1050	<.0001	NA
Notes	After multiplicity comparison adjustment, the effects comparing daridorexant vs PBO in ITT population at 10 mg are not statistically significant for all endpoints presented above. The effects comparing daridorexant vs PBO in ITT population at 25 mg are statistically significant only for WASO and sTST. They are not statistically significant for LPS and IDSIQ sleepiness domain.			
Analysis description	**Secondary analysis** Please refer to respective sections in the AR			

Multi-center, double-blind, parallel-group, randomized, placebo-controlled, three doses, 40-week extension to studies ID-078A301 and ID-078A302 to assess the long-term safety and tolerability of ACT-541468 in adult and elderly subjects with insomnia disorder.

Methods

Figure 9-1 Study design



Study Participants

The main inclusion criteria was *c*ompletion of the DB study treatment and placebo run-out period of 301 or 302 (Visit 1).

Main exclusion criteria are unstable medical condition, significant medical disorder or acute illness, or ECG, C-SSRS©, hematology or biochemistry test results in 301 or 302 study, which, in the opinion of the investigator,

could affect the subject's safety or interfere with the study assessments (Visit 1). Patients with positive urine drug test for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines or cocaine (Visit 1) were also excluded.

Treatments

Subjects who were assigned to a daridorexant arm in studies 301 and 302 were assigned to the same daridorexant dose, 10 mg, 25 mg, or 50 mg, in study ID-078A303 (abbreviated to 303), while subjects assigned to the placebo arm in studies 301 and 302 were re-randomized to receive either placebo or 25 mg daridorexant in a 1:1 ratio in the extension study.

Objectives

The primary objective was to assess the long-term safety and tolerability of 10, 25 and 50 mg daridorexant.

Efficacy of 10 mg, 25 mg, and 50 mg daridorexant on subjective sleep parameters (using a sleep diary questionnaire [SDQ]) and daytime functioning (using the dedicated Insomnia Daytime Symptoms and Impacts Questionnaire [IDSIQ]) in subjects with insomnia disorder during long-term treatment was exploratory.

Outcomes/endpoints

Exploratory efficacy endpoints

- Change from baseline over time in sTST, in (sLSO), in (sWASO)
- Change from baseline over time in IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores), on the SDQ VAS (mm)
- Change from baseline to Visit 3 (Week 14), Visit 4 (Week 27), and Visit 5 (Week 40) in Insomnia Severity Index© (ISI©) scores.
- Number (%) of subjects with ≥ 6-point decrease in ISI© total score from baseline to Visit 3 (Week 14), Visit 4 (Week 27), and Visit 5 (Week 40).
- Change from baseline over time in mean number of self-reported awakenings.
- Change from baseline over time in Patient Global Assessment of Disease Severity (PGA-S) scores (daytime symptoms).
- Change from baseline over time in Patient Global Impression of Change (PGI-C) scores (daytime symptoms).

Randomisation and blinding (masking)

As the extension study is an extension of the ID-078A301 and ID-078A302 Phase 3 studies, there are no statistical sample size considerations. It is expected that approximately 1260 subjects (i.e., ~70% of the total subjects in the combined pivotal studies) will enter the extension study.

The study is performed in a DB fashion. The subjects, the investigator and site personnel, and the monitors remain blinded to the study treatment until the end of the ID-078A303 extension study. Until the time of unblinding for ID-078A303 final data analysis, the randomization lists of studies ID-078A301 and ID-078A302 (and thus, also ID-078A303) are kept strictly confidential.

Statistical methods

As the 303 study was an extension of the 301 and 302 Phase 3 studies, there were no statistical sample size considerations. Approximately 1260 subjects (approx. 70% of the total number of subjects randomized in the confirmatory studies 301 and 302) were anticipated to enter the long-term extension study 303, assuming that all sites from the confirmatory studies participated in the study.

The final analysis was conducted as planned, when all subjects who did not prematurely discontinue study treatment had reached Week 44 (Visit 7, end of study).

Results

804 subjects consented to participate and were randomized (142 [10 mg], 270 [25 mg], 137 [50 mg], 128 [placebo], and 127 [ex-placebo/daridorexant 25 mg]).

801 subjects (99.6%) started DB treatment; 3 subjects discontinued from the study prior to starting DB treatment due to withdrawal by the subject (2 subjects, daridorexant 25 mg), and randomization in violation of an exclusion criterion (positive urine drug test at Visit 1; 1 subject, ex-placebo/daridorexant 25 mg).

559 of the 804 randomized subjects (69.5%) completed the study (EOS visit); 245 discontinued the study prematurely. 550 subjects (68.4% of randomized subjects) completed DB treatment (Week 40, corresponding to 52 weeks of cumulative treatment); 251 (31.2%) prematurely discontinued DB treatment. The most frequent reason for premature discontinuation from DB treatment was lack of efficacy (11.9% overall), which was at least twice as frequent in the placebo group (22.7%) compared to any other treatment group (10.6%, 10.7% and 9.5% in the daridorexant 10 mg, 25 mg and 50 mg groups, respectively, and 7.9% in the ex-placebo/daridorexant 25 mg group).

Demographic characteristics (at screening in the respective confirmatory study) for subjects enrolled into the extension study were overall balanced across treatment groups and similar to the baseline characteristics of the whole populations recruited into the 301 and 302 studies.

Table 2-1 Between treatment analysis for the change from baseline to Month 6, Month 9 and Month 12 in exploratory variables, Full analysis set

Visit Treatment group	n	LS Mean [95% CL]	Difference to placebo LS Mean [95% CL]	p-value (two-sided)
sTST: Change from baseline to Month 6				
ACT-541468 10 mg (N = 142)	108	63.42 [52.392, 74.443]	14.57 [–1.455, 30.590]	0.0747
ACT-541468 25 mg (N = 270)	220	58.73 [50.825, 66.635]	9.88 [–4.162, 23.924]	0.1675
ACT-541468 50 mg (N = 137)	105	69.20 [57.922, 80.485]	20.35 [4.168, 36.539]	0.0138
Placebo (N = 128)	98	48.85 [37.196, 60.503]	-	-
sTST: Change from baseline to Month 9				
ACT-541468 10 mg (N = 142)	99	66.91 [55.715, 78.110]	12.47 [–4.009, 28.949]	0.1377
ACT-541468 25 mg (N = 270)	191	61.63 [53.528, 69.722]	7.18 [–7.359, 21.724]	0.3323
ACT-541468 50 mg (N = 137)	97	70.26 [58.802, 81.713]	15.82 [–0.827, 32.458]	0.0625
Placebo (N = 128)	80	54.44 [42.324, 66.560]	-	-
sTST: Change from baseline to Month 12				
ACT-541468 10 mg (N = 142)	88	67.85 [55.659, 80.035]	10.46 [–7.506, 28.418]	0.2533
ACT-541468 25 mg (N = 270)	170	62.65 [53.847, 71.455]	5.26 [–10.592, 21.113]	0.5148
ACT-541468 50 mg (N = 137)	87	75.16 [62.718, 87.611]	17.77 [–0.353, 35.900]	0.0546
Placebo (N = 128)	70	57.39 [44.166, 70.615]	-	-
IDSIQ sleepiness domain score: Change from baseline to Month 6				
ACT-541468 10 mg (N = 142)	109	–5.94 [–7.094, –4.781]	–0.77 [–2.454, 0.909]	0.3674
ACT-541468 25 mg (N = 270)	218	–6.18 [–7.015, –5.349]	–1.02 [–2.494, 0.459]	0.1765
ACT-541468 50 mg (N = 137)	107	–7.71 [–8.894, –6.521]	–2.54 [–4.244, –0.841]	0.0035
Placebo (N = 128)	101	–5.16 [–6.389, –3.940]	-	-
IDSIQ sleepiness domain score: Change from baseline to Month 9				
ACT-541468 10 mg (N = 142)	98	–6.59 [–7.774, –5.402]	–1.33 [–3.075, 0.414]	0.1346
ACT-541468 25 mg (N = 270)	194	–6.65 [–7.505, –5.794]	–1.39 [–2.930, 0.146]	0.0759
ACT-541468 50 mg (N = 137)	97	–7.80 [–9.016, –6.582]	–2.54 [–4.306, –0.777]	0.0048
Placebo (N = 128)	80	–5.26 [–6.540, –3.975]	-	-
IDSIQ sleepiness domain score: Change from baseline to Month 12				
ACT-541468 10 mg (N = 142)	91	–7.10 [–8.391, –5.808]	–1.57 [–3.480, 0.349]	0.1089
ACT-541468 25 mg (N = 270)	175	–6.76 [–7.692, –5.823]	–1.22 [–2.917, 0.470]	0.1565
ACT-541468 50 mg (N = 137)	87	–8.25 [–9.578, –6.918]	–2.71 [–4.654, –0.773]	0.0062
Placebo (N = 128)	68	–5.53 [–6.951, –4.117]	-	-

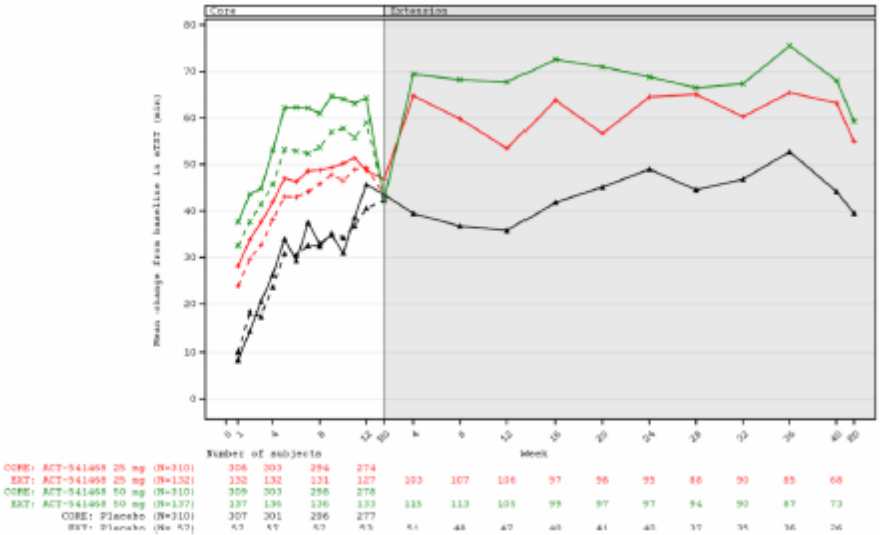
- Month 6 timepoint includes the duration of the confirmatory study and corresponds to Week 12 of the extension study, same for Month 9 (Week 24) and Month 12 (Week 36).
- Mixed effects model for repeated measures: Change from baseline = baseline value + stratified age group (< 65; >= 65 years) + treatment + visit + treatment * visit + baseline * visit.
- This analysis excludes the subjects that switched from placebo to 25 mg.

n is the number of subjects with non-missing values.

CL = confidence limit; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; LS Mean = Least Squares Mean; sTST = Subjective Total Sleep Time.

Source: Compiled from Table 15.2.2-1.1, Table 15.2.2-5.1.

Figure 2-1 **Mean changes from baseline in sTST (min) over time by core study for 25 mg, 50 mg and placebo groups (study 301, Full analysis set)**



RO = Run-out. Dotted lines represent all subjects in the core study; solid lines represent subjects who went into the extension study. Higher score represents greater burden of illness

Source: Table 15.2.7-1.3

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

Data from the same treatment groups that are common across the two pivotal Phase 3 studies ID-078A301 and ID-078A302 are pooled. Together, these studies contain efficacy data for 25 mg of ACT-541468 (in terms of number of subjects and extent of exposure) in a randomized placebo-controlled setting.

The pooled analysis were performed on the primary, secondary and 'other' endpoints.

Results from pooled analysis are presented with pivotal studies results.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Study 202	47 / 58	11 / 58	0 / 58
Study 301	310 / 930	51 / 930	3 / 930
Study 302	307 / 925	55 / 925	1 / 925
Study 303	282 / 804	52 / 804	1 / 804

Specific studies have been performed in patients with mild to moderate severe hepatic impairment (study ID-078-112), patients with severe renal impairment (study IIID-078-115), patients with COPD (study ID-078-109) and patients with OSA (study ID-078-110).

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The 2 pivotal phase 3 studies (301 and 302) were both large, multinational, multi-center, double-blind, randomized, placebo-controlled, parallel-group, 12-week studies including both adult and elderly subjects with insomnia disorders. The recommended daily dose (50 mg) is only assessed in one pivotal study.

The design and duration of phase 3 studies are in accordance with the Guideline on medicinal products for the treatment of insomnia: double-blind, randomised, parallel group trials with placebo of 12 week duration. The note for guidance recommended at least 2 to 4 week duration for the short term study. The patient numbers of around 1850 included and around 830 elderly patients are also well adapted. However the recommendation of an active comparator arm in at least one of the phase 3 studies as stated by the EMA guideline on clinical investigations of medicinal products for the treatment of insomnia was not followed by the Applicant. However the addition of zolpidem as an active comparator in one of the pivotal studies during the first 4 weeks would have complicated results interpretation and make them unsuitable for inclusion in the primary analysis. Also, one phase 2 study (201) includes zolpidem as active comparator for validation assay.

The population intended to be included in the pivotal trials is insomnia patients according to DSM-V (18th May 2013) criteria. These criteria include predominant complaint of dissatisfaction with sleep quantity or quality, associated with difficulty initiating or maintaining sleep, or early morning awakening with inability to return to sleep. The sleep disturbance induces clinically significant distress or impairment in social or other important areas of functioning. The sleep difficulty occurs at least 3 nights per week and is present for at least 3 months, and it occurs despite adequate opportunity for sleep. The insomnia is not attributable to the physiological effects of a substance (e.g., drug abuse, medication).

Furthermore, to be included patients needed to present with Insomnia Severity Index (ISI) ≥15. The validated Insomnia Severity Index (ISI) is a brief self-report instrument measuring the patient's perception of both nocturnal and diurnal symptoms of insomnia and has been validated in the past (Bastien CH, Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297-307). A total score ≥15 correspond to moderate to severe insomnia. A total score equal or higher than 22 correspond to severe insomnia.

The EMA guideline (2011) recommends to start the development of a medicinal product in adults in primary insomnia to establish efficacy and safety and only later to focus on secondary insomnia in addition to primary insomnia. However, there is no longer distinction between primary and secondary insomnia according to DSM-V criteria and ICSD-3.

Subjects with insomnia associated with major comorbidities, including sleep related breathing disorder and acute or unstable psychiatric disorders (e.g., depression, anxiety or dementia), were excluded according to exclusion criteria. Central nervous system-active drugs should be discontinued for 5 half-lives of the respective drug (but at least 2 weeks) prior to Visit 1. Overall the population is composed preferentially of primary insomnia since only a low percentage of patients with psychiatric co morbidity were studied.

The ability of daridorexant to treat insomnia and the impact on daytime functioning was evaluated using both objective and subjective efficacy parameters.

Co-primary endpoints are objective measures are: WASO and LPS. As already mentioned for phase 2 studies (same endpoints), WASO represents duration in minutes of awakenings. LPS measures the time in minutes to sleep onset.

The applicant did not follow the EMA guideline that recommended to establish efficacy on clinically relevant improvements on subjective sleep parameters of the patients in their natural setting and that results should be supported by objective data. The Applicant chose to do so to comply with FDA requirements.

The expected treatment effect compared to placebo for primary endpoints WASO and LPS (15 minutes decrease) and sTST secondary endpoint (20 min increase) could be considered as relatively small gain as compared to the placebo response. The corresponding effect size (mean/SD) was approximately 0.37 corresponding to a small to medium effect size. It is well known that there is an important placebo effect insomnia treatment. The Applicant had to further justify why the choice of these differences for WASO, LPS and sTST reflect a clear clinical benefit for patients presenting with insomnia.

For IDSIQ sleepiness domain score (ranging from 0 to 40), the difference compared to placebo in the mean change from baseline to Month 1 and Month 3 was assumed to be 5 (±5) (based on data from study AC-078A203). The corresponding effect size (mean/SD) was approximately 1 which is a large effect size.

The sample size was appropriately justified. The randomisation was balanced across the 3 treatment arms and within the two planned stratification levels (patients < 65 years and ≥ 65 years). Missing data were adequately managed. The overall type-one error was adequately controlled.

Long term efficacy and safety study

Long term efficacy and safety at the three doses 10 mg, 25 mg and 50 mg is assessed as part of study 303 that remain in DB fashion. After a 7-day single-blind placebo run-out, subjects could enter the 9-month extension study and placebo patients were re-randomized either to 25 mg dose or placebo. Final report of this extension study was submitted during the assessment.

Efficacy data and additional analyses

The analysis were performed using the Full analysis set, which is consistent with the intent-to-treat principle. Population randomized was 930 patients in study 301 and 924 patients in study 302 and well balanced between treatment arms. Data from both studies were pooled for the 25 mg dose and placebo.

There was a large number of non-eligible patients in the pivotal trials with a potential impact on the generalizability of pivotal study results.

The rate of patients completing the double-blind treatment period was high with more than 90% of randomized patients in each arms of the two phase 3 studies including in the placebo arm. Main reasons for premature discontinuation of double blind treatment were adverse events (between 1% and 2.3% in each arms), lack of efficacy (between 1.3% and 1.9% in each arms) or withdrawal by subject (between 1.3% and 4.2%). No clear difference on reason for premature discontinuation is observed between arms including with the placebo arms.

Patient mean age at screening was around 55 years (age range between 18 and 88 years in study 301 and between 19 and 85 years in study 302) and 39% in each arms were higher than 65 years reflecting the predominantly old target population. The high percentage of patients higher than 65 years is appreciated.

Ethnicity was well balanced with around 90% Caucasians in each arm of both studies. About two thirds of recruited subjects were female corresponding to the epidemiology of the disease. Mean BMI at screening was high (around 26 kg/m^2) with most patients obese (around 18%) or overweight (around 40%). Few patients with psychiatric comorbidities (between 6 % and 8 % depending on the study) such as depression and anxiety were included.

Insomnia severity at baseline assessed by ISI score is the same in each arm of both studies and was around 19 (moderate insomnia) ranging between 2 and 28 in study 301 and between 5 and 28 in study 302). Percentage of patients with severe insomnia (ISI score $\geq$ 22) was well balanced between arms and was around 30% in each arm. The mean time since insomnia diagnosis is more than 10 years. The applicant did describe the type of insomnia disorders: characterized mainly by difficulty to falling asleep, or maintaining or waking up early in the morning; with or without reduced sleeping time and with or without psychiatric comorbidity.

Objective duration of wake after sleep onset (WASO) at baseline is around 100 minutes on average per night and slightly higher in study 302 compared to study 301. Latency to sleep onset (LSO) is around 1 hour on average. Subjective sleeping duration assessed by sTST is also well balanced between arms and studies, and around 5 hours per night. Although insomnia severity is not formally defined by total sleep duration, WASO duration and LSP duration, insomnia patient characteristics at baseline support insomnia severity as assessed by ISI score.

For the primary endpoint WASO, the decrease as compared to placebo is statistically significant at 50 mg at month 1 and month 3 in study 301 and at 25 mg in both studies (301 and 302). The decrease of wake after sleep onset (WASO) compared to placebo is higher with 50 mg per day (-22.8 [-28.0; -17.6] min and -18.3 [-23.9; -12.7] min at Month 1 and Month 3) compared to the 25 mg dose (study 301: -12.2 [-17.4; -7.0] min and -11.9 [-17.5; -6.2] min at Month 1 and Month 3; study 302: -11.6 [-17.6; -5.6] min and -10.3 [-17.0; -5.6] min at month 1 and month 3). The effect is maintained at 3 months. Responder analysis on WASO was provided as part of D120 answers to LoQ. For the higher value of the responder threshold (-30 min), 49.5% of treated patients in the 50 mg group (study 301) are considered as responders with 37.5% of responders in placebo groups (p=0.0041).

For the primary endpoint LPS, the decrease is statistically significant at 50 mg at month 1 and month 3 in study 301. The decrease is not statistically significant at 25 mg in study 302 and is statistically significant in study 301. In study 301, the decrease of LPS compared to placebo is higher with 50 mg per day (-11.4 [-16.0;-6.7] min and - 11.7 min [-16.3; -7.0] at Month 1 and Month 3) compared to the 25 mg dose (-8.3 [-13.0; -3.6] min and -7.6 [-12.3; -2.9] min at Month 1 and Month 3). Based on the responders definition for LPS provided by the Applicant at month 3, for the higher value of the responder threshold (-25 min), 56.1% of treated patients in the 50 mg group (study 301) are considered as responders with 45.2% of responders in placebo groups (p=0.0096) (please see Q129).

With regard to the assumed difference compared to placebo in the mean change from baseline for WASO (-15 min) and LPS (- 15 min), and the confidence intervals of the mean difference to placebo at 25 mg for these endpoints, the clinical relevance of the 25 mg dose is questionable. The results for the 50 mg dose seem clinically relevant. The assumed difference compared to placebo in the mean change from baseline for WASO (-15 min) and LPS (- 15 min) was further discussed and can be considered as acceptable.

LPS log-transformed analysis is consistent with analysis performed on raw LPS values.

For the subjective secondary endpoint sTST, the increase of sleep duration is statistically significant at 25 mg and 50 mg at month 1 and month 3. The increase compared to placebo at 50 mg is 22.1 [14.4; 29.7] and 19.8 [10.6; 28.9] at Month 1 and Month 3. The increase compared to placebo at 25 mg is 12.6 [5.0; 20.3] min and

9.9 [0.8; 19.1] min at Month 1 and Month 3 in study 301; 16.1 [8.2; 24] min and 19.1 [10.1; 28.0] min at Month 1 and Month 3 in study 302. It seems that the effect observed at Month 1 is maintained at Month 3. With regard to the assumed difference compared to placebo in the mean change from baseline for this endpoint (-20 min) and the confidence intervals of the mean difference to placebo at 25 mg at month 1 and month 3 in study 301, the clinical relevance of the 25 mg dose is questionable. The results with 50 mg seem clinically relevant.

The Applicant provided responders analysis on sTST with a minimum change in sTST of clinical importance at an individual level of 55 minutes. 48.4% of treated patients in the 50 mg group are considered as responders based on this definition with 36.7% of responders in placebo groups. In the 25 mg dose group, 41.1% of patients treated are considered as responders in both studies that is close to placebo.

For the subjective secondary endpoint IDSIQ sleepiness domain score, the subjective effect on daytime sleepiness is statistically significant versus placebo only at 50 mg at month 1 and month 3. The mean difference to placebo at 50 mg is -1.8 [-2.5;-1] and -1.9 [-2.9;-0.9] at month 1 and month 3. The effect observed at month 1 seems maintained at month 3. With regard to the assumed difference compared to placebo in the mean change from baseline for this endpoint (-5 points) and the confidence intervals of the mean difference to placebo at 50 mg, the clinical relevance is questionable.

The Applicant provided responder analysis on IDSIQ sleepiness domain with a 4 points or 8 points change. Taking into account the 0-40 scale, the 8 points change could be considered as particularly clinically relevant. In study 301, at the 50 mg dose at 3 month, 37% of treated patients reported at least 8 points decrease at 3 months compared to 24.0% of responders in the placebo group. In the same study, the percentage of subjects showing a decrease from baseline at Month 3 of at least 4 points was 52.9% in the daridorexant 50 mg group, 50.0% in the 25 mg group and 44.4% in the placebo group. The impact on daytime functioning assessed by IDSIQ scores is supported by results observed on VAS daytime alertness and on VAS on ability to function. Same trend of improvement is observed through these tools leading to a positive impact of daridorexant at 50 mg per day on daytime functioning.

The multiplicity testing procedure set up in both trials for the formal statistical demonstration of efficacy was rigorously applied by the Applicant. In study 301, 25 mg and 50 mg doses have achieved efficacy objectives for the primary and key secondary endpoints at month 1 and 3, except for IDSIQ at 25 mg. In study 302, none of the tested dose (10 mg and 25 mg) has formally demonstrated its efficacy.

In conclusion, 50 mg dose can be validated as clearly efficient dose. The 25 mg dose used in both phase 3 trials failed to demonstrate consistent and robust efficacy results from statistical point of view on primary efficacy parameters.

For the main other secondary efficacy endpoint, TST (objective sleep duration), significant differences are observed at 50 mg and at 25 mg in both studies at month 1 and month 3. The difference to placebo at 50 mg is 33.4 [26.3; 40.4] at month 1 and 28.6 [21.5; 35.8] at month 3. The difference to placebo at 25 mg is 20.6 [13.5; 27.7] at month 1 and 18.4 [11.2; 25.5] at month 3 in study 301; 17.7 [10.2; 25.2] at month 1 and 17.4 [9.2; 25,5] at month 3 in study 302. The effect is similar at 1 month and 3 months, and thus maintained. The improvement of TST at all daridorexant doses compared to placebo is lower when assessed subjectively by the patient compared to objective assessment. At the 50 mg dose, the improvement of TST compared to placebo is about 20 minutes when assessed subjectively and around 30 minutes when assessed objectively. However the results on responders for sTST confirm the clinical relevance of the effect: 48.4% of treated patients in the 50 mg group have a minimum change in sTST of clinical importance at an individual level of 55 minutes compared to 36.75% in placebo groups.

For the assessment of awakenings duration reported by the patient (sWASO), the mean improvement compared to baseline at 50 mg is -23.1 [-27.6; -18.5] min at month 1 (mean difference to placebo -7.1 [-13.5, -0.7] min) and -28.8 [-33.9; -23.7] min at month 3 (mean difference to placebo -4.8 [-11.9, -2.4] min). The effect increasing with the dose observed for objective WASO is no longer observed with subjective WASO.

Regarding the assessment of latency to sleep onset by the patient (sLSO), the mean improvement compared to baseline at 50 mg is -15.3 [-18.5; -12.1] min at month 1 (mean difference to placebo -7.8 [-12.3, -3.3] min) and -18.3 [-31.8; -14.6] min at month 3 (mean difference to placebo -6.5 [-11.6, -1.4] min). No clear difference of the effect between doses is observed.

The patient complaints which are assessed by subjective measures (sTST, sWASO, sLSO) are important points to consider in insomnia. The values of subjective measures are lower with daridorexant than the objective values. This was discussed by the Applicant during the assessment. There is a weak correlation of the parameters which may be explained by the different in nature and collection methods of objective and subjective endpoints.

In exploratory endpoints, the Applicant proposed a responders analysis based on ISI improvement corresponding to insomnia severity. Patients were considered as responders if their ISI change score relative to baseline was greater than 6. The analysis is also performed with patients with ISI score < 10 corresponding to none or mild insomnia. The proportion of subjects with an ISI© score < 10 at the end of the study was higher in daridorexant 50mg group (about 35% at month 3) compared to the placebo groups (about 24% at month 3). The proportion in daridorexant 25 mg group was about 20%. The proportion of subjects with a decrease in ISI© score of ≥ 6 points from baseline was higher in daridorexant 50 mg group (56.5% at month 3) compared to the placebo groups (46% at month 3). The proportion in daridorexant 25 mg group was about 50% at month 3. Difference between daridorexant doses is low with a slight higher proportion with the 50 mg dose. This responder analysis was completed with a post hoc analysis according to the responder definition from Morin et al. (JAMA, 2009) which confirm the benefit of daridorexant 50 mg compared to placebo (please see Q131).

Daridorexant does not seem to have an impact on sleep architecture in humans based on polysomnography data as well as in animals as reported in preclinical data.

Results of pooled analysis at the 25 mg dose are consistent with the results observed at 25 mg in each pivotal study.

In the individual studies, subgroup analyses were performed by age (< 65; ≥ 65 years), sex and region (US; other). An additional post-hoc subgroup analysis by region (Europe; other) at Month 1 and Month 3 was performed for the 2 studies separately. For the pooled data, subgroups of interest included age (< 65 years vs ≥ 65 years, and < 75 years vs ≥ 75 years) and BMI (> 30 kg/m2 vs ≤ 30 kg/m2).

Results by subgroups for primary (WASO, LPS) and secondary endpoints (sTST, IDSIQ sleepiness domain score) were consistent with the overall results. There is no apparent difference depending on the sex, age or region. In all demographic subgroups, the 50 mg dose provided a larger benefit than the 25 mg dose across almost all endpoints.

It appears that 50 mg daridorexant performs slightly better in elderly subjects (> 65 years) compared to adults for the WASO, LPS, sTST and IDSIQ sleepiness domain score.

The Applicant included approximately 40% of patients ≥ 65 years (364/930 in study 301 and 363/925 in study 302) in the pivotal Phase 3 studies that could be considered acceptable overall. There are around 100 patients older than 75 years (54/930 in study 301 and 56/925 in study 302). However there are almost no patient older

than 85 years (3/930 in study 301 and 1/925 in study 302). Data on patients older than 75 years at 50 mg (19 patients and 11 patients in phase 2 study) are limited. The Applicant further discussed the benefit risk balance at 50 mg in patients older than 75 years and advantage of a lower dose/ Based on data analysis over the full age range, the higher efficacy of the 50 mg dose on primary and secondary endpoints in patients aged from 65 to 75 years is considered as demonstrated and seems maintained in patients older than 75 years. Although there is no risk signal in elderly population at this time, caution should be used in this population.

Additional subgroups analysis was provided according to ISI score at baseline (patients with moderate insomnia and patients with severe insomnia), predominant type of insomnia at baseline (difficulty to falling asleep, maintaining or waking up early in the morning; insomnia with or without reduced sleeping time), patients with psychiatric co-morbidity at baseline.

Long term efficacy and safety study

The long term extension study assessing daridorexant 10 mg, 25 mg and 50 mg doses is completed. This extension study also includes a placebo arm. The main objective was the assessment of long term safety. 559 of the 804 randomized subjects (69.5%) completed the study (EOS visit); 245 discontinued the study prematurely. 550 subjects (68.4% of randomized subjects) completed DB treatment (Week 40, corresponding to 52 weeks of cumulative treatment); 251 (31.2%) prematurely discontinued DB treatment.

Efficacy endpoints are explorative and assessed by subjective endpoints (sTST, IDSIQ scores, sLSO, sWASO).

Baseline values are those from the beginning of pivotal studies. Subjects assigned to a daridorexant arm in the 301 or 302 study were assigned to the same daridorexant dose. Subjects assigned to the placebo arm in the 301 or 302 studies were re-randomized to receive either placebo or 25 mg daridorexant in a 1:1 ratio. The blind was maintained between pivotal and extension studies.

In the placebo arm, patients were already on placebo in phase 3 study. As these patients accepted to continue the treatment in study 303, they can be considered as good responders under placebo. This could explained the higher values for sTST, sWASO and sLSO reported with placebo compared to the values for same endpoints observed with placebo in the phase of 3 month pivotal studies.

As for patients treated with placebo, patients treated with daridorexant at all doses who accepted to continue in the extension study were satisfied by the treatment. This could explained high values at 10 mg especially for sLSO and sWASO.

There is no efficacy decrease on sTST endpoint at 1 year. The within-patient LS mean difference from baseline at 50 mg was 57.7 min [51.2; 64.2] at month 3 in study 301. At 1 year the LS mean difference from baseline is maintained in patients receiving the 50 mg and even a bit increased to 75.1 min [62.7; 87.6]. When compared to the placebo, the 50 mg dose treatment effect is also maintained between 3 and 12 months treatment and is close to the 20 minutes treatment effect targeted in the trial. The LS mean difference to placebo is 19.8 min at 3 months versus 17.8 at 12 months. The effect on IDSIQ score are also maintained.

Regarding the importance of sWASO and sLSO as subjective endpoints compared to sTST, please see question 121. sTST can be considered as a good subjective endpoint.

The efficacy of daridorexant 50 mg can be considered as maintained at 1 year.

Overall, to be noticed that patients treated with daridorexant 50 mg sleep more than 6 hours per night, with a sleep latency of around 30 minutes and have less than 1 hour of awakenings during the night. An important

placebo effect on subjective endpoints (sTST, sLSO, sWASO) is observed for patients treated with placebo in the long term study.

The initially proposed indication for daridorexant was "the treatment of adult patients with insomnia to improve sleep and daytime functioning".

The CHMP considered that the indication should reflect the characteristic of chronic insomnia and so mentioned insomnia duration (at least 3 months) and the impact on daytime functioning to allow clear characterisation of the patients who could be treated with daridorexant. The indication was agreed to be "*the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning*".

The applicant was requested to present the results of these two outcomes "to improve sleep and daytime functioning" in SmPC section 5.1.

To inform prescribers on insomnia severity of patients included in pivotal studies, insomnia severity according to ISI score at baseline was also mentioned in section 5.1 of the SmPC.

The Applicant recommended dosing regimen is one tablet of 50 mg once per night in adults and elderly, taken orally in the evening within 30 minutes before going to bed. The recommended dose in patients with moderate hepatic impairment or using moderate CYP3A4 inhibitors is one tablet of 25 mg once per night.

The indication does not indicate a time limit for treatment. A discussion was requested on limitation of the treatment duration, stopping rules and inclusion in the SmPC. Chronic insomnia is defined in ICSD-III and DSM-5. Both definitions defines a patient with chronic insomnia disorders as patient who experiences sleep disturbances for the last three months, corresponding to patients included in pivotal studies. The treatment efficacy improves until 3 months and efficacy seems maintained on the long term up to 12 months without safety signal on long term use. Thereby the CHMP agreed that no specific treatment duration can be mentioned in the SmPC. Nevertheless, the appropriateness of continuing the treatment should be reassessed within 3 months and the treatment should be as short as possible. Also, as there is no risk of withdrawal or rebound effect, treatment can be stopped without specific stopping rules. The evidence of the efficacy of Quviviq (daridorexant) in the intended indication is based on data from 2 pivotal phase 3 studies versus placebo (study 301 and study 302), supported by the interim results from one ongoing DB Phase 3 extension study (study 303), and two Phase 2 dose-finding studies one in adult subjects versus placebo with an active arm (zolpidem) (study 201) and one cross-over versus placebo in elderly (study 202).

2.6.7. Conclusions on clinical efficacy

The statistically significant and clinical relevant difference over placebo is achieved for the 2 primary objective endpoints (WASO, LPS) at 50 mg in one of the 2 pivotal study since this dose was studied in only one pivotal study. Although it would have been appreciated to confirm the data observed at the 50 mg dose in another pivotal study with the same dose, the results of the 2 studies remain supportive. Objective endpoints are supported by subjective endpoints, although to a lesser extent. Efficacy could be considered statistically demonstrated to decrease wake after sleep onset, latency to persistent sleep and increase of total sleep time over 3 months.

The analysis of responders defined as patients with minimum change in sTST of clinical importance at an individual level of 55 minutes support the clinical relevance of the effect. A clinical relevance of the effect is also observed at 50 mg with the responder analysis for WASO, LPS and ISI score.

The responder analysis on IDSIQ sleepiness domain with a 4 points or 8 points change were provided. The results are not impressive. However, the impact on daytime functioning assessed by IDSIQ scores is supported by results observed on VAS daytime alertness and on VAS on ability to function. Same trend of improvement is observed through these tools that could confirm the positive impact of daridorexant at 50 mg per day on daytime functioning.

Statistically significant difference over placebo is achieved for the 2 primary endpoints (WASO, LPS) at 25 mg in study 301 and not achieved for one of the primary endpoint (LPS) at 25 mg in study 302. The efficacy of 10 mg dose is not demonstrated.

Maintenance of the effect is assessed as part of the long term extension study 303. The effect on subjective endpoints seems maintained at 1 year for daridorexant 50 mg.

From the efficacy perspective, the clinical development adequately supports the proposed indication at 50 mg. Available data could support the use of the 25 mg dose, when in judgement of the clinician a lower dose than 50 mg could be appropriate, for example in patients already treated with CNS depressant.

A discussion was requested on limitation of the treatment duration. If it could be agreed to not specify a maximum treatment duration, the treatment should be as short as possible and appropriateness of continued treatment should be reassessed within 3 months. Also, as there is no risk of withdrawal or rebound effect, treatment can be stopped without specific stopping rules.

2.6.8. Clinical safety

The main focus of the safety analysis for daridorexant is based on placebo controlled safety data from the pivotal Phase 3 studies of 3-month duration, i.e., the two individual studies 301 (daridorexant 25 and 50 mg, and placebo) and 302 (daridorexant 10 and 25 mg, and placebo).

The safety data from the long-term, double-blind, placebo-controlled extension study 303 were also assessed. Study 303 was ongoing at the time of submission; therefore, interim data are provided initially. At the time of the interim cut-off (22 July 2020), all subjects who were included to study 303 without prematurely discontinuation had completed at least 6 months of double-blind daridorexant treatment overall (i.e., 3 months in study 301 or 302, and 3 months in study 303); a subset of subjects had been treated for 9 months: 473 subjects (67.3%) or 12 months: 314 subjects (46.7%) of the 303 treated cohort.

A pre-planned pooled safety data set of daridorexant 25 mg and placebo groups was also used, since these two groups were the only treatment groups replicated across studies 301 and 302. This pooled safety analysis was used to compare the rates of AEs within subgroups and to compare withdrawal symptoms in the 25 mg group vs placebo.

In addition, safety data from Phase 2 studies in subjects with insomnia (studies 201 and 202, as well as study 206 performed in Japanese subjects) were also considered. Furthermore, data from 18 Phase 1 clinical pharmacology studies are presented, particularly those studies that assessed special populations (insomnia subjects with hepatic or renal impairment and with respiratory disease) or with addressed specific safety topics

(human abuse potential and potential negative effects on driving performance for example), and safety data related to higher doses (up to 200 mg).

Of note, the impact of the COVID-19 pandemic had slight impact on study 115 and 117 that were put on hold. In study 117 (Thorough QT study), 1 subject discontinued due to the need to quarantine following a visit to a COVID-19 risk region; in study 115 (renal impairment study), 1 subject was not enrolled due to the ongoing situation.

The overall development program is considered adequate for the intended treatment in subjects with insomnia.

Patient exposure

The overall exposure during the double-blind treatment period in subjects with insomnia in the completed Phase 2 and 3 studies, and up to the cut-off date for the interim analysis of study 303 is shown in Table 3 below.

Table 3 Overall and individual Phase 2 and 3 treatment exposure in subjects with insomnia (studies 201, 202, 301, 302, and 303)

	Daridorexant						Placebo
	5 mg	10 mg	25 mg	Ex-placebo/ 25 mg	50 mg	Overall	
Study 201							
N	60	58	60	-	61		60
Subject-years	4.7	4.6	4.7	-	4.8		4.7
Study 301							
N	-	-	310	-	308		309
Subject-years	-	-	68.1	-	69.2		69.3
Study 302							
N	-	306	308	-	-		306
Subject-years	-	68.8	68.3	-	-		68.6
Study 303 [a]							
N	-	142 [b]	268 [b]	126	137 [b]		128 [b]
Subject-years	-	79.1	159.4	74.3	80.7		67.6
Overall (studies 201, 301, 302 and 303)							
N	**60**	**364**		**804***	**369**	**1597**	
At least 3 months	-	285		681*	289	1255	
At least 6 months	-	126		335*	122	583	
At least 9 months	-	100		270*	103	473	
At least 12 months [d]	-	72		159	83	314	
Subject-years	4.7	152.5		374.8*	154.7	686.7	210.2
Study 202 [c]							
N	56	54	55		56	58	54

A total of 1655 subjects with insomnia in phase 2 and phase 3 studies including the ongoing phase 3 study received at least one dose of daridorexant all doses combined, and 729 subjects received at least one dose of placebo. Of these 1655 subjects, 804 subjects received 25 mg, 369 subjects received 50 mg and 364 subjects received 10 mg.

The clinical pharmacology program for daridorexant consisted of 18 completed Phase 1 trials (567 subjects exposed to daridorexant), including single and repeated dose studies. Of these 567 subjects, 194 were exposed to single doses of daridorexant (up to 200 mg) and 373 received multiple doses of daridorexant (up to 100 mg).

Due to the prevalence of insomnia in elderly, nearly 40% of subjects ≥ 65 years were recruited in the phase 2 and 3 studies. Some other subgroup analyses were performed for the combined safety set in particular by sex, in which female subjects constituted two-thirds of the overall population, reflecting the higher prevalence of insomnia in females than in males.

According to the ICH Topic E 1 "Population Exposure: The Extent of Population Exposure to Assess Clinical Safety", it is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500. This recommendation is satisfied as from phase 2 and phase 3 studies, a total of 1655 subjects with insomnia received at least one dose of daridorexant, at any dose.

Subjects from the phase 3 studies were exposed to 12 months of treatment to determine the long-term safety of daridorexant at doses of 25 or 50 mg, as recommended in the regulatory guidance [ICH 1995]. Regarding the safety database, 126 (10 mg), 122 (50 mg) and 335 (25 mg) patients had been exposed to daridorexant for at least 6 months, and 72 (10 mg), 83 (50 mg) and 159 (25 mg) subjects had been exposed for at least 1 year. This represents 583 patients exposed for at least 6 months, at any daridorexant dose, with 20% of patients in the 50 mg group and 57% in the 25 mg group. For the one-year exposure, a total of 314 subjects were exposed to daridorexant, at any dose, with 26% of patients in the 50 mg group and 50% in the 25 mg group.

Adverse events

The collection of AEs were coded to MedDRA PTs. In the individual pivotal Phase 3 studies and in the pooled safety analysis, TEAEs were defined as AEs occurring or worsening between the start of double-blind study treatment up to 30 days after the end of DB study treatment, or enrolment in the extension study 303.

All AE, TEAE whatever the study period, TEAE related to study treatment, AE leading to premature discontinuation or temporary interruption of treatment, TESAE, TESAE related to study treatment and TEAESI after ISB (Independent Safety Board) adjudication were presented and discussed for the overall treatment-emergent period, as well as for the double-blind treatment period, the placebo run-out and the follow-up period.

The incidence of AEs was explored in the pooled safety data set across the following subgroups: Age group (< 65 years, ≥ 65 years and < 75 years, ≥ 75 years); Sex (male / female); BMI (low [< 25 kg/m2], middle [≥ 25 - ≤ 30 kg/m2], and high [> 30 kg/m2]); Ethnicity (White / Black or African American) and Region (US / non-US).

Based on the mechanism of action of daridorexant, the potential for narcolepsy-like symptoms was carefully considered and narcolepsy-like symptoms monitored during the daridorexant clinical program. The use of hypnotics may increase the risk of suicidality and self-injury (McCall 2017). These risks were adjudicated by the ISB as potential AESIs. Overall, from the nonclinical and clinical program, no off-target effect was identified. Specifically, from a non-clinical aspect, off-target risk is not considered relevant for human for daridorexant as well as for its major human metabolites.

Based on information with other products commonly used in insomnia, additional safety topics of importance were identified and thoroughly assessed: 1) next-morning residual effects, 2) risks associated with driving, 3) daytime somnolence and other CNS-depressant effects, 4) falls, accidents and injuries, 5) anxiety, 6) drug abuse potential, 7) overdose (accidental/intentional), 8) withdrawal symptoms and 9) rebound insomnia.

Regarding the overview of AE, in the Phase 3 studies 301 and 302, the percentage of subjects experiencing TEAEs was numerically slightly higher in the daridorexant treatment groups compared to the placebo groups (by 41.3% vs 37.2% in study 301 and 43.1% vs 36.3% in study 302) with however a similar incidence in the daridorexant groups of each study.
On the contrary, the rate of treatment-emergent SAEs, or TEAEs leading to discontinuation during the DB study period, was slightly higher in the placebo groups compared to the daridorexant treatment groups. Indeed, the rates of treatment-emergent SAEs are 0.6% and 1% in all daridorexant groups whereas it is slightly higher (1.3% and 2.3%) in the placebo groups of both studies. The rate of TEAEs leading to discontinuation is 2.3% and 3.2% in the placebo groups whereas it is slightly lower (1.0%, 1.3%, 2.0% or 2.3%) in the daridorexant groups of both studies. The rate of Treatment-emergent AESI is overall higher in the daridorexant groups (10 mg, 25 mg and 50 mg) compared to the placebo groups for both studies. However no trend for a dose dependence is highlighted as the incidence rate in the 50 mg group (0.6%) for study 301 is similar to the incidence rate in the 10 mg group (0.7%) for study 302, and lesser to the incidence rate in 25 mg groups of both studies (1.3% and 2.3%). One treatment-emergent SAE with fatal outcome in study 301 was not related to study drug (see dedicated section "deaths").

For study 303, a slightly higher incidence of TEAEs was observed in the daridorexant groups compared to the placebo group however not carried out by any specific PT, except for nasopharyngitis which was more frequent in the 50 mg group and the ex-placebo / 25 mg group compared to any other groups. Nevertheless, regarding the mechanism of action of daridorexant, nasopharyngitis is not expected to be related to the study treatment. Two treatment-emergent not drug related SAEs with fatal outcome were observed in study 303 (see dedicated section "deaths").

Overall, a trend for a dose dependence in the incidence of AE is uncertain.
Regarding the TEAE, the three most commonly reported primary SOCs were infections and infestations, nervous system disorders, and gastrointestinal disorders, in both phase 3 studies 301 and 302.
Nasopharyngitis and headache were the most frequently reported TEAEs, with quite similar rates in daridorexant compared to the placebo groups. Fatigue was numerically more frequent in daridorexant groups compared to placebo in both studies, which could be expected regarding the mechanism of action (antagonism of the orexin receptors). However, no clear dose-related increase was observed for somnolence regarding the comparative rates between the different daridorexant groups and the placebo groups of both studies (either the highest rate is observed for the 25 mg dose and not the 50 mg dose or the rate is equivalent with the placebo rate). Same remark can be made for dizziness, even if less obvious numerically.

For the accidental overdose, the highest rate is 2.6% for daridorexant 50 mg although no dose dependence is particularly highlighted (the rate in the placebo group of 1.6% is higher than the rate in the 25 mg group). Same trend for nausea (2.3%) without any consistent dose dependence.

In the 301 study, falls were reported more frequently in the placebo group in 8 subjects (2.6%) than in either daridorexant group in 1 subject (0.3%) in each. In study 302, the events of falls were balanced and consistent across treatment groups: 3 subjects (1%) in placebo group vs 7 subjects in each daridorexant 10 mg and 25 mg group (1.3% and 1%) respectively. There seems to be no dose dependence for the events of fall. None of the cases of fall occurred during the night. Cases of falls were systematically sent for adjudication as a potential AESI and none were finally considered as AESIs.

Overall, somnolence, fatigue, dizziness, falls, and accidental overdoses are discussed in more details as AESI, as they are of special significance given the indication.

The pattern of TEAEs during the 9-month long-term extension study (up to the interim cut-off) was similar to the observations on studies 301 and 302. No specific safety signal appeared during the long-term study regarding the safety of daridorexant. The most commonly reported TEAE was nasopharyngitis. TEAEs with an incidence of ≥ 2% in any treatment group and reported more frequently for daridorexant than placebo (≥1% difference) included nasopharyngitis (8.0% in the daridorexant 50 mg group), somnolence (2.9% in the daridorexant 50 mg group), accidental overdose, urinary tract infection (2.8% each, in the daridorexant 10 mg group), and less frequent cough, tonsillitis, pneumonia, fall, hepatic enzyme increased and myalgia. Specifically, the incidence of somnolence was very low in the placebo, 10 mg, 25 mg and ex-placebo/25 mg daridorexant groups (0%, 0%, and 0.7% and 0.8% respectively) compared to the 50 mg group (2.9%). The high rate of incidence of this AE in the 50 mg group (2.9%) compared to the other treatment groups (placebo, 10 mg, 25 mg and ex-placebo/daridorexant groups with 0%, 0%, and 0.7% and 0.8% respectively) of study 303 have been clarified by the Applicant.

TEAEs of fall were reported with a quite similar rate in the daridorexant groups, slightly higher than in the placebo group. None of the falls occurred during the night or was reported as an AESI.

For the phase 2 studies, the TEAE profile was similar to the observations on studies 301, 302 and 303. It could however be noted that the AE gait disturbance occurred in 6 subjects, 1 subject in placebo, 2 subjects on daridorexant 5 mg, and 1 subject each on daridorexant 10, 25 and 50 mg which resolved before leaving the study center. No dose-dependence emerge for this AE regarding its consistent distribution amid the treatment groups. A few isolated cases (7) of gait disturbance occurred in both studies 301 and 302 without being considered clinically significant and resolved without treatment.
Overall, no new safety signal appeared during these phase 2 studies regarding the safety of daridorexant as compared to pivotal studies.

Adverse Events considered drug related are displayed in the table below:

Table 5-1 Daridorexant adverse drug reactions table (studies 301 and 302)

System organ class	Daridorexant 50 mg* (N = 308)	Daridorexant 25 mg* (N = 618)	Daridorexant 10 mg (N = 306)	Placebo* (N = 615)
Nervous System Disorders				
Headache	6%	5%	4%	4%
Somnolence	2%	3%	2%	2%
Dizziness	2%	2%	1%	1%
General disorders and administration site conditions				
Fatigue	2%	3%	2%	1%
Gastrointestinal disorders				
Nausea	2%	1%	1%	1%

* 50 mg rates come from the 301 study, 25 mg rates and placebo rates from pooled 301/302 data.

The majority of ADRs (headache, somnolence, dizziness, fatigue and nausea) were mild to moderate in intensity and no evidence of a dose-relationship for the frequency or the severity of ADRs is observed. Sleep paralysis (transient, dissociated sleep state during which REM sleep atonia continues into wakeful consciousness) were observed with daridorexant 25 mg and 50 mg at a frequency lesser than 1% (0.5% for 25 mg and 0.3% for 50 mg) and no case observed with placebo. Cases of sleep-related hallucinations were only observed in the

daridorexant 25 mg group in 0.8% of subjects and no case with placebo or daridorexant 50 mg. In the SmPC, the frequency of sleep-related hallucinations is reported at a frequency of 0.6%. The Applicant has provided justification for these observations and these AE are classified as "uncommon" in the SmPC.

Regarding the severity of TEAE, a majority of TEAEs reported during the studies 301 and 302 were of mild or moderate intensity. A low rate of TEAE were of severe intensity, around 1% to 2% in the daridorexant and placebo groups. TEAEs of severe intensity were reported with a frequency similar or even higher in the placebo groups than in the daridorexant groups. Most of the AEs of severe intensity were also reported as SAEs and/or AEs leading to discontinuation of study treatment.
Moreover, the cases of mixed hallucination, sleep paralysis and suicidal ideation in studies 301 and 302 are scrutinized and discussed among the AESI. The same trend is observed during the Phase 3 extension study 303. And no specific pattern of severity of TEAE is observed in the phase 2 or phase 1 studies.

Regarding the AESI, considering the mechanism of action of daridorexant which intends to stimulate sleep-promoting effects, special attention was given to several safety topics of medical significance.

The AESI were assessed according to the following 4 categories: narcolepsy-like symptoms related to EDS (excessive daytime somnolence), narcolepsy-like symptoms related to complex sleep behavior, including hallucinations and sleep paralysis, narcolepsy-like symptoms related to cataplexy-like events and suicide/self-injury (and worsening of depression).

The other safety topics of medical significance are next-morning residual effects; ability to drive or operate machinery; daytime somnolence / CNS-depressant effects; falls, accidents and injuries, which may result from EDS; anxiety; drug abuse potential; cases of overdose; withdrawal symptoms; and rebound insomnia. It is to be noted that the ability to drive or operate machinery, drug abuse potential and withdrawal symptoms are safety topics assessed in the clinical pharmacology safety studies.

Narcolepsy-like symptoms

A total of 453 potential AESIs occurring in 367 subjects were submitted to the ISB for adjudication during the Phase 2 and 3 programs. Of these, 31 events (6.8%) in 24 subjects of submitted potential AEs were adjudicated by the ISB as AESIs.

For the narcolepsy-like symptoms, three quarters (3/4) of the narcolepsy-like AESIs (15/20) occurred in the 25 mg daridorexant groups (and 2 in the daridorexant 50 mg, 2 in the 10 mg daridorexant group and 1 in the placebo group) for both 301 and 302 studies.

The majority of narcolepsy-like symptoms related to EDS and the narcolepsy-like symptoms related to complex sleep behaviour including hallucinations and sleep paralysis occurred in the 25 mg daridorexant groups without any clear trend for a dose dependence. None of the events evoked a typical narcolepsy phenotype with an increase in sleep propensity and recurrence, for example. No hallucinations and sleep paralysis occurred in the placebo groups of both studies. Most AESIs were non-serious and required no intervention.

Based on the evaluation of the 3 subcategories of "narcolepsy-like symptoms", the main facts could be pointed out:

- No AESIs belonging to the category "narcolepsy-like symptoms related to cataplexy" occurred in the Phase 2 and Phase 3 studies. Indeed, among the 6 cases of muscle weakness observed with high doses administered during the daytime in Phase 1 studies (2/8 subjects at 75 mg and 4/6 subjects at 200 mg), 1 case (at 200 mg) was considered to be possibly a cataplexy-like event which could be explained by the high daridorexant dose of 200 mg. All the more that in phase 1 studies it was highlighted that the duration of AEs related to depression

of the CNS showed a trend to an increase with dose, in particular above 50 mg. In the Phase 2 and 3 studies, muscle weakness was reported for 1 subject at 10 mg and 1 subject at 25 mg in study 302 only.

- The total number of AESIs belonging to the category "narcolepsy-like symptoms related to EDS" was rather low: in total, 13/1597 subjects in studies 201, 301, 302, and 303 combined treated with daridorexant (0.8%), in comparison to 2/675 subjects (0.3%) treated with placebo. In study 301, this AESI was quite similarly distributed across treatment groups: 2 (25 mg), 1 (50 mg), and 1 (placebo). In study 302, most EDS occurred in the 25 mg group: 1 (10 mg), 4 (25 mg), 1 (placebo). In study 303: only 1 subject (25 mg), out of 673 treated with daridorexant (0.2%) with no case reported in the 50 mg group. For the 3 studies, a slight predominance of the AESI in the 25 mg group is observed. One case of moderate somnolence in study 303 required nearly 50 days of duration for the resolution of the event in a 57-year-old Caucasian female which is questionable. The Applicant has justified this rather long time (50 days) before resolution of the event and no specific pattern is raised from this observation.

- Seven cases (5 in 25 mg, 2 in 50 mg) of sleep paralysis and/or hallucinations, with a low incidence rate (< 1%), were reported in subjects who received daridorexant in the Phase 2 and 3 studies. One subject presents 3 events of intermittent sleep paralysis, occurring on different days, and each lasting approximately 1.5 min (study 301: 50 mg), and 1 other subject presents 3 events of abnormal dreams (study 303: 50 mg). The reported cases of sleep paralysis and/or hallucinations occurred independently of any symptoms suggestive of narcolepsy. No dose dependency was observed.

Apart from sleep paralysis and hallucinations, no cases of other complex sleep behaviours such as sleep walking / somnambulism, sleep driving, sleep talking, sleep eating, or sleep sex were reported in the 50 mg daridorexant group. The Applicant has explained the highest incidence of this AESI in the 25 mg daridorexant group in comparison to the other groups and to the incidence in the general population. The Applicant has also justified the less frequent incidence of these AESI, sleep paralysis and/or hallucinations, in the long-term extension study than in the 3-month pivotal studies.

Suicide/self-injury

AESIs denoting suicide / self-injury were assessed based on a) reported TEAEs pertaining to suicide / self-injury and b) findings of suicidal ideation and/or behaviour on the C-SSRS.

A total of 8 cases of suicide / self-injury were noted across the Phase 1 to 3 studies: 7 in the Phase 2 and 3 studies, and 1 in Phase 1 study (HAP study 107).

The AEs of suicidal ideation in Phase 3 studies were reported in 4 isolated cases, 2 in study 302 and 2 in study 303, equally distributed across daridorexant treatment and placebo groups (1 subject in each treatment group : 10 mg, 25 mg, 50 mg and placebo). All events reported with daridorexant occurred in subjects with pre-existing psychiatric disorders known to be associated with high suicidal risk (paranoid schizophrenia undeclared at screening in 1 subject, who should not have been randomized; depression in the other subject, stable and asymptomatic at screening) and/or acute difficult circumstances (family stress, financial stress, illicit drug use). In addition, there was 1 case of suicidal ideation detected on the C-SSRS in study 201 (on 5 mg), which was mistakenly not reported as an AE. The Applicant has provided the narrative and justified the lack of adjudication as an AESI. Based on the C-SSRS scores assessment of the individual cases, there was no evidence of increased risk of suicidal ideation or behaviour during treatment with daridorexant, as well as no dose-dependent trend, however this potential risk need to be followed in the RMP.

In the SmPC, there is a precaution for use in the SmPC in accordance with these observations: "As with other hypnotics, QUVIVIQ should be administered with caution in patients exhibiting symptoms of depression" as "In

primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions have been reported". This precaution for use is in accordance with these observations.

Depression/worsening of depression

There were 4 TEAEs of depression in study 301, 5 events in study 302 and 5 events in study 303 in subjects receiving daridorexant. They were balanced across treatment groups within each study and did not occur in patients with a medical history of depression. The majority of AEs were non-serious except 3 events (2 in study 301 and 1 in study 303) of depression each in the placebo group.

A medical history within the psychiatric disorders SOC was reported in a total of 54 subjects (approximately 6%) in study 301 and 63 subjects (approximately 7%) in study 302. No AEs pertaining to depression or worsening of depression occurred in these subjects.

In summary, the number of AEs denoting depression was rather low and balanced between treatment groups and study periods (run-in, double blind and run-out periods). There was no evidence of depression or worsening of depression during treatment with daridorexant, in particular in subjects with a medical history of psychiatric disorders, including depression. However, this risk is followed as an important potential risk in the RMP under the safety concern "Suicidal behaviour in high-risk patients (with a medical history of depression or other psychiatric disorders)".

Next-morning residual effects

In parallel to improve sleep through the daridorexant treatment, it is important for the subjects not to present next-morning residual effects from the treatment. Therefore, assessing the risk of increased morning sleepiness with the use of a drug that induce sleep is a major issue of its safety.

The Morning Sleepiness VAS scores improved (morning sleepiness was decreased) as early as Day 1 following the start of treatment until at least Month 3, with a larger dose-dependent improvement in the daridorexant treatment groups compared to placebo, revealing a lack of signal of next-morning residual somnolence under treatment. The beneficial effect of daridorexant on morning sleepiness seems to be maintained over three months of time. When assessing the next-morning residual effects through other validated methods (coding sub-test, neurological examination, Karolinska Sleepiness Scale), the same trend is observed.

Overall, the various assessments did not reveal any propensity of a next-morning residual effect. On the contrary, it was shown that the morning sleepiness, which could also be a consequence of insomnia, improved on daridorexant treatment, according to the results of the daily morning sleepiness VAS.

Ability to drive or operate machinery

The driving performance seems not significantly impaired after a few days of daridorexant treatment although slightly impaired at the beginning of the treatment. Clarifications have been provided regarding the methodology of the study. Concerning the SmPC, caution are stated in sections 4.4 and 4.7.

Daytime somnolence / CNS-depressant effects

In studies 301 and 302, the observed changes in ESS total score from baseline to the last value during the double-blind treatment period were similar across the treatment groups, indicating no trend in excessive daytime sleepiness linked to treatment.

In parallel to a positive impact of daridorexant in daytime sleepiness (IDSIQ, see clinical efficacy part of the AR), it was also important to examine the TEAEs of somnolence and CNS-depressant effects. The overall

incidence rate of TEAEs pertaining to CNS-depressant effects in the 10 mg, 25 mg, and 50 mg groups remained low (2.3%, 3.6%, and 1.6%, respectively) compared to 2.1% in the placebo group.

Both MedDRA searches have shown a slightly increased incidence of events for daridorexant compared to placebo, with the highest incidence for 25 mg. The main CNS-depressant AE is somnolence (22/26 subjects in 301 and 20/22 in 302) with no observed dose dependence (the incidence rate in the 50 mg group is similar or even smaller than in the placebo group).

Overall, fatigue and somnolence are the most frequent CNS-depressant AE, of mild or moderate intensity, in the daridorexant groups. These AE are could be expected regarding the mechanism of action of the DORA (antagonism of the orexin receptors, stimulation of sleep-promoting effects).

Accidents and injuries (including falls)

In the individual pivotal studies 301 and 302, there was a consistently lower or similar incidence rate of TEAEs pertaining to accidents and injuries including falls in the daridorexant groups compared to the placebo group.

In the long-term study 303, the rates of TEAEs of falls, accidents and injuries in the different groups, were comparable. The rate in the 50 mg group even tended to be lower than in any other group.

The 3 cases of treatment-emergent road traffic accidents reported were all due to external factors and not related to the study drug.

More than half of falls occurred in elderly (aged $\geq$ 65 years). There were external contributing factors for each case and none was treatment related. There was no evidence of any CNS-depressant effects, such as somnolence or impaired attention, reported for any subject reporting accidents (including the road traffic ones), or injuries with or without falls. No falls occurred during the night.

Overall, there was no evidence of any drug effect or dose dependence as there was no evidence of any CNS-depressant effect that may have caused the reported falls, accidents or injuries AEs following treatment with daridorexant. None of the falls was considered as AESIs, which could exclude a signal for cataplexy. The addition of a caution in elderly is added in the SmPC, similarly to other hypnotics .

Anxiety symptoms

There was no evidence of any causal relationship between daridorexant treatment and anxiety.

Drug abuse potential

An abuse potential for daridorexant was observed as compared to placebo and seems comparable to that of suvorexant (150 mg), and zolpidem (30 mg) at supratherapeutic doses (100 mg and 150 mg). The analysis of data from phase 3 studies did not permit to confirm the abuse risk of daridorexant for the target population of patients with insomnia under experimental conditions. In conclusion, the mechanism of action, the pharmacological and safety data are relevant enough to constitute substantial evidence of potential for abuse of daridorexant. The Applicant's proposal to add "drug abuse" safety concern as important potential risk on the RMP is supported. The warning in section 4.4 has been amended.

Overdose

A total of 44 subjects reported AE of overdose during the double-blind treatment periods of the Phase 3 studies, of whom 35/44 were reported as accidental overdose, referring to taking 1 additional tablet on 1 or more than 1 occasion. Intentional overdose was reported in 2 subjects on placebo in study 302 and was asymptomatic.

All AEs of accidental overdose were non-serious, mild and asymptomatic except for 2 cases: 1 subject in study 301, in the 25 mg group, who reported AEs of disturbance in attention and hypersomnia during the placebo run-out period, and 1 subject in study 302, in the 25 mg group, who reported AE of mixed hallucination and sleep paralysis during the DB treatment period (this case has already been discussed among the narcolepsy-like symptoms). Nearly half of the overdose AE (19/44) were reported during the placebo run-in period (10 events, including an intentional overdose in study 302) and the placebo run-out period (9 events) in studies 301 and 302. No clear reason is provided for these cases of overdose in the placebo groups, and the lack of efficacy could be supposed.

There is no specific antidote for daridorexant. In the event of an overdose, symptomatic and supportive medical care should be provided, and subjects should be carefully monitored, as appropriate. Dialysis is unlikely to be effective as daridorexant is highly protein-bound.

Overall, these data did not raise any specific concern across all studies.

Withdrawal symptoms

Overall assessment of withdrawal effects showed no evidence of a withdrawal syndrome after daridorexant treatment abrupt discontinuation, regardless of the dose.

In 301, 303 and pool safety data, no AEs indicating a withdrawal syndrome were observed while significant higher proportion of subjects with at least one symptom BWSQ item scored as severe (>20) at the end of treatment withdrawal period in the daridorexant group was observed as compared to placebo (respectively, 5.6% and 2.8%).

The Applicant was asked to (1) provide the list of AEs indicating a withdrawal syndrome used, (2) provide the frequency of each BWSQ symptom scored as severe (>20), and (3) compare AEs to BWSQ symptoms. According to submitted data, the raised issues were solved.

Rebound insomnia

Compared to baseline, there was no mean increase in WASO, LPS or decrease in sTST in any treatment group. Overall, based on the change from baseline to the run-out period in objective (WASO and LPS) and subjective (sTST) sleep parameters, no evidence of rebound insomnia was observed. Moreover, no AEs suggesting rebound insomnia or exacerbated insomnia were reported during the placebo run-out period of both DB studies 301 and 302.

Rebound insomnia after 12 months of treatment was also assessed based on the change in sTST from baseline to the placebo run-out period in study 303 for those subjects who had already completed the placebo run-out period. The observations were similar to those obtained after studies 301 and 302. There was also no sign of rebound insomnia following a 12-month treatment with daridorexant, whatever the dose.

Serious adverse events and deaths

Serious adverse events

In studies 301 and 302, a total of 22 SAE occurred. In both daridorexant treatment groups, the incidence of SAE were numerically higher in the placebo groups than in each daridorexant groups: 2 subjects in the daridorexant 25 mg group (0.6%), 3 subjects in the daridorexant 50 mg group (1.0%), and 7 subjects in the

placebo group (2.3%) for study 301; 3 subjects in the daridorexant 10 mg group (1.0%), 3 in the daridorexant 25 mg group (1.0%), and 4 in the placebo group (1.3%) for study 302.

All SAE in studies 301 and 302, except one in study 302, were assessed as not related to study treatment. According to the analysis of the narratives, this position is endorsed, except for the SAE considered as related. Indeed, the case of microvascular coronary artery disease for a 60-70-year-old female subject (with many comorbidities in daridorexant 10 mg group considered as related to study treatment although not resolved at EOS after treatment discontinuation) has probably been erroneously considered related to daridorexant 10 mg.

For both studies, each SAE PT was reported for 1 subject only, except for 2 cases of syncope and 2 cases of depression in the placebo groups. No trend in relation to a system organ class was thus identified.

Among the 22 SAE for both studies, two SAE led to study discontinuation in study 302: the one in subject discussed above and the other in a subject within the context of "worsening of paranoid schizophrenia". This last discontinuation is justified, all the more that an AESI of suicidal ideation was also reported for this subject.

In study 303, three cases of diverticulitis (25 and 50 mg), two confusional state (25 and 50 mg), and two myocardial infarctions (10 and 25 mg) were reported in various daridorexant treatment groups vs no case in the placebo group. Otherwise, each SAE was reported for 1 subject only, mostly in the 25 mg and 50 mg daridorexant groups

Among the 27 SAEs mainly reported as not related to study treatment, 2 cases were reported as related to the study treatment. Another not study treatment related SAE occurred after the interim cut-off date (22 July 2020) in the daridorexant 10 mg group: The event was assessed as a "cerebrovascular accident" and finally categorized as "chronic ischemic changes" in a 70-80 year old female. The narrative has been thoroughly assessed and this final categorization seems appropriate and is endorsed. The lack of relation to treatment could be explained by the medical history and comorbidities of the subject.

In the phase 2 study 201, three SAE (2 cases in the 10 mg daridorexant group and 1 case in the 50 mg daridorexant group) not related to study drug were reported. After assessment of the narrative for the minor septal myocardial infarction, the lack of treatment relation is considered appropriate regarding the pre-existing stenosis of the artery of the subject, but undetected at enrolment. For the other two subjects, the TESAE were obviously not treatment related. The three subjects completed the study. There was no SAE with a fatal outcome.

No SAE was reported in study 202.

During the phase 1 study program, two SAE in the 50 mg daridorexant group were reported, both were considered as not related to study drug which is endorsed after assessment of their narratives.

Overall, during the phase 1 to 3 studies, most SAE that occurred were not treatment related or erroneously treatment related, with various medical histories or comorbidities underlying the occurrence of the SAE. There was not specific pattern of any system organ class or PT that could be highlighted from these SAE in any study treatment group, even if numerically most of the SAE (mainly related to orthopaedic injuries, cardiovascular disorders, infectious situations or cancer events) occurred in the 25 mg and 50 mg daridorexant groups. A few SAE led to discontinuation, mainly in relation to comorbidities as not treatment related. None of these SAE led to death.

Deaths

A total of 4 deaths were reported during the development program of daridorexant, three of them during the 301 and 303 studies and one non-treatment emergent SAE (metastatic lung cancer) at the end of study 303.

The 4 narratives have been extensively read, analyzed and summarized to keep the relevant information related to the deaths.

None of these cases was considered related to study treatment which is endorsed. Indeed the deaths could be attributed to the subjects' confounding pre-existing risk factors and comorbidities such as age and relevant medical history.

Laboratory findings

Haematology

Overall, marked abnormalities in haematology parameters without clinical significance were reported in similar proportions of subjects in the 3 treatment groups and placebo of the phase 2 and 3 studies. No pattern of haematology abnormalities related to daridorexant was observed with no consistent treatment or dose-dependent trend for any of the haematology parameter. No SAE related to haematology abnormalities was reported.

Chemistry

Overall, marked abnormalities in clinical chemistry parameters without clinical significance were reported in similar proportions of subjects in the 3 treatment groups and placebo of the phase 2 and 3 studies. No pattern of chemistry abnormalities related to daridorexant was observed with no consistent treatment or dose-dependent trend for any of the chemistry parameter. No SAE related to chemistry abnormalities was reported.

Vital signs and ECG findings

Vital signs

Daridorexant did not have any clinically relevant effect on vital signs following its administration in any of the Phase 1–3 clinical studies.

ECG findings

For all ECG findings during double-blind period, no treatment or dose-related pattern was observed. And the incidence of marked ECG abnormalities during the phase 2 and 3 studies was comparable across treatment groups, with no consistent treatment or dose-related trend. There was no indication of any systematic effect when compared to placebo. This lack of concern is corroborated by the safety pharmacology TQT study .

Safety in special populations

The safety in special populations was mainly focused on a comparison of safety data (overall incidence of TEAE) in the elderly (≥ 65 years) compared to the younger adult (<65 years) subgroups, in male compared to female subjects. Indeed, taking into account the epidemiology of insomnia, subjects aged ≥ 65 years constituted nearly 40% of the overall included population. Moreover, elderly subjects may be more sensitive to the AE of insomnia therapies than younger adults justifying that the pattern of AE between age groups was carefully scrutinized.

According to the pooled data set, the overall incidences of TEAEs were higher in daridorexant dose groups than in placebo groups in both the < 65 years and ≥ 65 years subgroups and the pattern of the most frequently

reported TEAE was consistent between the age subgroups. Although there were a few numerical differences regarding the incidence of the AE falls and dizziness between the age subgroups, both in the daridorexant and the placebo groups, there was no specific signal of increased incidence of falls or dizziness in the elderly treated with daridorexant vs those treated with placebo. This is supported by a lesser incidence rate of falls and dizziness in the 50 mg daridorexant vs 25 mg for both AE. Regarding the AE somnolence and fatigue, the same trend is observed in the elderly vs adults, with a lesser incidence in the 50 mg daridorexant for both AE.

Overall, for the most frequent AE of somnolence, dizziness, and fatigue, the incidence was slightly higher in the elderly at 25 mg compared to subjects < 65 years, this difference is however not seen in elderly subjects at 50 mg. In the SmPC, the following sentence is stated: "The adverse reaction profile in elderly subjects was consistent with younger subjects".

The overall pattern of the most frequently reported TEAE was consistent between male and female subjects with no clear sex-associated effect on the incidence of these TEAE in the pooled daridorexant 25 mg group compared to the pooled placebo group.

Regarding other criteria, there is no difference in the incidence of TEAE when comparing US subjects vs Europeans, low vs high BMI subjects and White vs Black or African American, although the small number of subjects in the Black or African American and other ethnic subgroups (around 10%) limits the ability to detect risk differences by ethnicity and limits the interpretation of the data.

In summary, no trend of specific safety concern has been highlighted in special populations, considering the age, the sex, the ethnicity, the region and the BMI. There is a lack of data about the use of daridorexant during pregnancy and breastfeeding.

Immunological events

NA

Safety related to drug-drug interactions and other interactions

In accordance with the data assessed in the AR, safety related to DDI and other interactions are mandatory and the following statement are displayed in the SmPC:

- Caution should be exercised when prescribing QUVIVIQ concomitantly with CNS-depressant medicinal products due to potentially additive effects, and a dose adjustment of either QUVIVIQ or the concomitant CNS depressants should be considered.

- Patients should be cautioned about drinking alcohol during treatment with QUVIVIQ (see section 4.5). Co-administration of 50 mg daridorexant with alcohol led to additive effects on psychomotor performance.

- Concomitant use of QUVIVIQ with strong inhibitors of CYP3A4 is not recommended and the MAH is asked to list them in the SmPC.

- The consumption of grapefruit or grapefruit juice in the evening should be avoided.

- Based on these results, concomitant use with a moderate or strong CYP3A4 inducer substantially decreases exposure to QUVIVIQ, which may reduce efficacy

The statements in the SmPC of cautions when using daridorexant concomitantly with CNS-depressant medicinal products, with alcohol, with strong inhibitors of CYP3A4 and with moderate or strong CYP3A4 inducer is endorsed and fully justified.

Discontinuation due to AES

Sixty-nine (69) subjects prematurely discontinued from studies 301, 302 and 303. Additional 9 subjects discontinued from phase 1 and phase 2 studies. A total of 76 discontinuations in phase 2 and phase 3 studies represents a rate of 4.5% of premature discontinuation which is rather low.

The proportion of subjects with at least 1 TEAE leading to premature discontinuation of studies 301 and 302 was low (from 1.0 to 3.2%). There was no dose relationship and the incidence of these AEs was numerically higher in the placebo group than in either daridorexant group.

In study 303, the proportion of subjects who discontinued treatment due to an AE was higher than in pivotal studies in each daridorexant group or placebo group (3.7% for 25 mg, 6.6% for 50 mg and 4.7% for placebo) except in the daridorexant 10 mg group (0.7%). Although a higher rate of discontinuation could be explained by the longer treatment exposure, the low rate of discontinuation observed in the 10 mg daridorexant group may be due to a lower occurrence of AE in this low-dose group.

Across the pivotal studies and the long-term extension study, most of the AE leading to discontinuation were reported in 1 subject. However, in terms of CNS effects, some AE were noted in more than 1 case and shared out between the treatment groups: there were 3 cases of dizziness (daridorexant 10 and 25 mg), 2 cases of syncope (placebo), 3 cases of suicidal ideation (daridorexant 10 and 50 mg, and placebo), 3 cases of fatigue (daridorexant 50 mg, placebo and ex-placebo/daridorexant 25 mg), 2 cases of sedation complication (daridorexant 25 mg and placebo) and 2 cases of confusional state (daridorexant 25 and 50 mg). No discontinuation for morning somnolence, sleepiness, or daytime somnolence was reported.

No specific trend could be observed from these AE leading to discontinuation in any group as there was no dose relationship and the incidence of AE leading to discontinuation was numerically higher in the placebo groups of the pivotal studies than in the daridorexant groups.

Post marketing experience

NA

2.6.9. Discussion on clinical safety

The main focus of the safety analysis for daridorexant is based on placebo controlled safety data from the pivotal Phase 3 studies of 3-month duration, i.e., the two individual studies 301 (daridorexant 25 and 50 mg, and placebo) and 302 (daridorexant 10 and 25 mg, and placebo). The safety data from the long-term, double-blind, placebo-controlled extension study 303 were also assessed. Study 303 was ongoing at the time of submission; therefore, interim data are provided initially. A pre-planned pooled safety data set of daridorexant 25 mg and placebo groups was also used, since these two groups were the only treatment groups replicated across studies 301 and 302. This pooled safety analysis was used to compare the rates of AEs within subgroups and to compare withdrawal symptoms in the 25 mg group vs placebo.

In addition, safety data from Phase 2 studies in subjects with insomnia (studies 201 and 202, as well as study 206 performed in Japanese subjects) and from 18 Phase 1 clinical pharmacology studies are also considered.

The overall development program is considered adequate for the intended treatment in subjects with insomnia.

Exposure

The overall exposure during the double-blind treatment period in subjects with insomnia in the completed Phase 2 and 3 studies, and up to the cut-off date for the interim analysis of study 303 (22 July 2020)

A total of 1655 subjects with insomnia in phase 2 and phase 3 studies including the ongoing phase 3 study received at least one dose of daridorexant all doses combined, and 729 subjects received at least one dose of placebo. Of these 1655 subjects, 804 subjects received 25 mg, 369 subjects received 50 mg and 364 subjects received 10 mg.

The clinical pharmacology program for daridorexant consists of 18 completed Phase 1 trials (567 subjects exposed to daridorexant), including single and repeated dose studies. Of these 567 subjects, 194 were exposed to single doses of daridorexant (up to 200 mg) and 373 received multiple doses of daridorexant (up to 100 mg).

Due to the prevalence of insomnia in elderly, nearly 40% of subjects ≥ 65 years were recruited in the phase 2 and 3 studies. Some other subgroup analyses were performed for the combined safety set in particular by sex, in which female subjects constituted two-thirds of the overall population, reflecting the higher prevalence of insomnia in females than in males.

Safety profile

Safety data are driven by the subjects with insomnia included in the phase 3 studies, including 40% elderly. Based on the mechanism of action of daridorexant, the potential for narcolepsy-like symptoms was carefully considered and narcolepsy-like symptoms monitored during the daridorexant clinical program.

In the Phase 3 studies 301 and 302, the percentage of subjects experiencing TEAEs was numerically slightly higher in the daridorexant treatment groups compared to the placebo groups (by 41.3% vs 37.2% in study 301 and 43.1% vs 36.3% in study 302) with however a similar incidence in the daridorexant groups of each study. For study 303, a slightly higher incidence of TEAEs was observed in the daridorexant groups compared to the placebo group however not carried out by any specific PT.
On the contrary, the rate of treatment-emergent SAEs, or TEAEs leading to discontinuation during the DB study period, was slightly higher in the placebo groups compared to the daridorexant treatment groups. Overall, a trend for a dose dependence in the incidence of AE is uncertain.

- **TEAE**

The three most commonly reported primary SOCs were infections and infestations, nervous system disorders, and gastrointestinal disorders, in both phase 3 studies 301 and 302.

The majority of ADRs (headache, somnolence, dizziness, fatigue and nausea) were mild to moderate in intensity and no evidence of a dose-relationship for the frequency or the severity of ADRs is observed. Sleep paralysis (transient, dissociated sleep state during which REM sleep atonia continues into wakeful consciousness) were observed with daridorexant 25 mg and 50 mg at a frequency lesser than 1% (0.5% for 25 mg and 0.3% for 50 mg) and no case observed with placebo. Cases of sleep-related hallucinations were only observed in the daridorexant 25 mg group in 0.8% of subjects and no case with placebo or daridorexant 50 mg.

- **AESI**

Considering the mechanism of action of daridorexant which intends to stimulate sleep-promoting effects, special attention was given to several safety topics of medical significance.

The AESI were assessed according to the following 4 categories: narcolepsy-like symptoms related to EDS (excessive daytime somnolence), narcolepsy-like symptoms related to complex sleep behavior, including hallucinations and sleep paralysis, narcolepsy-like symptoms related to cataplexy-like events and suicide/self-injury (and worsening of depression).

The other safety topics of medical significance are next-morning residual effects; ability to drive or operate machinery; daytime somnolence / CNS-depressant effects; falls, accidents and injuries, which may result from EDS; anxiety; drug abuse potential; cases of overdose; withdrawal symptoms; and rebound insomnia.

Narcolepsy-like symptoms

A total of 453 potential AESIs occurring in 367 subjects were submitted to the ISB for adjudication during the Phase 2 and 3 programs. Of these, 31 events (6.8%) in 24 subjects of submitted potential AEs were adjudicated by the ISB as AESIs.

For the narcolepsy-like symptoms, three quarters (3/4) of the narcolepsy-like AESIs (15/20) occurred in the 25 mg daridorexant groups (and 2 in the daridorexant 50 mg, 2 in the 10 mg daridorexant group and 1 in the placebo group) for both 301 and 302 studies.

The majority of narcolepsy-like symptoms related to EDS and the narcolepsy-like symptoms related to complex sleep behaviour including hallucinations and sleep paralysis occurred in the 25 mg daridorexant groups (seven cases: 5 in 25 mg, 2 in 50 mg) with a low incidence rate (< 1%), without any clear trend for a dose dependence. None of the events evoked a typical narcolepsy phenotype with an increase in sleep propensity and recurrence, for example. No hallucinations and sleep paralysis occurred in the placebo groups of both studies. Most AESIs were non-serious and required no intervention.

- No AESIs belonging to the category "narcolepsy-like symptoms related to cataplexy" occurred in the Phase 2 and Phase 3 studies.

- The total number of AESIs belonging to the category "narcolepsy-like symptoms related to EDS" was rather low: in total, 13/1597 subjects in studies 201, 301, 302, and 303 combined treated with daridorexant (0.8%), in comparison to 2/675 subjects (0.3%) treated with placebo. For the 3 studies, a slight predominance of the AESI in the 25 mg group is observed. One case of moderate somnolence in study 303 required nearly 50 days of duration for the resolution of the event in a 57-year-old Caucasian female which is questionable. The Applicant has justified this rather long time (50 days) before resolution of the event and no specific pattern is raised.

Apart from sleep paralysis and hallucinations, no cases of other complex sleep behaviours such as sleep walking / somnambulism, sleep driving, sleep talking, sleep eating, or sleep sex were reported in the 50 mg daridorexant group. The Applicant has explained the highest incidence of this AESI in the 25 mg daridorexant group in comparison to the other groups and to the incidence in the general population. The Applicant has also justified the less frequent incidence of these AESI, sleep paralysis and/or hallucinations, in the long-term extension study than in the 3-month pivotal studies, with a statement in the SmPC that these events more often occur during the first weeks after treatment initiation.

Suicide/self-injury

AESIs denoting suicide / self-injury were assessed based on a) reported TEAEs pertaining to suicide / self-injury and b) findings of suicidal ideation and/or behaviour on the C-SSRS.

A total of 8 cases of suicide / self-injury were noted across the Phase 1 to 3 studies: 7 in the Phase 2 and 3 studies, and 1 in Phase 1 study (HAP study 107).

In summary, the AEs of suicidal ideation in Phase 3 studies were reported in 4 isolated cases, 2 in study 302 and 2 in study 303, equally distributed across daridorexant treatment and placebo groups (1 subject in each treatment group : 10 mg, 25 mg, 50 mg and placebo). All events reported with daridorexant occurred in subjects with pre-existing psychiatric disorders known to be associated with high suicidal risk (paranoid schizophrenia undeclared at screening in 1 subject, who should not have been randomized; depression in the other subject, stable and asymptomatic at screening) and/or acute difficult circumstances (family stress, financial stress, illicit drug use). In addition, there was 1 case of suicidal ideation detected on the C-SSRS in study 201 (on 5 mg), which was mistakenly not reported as an AE. The Applicant has provided the narrative and justified the lack of adjudication as an AESI. Based on the C-SSRS scores assessment of the individual cases, there was no evidence of increased risk of suicidal ideation or behaviour during treatment with daridorexant, as well as no dose-dependent trend, however this potential risk need to be followed in the RMP (see RMP part).

In the SmPC, there is a precaution for use in the SmPC in accordance with these observations: "As with other hypnotics, QUVIVIQ should be administered with caution in patients exhibiting symptoms of depression" as "In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions have been reported". This precaution for use is in accordance with these observations.

Depression/worsening of depression

There were 4 TEAEs of depression in study 301, 5 events in study 302 and 5 events in study 303 in subjects receiving daridorexant. They were balanced across treatment groups within each study and did not occur in patients with a medical history of depression. The majority of AEs were non-serious except 3 events (2 in study 301 and 1 in study 303) of depression each in the placebo group. A medical history within the psychiatric disorders SOC was reported in a total of 54 subjects (approximately 6%) in study 301 and 63 subjects (approximately 7%) in study 302. No AEs pertaining to depression or worsening of depression occurred in these subjects.

In summary, the number of AEs denoting depression was rather low and balanced between treatment groups and study periods (run-in, double blind and run-out periods). There was no evidence of depression or worsening of depression during treatment with daridorexant, in particular in subjects with a medical history of psychiatric disorders, including depression. However, this risk is followed as an important potential risk in the RMP under the safety concern "Suicidal behaviour in high-risk patients (with a medical history of depression or other psychiatric disorders)".

Next-morning residual effects

In parallel to improve sleep through the daridorexant treatment, it is important for the subjects not to present next-morning residual effects from the treatment. Therefore, assessing the risk of increased morning sleepiness with the use of a drug that induce sleep is a major issue of its safety. Overall, the various assessments did not reveal any propensity of a next-morning residual effect. On the contrary, it was shown that the morning sleepiness, which could also be a consequence of insomnia, improved on daridorexant treatment, according to the results of the daily morning sleepiness VAS.

Ability to drive or operate machinery

The driving performance seems not significantly impaired after a few days of daridorexant treatment although slightly impaired at the beginning of the treatment. Clarifications have been provided regarding the methodology of the study. Concerning the SmPC, caution are stated in sections 4.4 and 4.7.

Daytime somnolence / CNS-depressant effects

In studies 301 and 302, the observed changes in ESS total score from baseline to the last value during the double-blind treatment period were similar across the treatment groups, indicating no trend in excessive daytime sleepiness linked to treatment. In parallel to a positive impact of daridorexant in daytime sleepiness (IDSIQ, see clinical efficacy part of the AR), it was also important to examine the TEAEs of somnolence and CNS-depressant effects. The overall incidence rate of TEAEs pertaining to CNS-depressant effects in the 10 mg, 25 mg, and 50 mg groups remained low (2.3%, 3.6%, and 1.6%, respectively) compared to 2.1% in the placebo group.

Overall, fatigue and somnolence are the most frequent CNS-depressant AE, of mild or moderate intensity, in the daridorexant groups. These AE are could be expected regarding the mechanism of action of the DORA (antagonism of the orexin receptors, stimulation of sleep-promoting effects).

Accidents and injuries (including falls)

In the individual pivotal studies 301 and 302, there was a consistently lower or similar incidence rate of TEAEs pertaining to accidents and injuries including falls in the daridorexant groups compared to the placebo group. In the long-term study 303, the rates of TEAEs of falls, accidents and injuries in the different groups, were comparable. More than half of falls occurred in elderly (aged $\geq$ 65 years). There were external contributing factors for each case and none was treatment related. There was no evidence of any CNS-depressant effects, such as somnolence or impaired attention, reported for any subject reporting accidents (including the road traffic ones), or injuries with or without falls. No falls occurred during the night.

Overall, there was no evidence of any drug effect or dose dependence as there was no evidence of any CNS-depressant effect that may have caused the reported falls, accidents or injuries AEs following treatment with daridorexant. None of the falls was considered as AESIs, which could exclude a signal for cataplexy. However, a caution in elderly is added in the SmPC, similarly to other hypnotics.

Drug abuse potential

An abuse potential for daridorexant was observed as compared to placebo and seems comparable to that of suvorexant (150 mg), and zolpidem (30 mg) at supratherapeutic doses (100 mg and 150 mg). The analysis of data from phase 3 studies did not permit to confirm the abuse risk of daridorexant for the target population of patients with insomnia under experimental conditions. In conclusion, the mechanism of action, the pharmacological and safety data are relevant enough to constitute substantial evidence of potential for abuse of daridorexant. The Applicant's proposal to add "drug abuse" safety concern as important potential risk on the RMP is supported. The warning in section 4.4 has been also amended.

Overdose

A total of 44 subjects reported AE of overdose during the double-blind treatment periods of the Phase 3 studies, of whom 35/44 were reported as accidental overdose, referring to taking 1 additional tablet on 1 or more than 1 occasion. Intentional overdose was reported in 2 subjects on placebo in study 302 and was asymptomatic.

All AEs of accidental overdose were non-serious, mild and asymptomatic except for 2 cases in the 25 mg group (disturbance in attention and hypersomnia during the placebo run-out period, and mixed hallucination and sleep paralysis during the DB treatment period). Nearly half of the overdose AE (19/44) were reported during the placebo run-in period (10 events, including an intentional overdose in study 302) and the placebo run-out period (9 events) in studies 301 and 302. No clear reason is provided for these cases of overdose in the placebo groups, and the lack of efficacy could be supposed.

Overall, these data did not raise any specific concern across all studies. The potential for abuse has otherwise been discussed and added in the RMP.

Withdrawal symptoms

Overall assessment of withdrawal effects showed no evidence of a withdrawal syndrome after daridorexant treatment abrupt discontinuation, regardless of the dose. In 301, 303 and pool safety data, no AEs indicating a withdrawal syndrome were observed while significant higher proportion of subjects with at least one symptom BWSQ item scored as severe (>20) at the end of treatment withdrawal period in the daridorexant group was observed as compared to placebo (respectively, 5.6% and 2.8%). The Applicant has provided clarifications. According to this analysis, withdrawal syndrome was not added in the RMP as a safety concern and a statement that there is no evidence of withdrawal symptoms was included the SmPC.

Rebound insomnia

Based on the change from baseline to the run-out period in objective (WASO and LPS) and subjective (sTST) sleep parameters, no evidence of rebound insomnia was observed. Moreover, no AEs suggesting rebound insomnia or exacerbated insomnia were reported during the placebo run-out period of both DB studies 301 and 302. There was also no sign of rebound insomnia following a 12-month treatment with daridorexant, whatever the dose.

SAE

Overall, during the phase 1 to 3 studies, most SAE that occurred were not treatment related or erroneously treatment related, with various medical histories or comorbidities underlying the occurrence of the SAE. There was not specific pattern of any system organ class or PT that could be highlighted from these SAE in any study treatment group, even if numerically most of the SAE (mainly related to orthopaedic injuries, cardiovascular disorders, infectious situations or cancer events) occurred in the 25 mg and 50 mg daridorexant groups. A few SAE led to discontinuation, mainly in relation to comorbidities as not treatment related. None of these SAE led to death.

Vital signs and ECG findings

Daridorexant did not have any clinically relevant effect on vital signs following its administration in any of the Phase 1–3 clinical studies.

For all ECG findings during double-blind period, no treatment or dose-related pattern was observed. There was no indication of any systematic effect when compared to placebo. This lack of concern is corroborated by the safety pharmacology TQT study.

Safety in special populations

The safety in special populations was mainly focused on a comparison of safety data (overall incidence of TEAE) in the elderly (≥ 65 years) compared to the younger adult (<65 years) subgroups, in male compared to female subjects. Indeed, elderly subjects may be more sensitive to the AE of insomnia therapies than younger adults justifying that the pattern of AE between age groups was carefully scrutinized.

According to the pooled data set, the overall incidences of TEAEs were higher in daridorexant dose groups than in placebo groups in both the < 65 years and ≥ 65 years subgroups and the pattern of the most frequently reported TEAE was consistent between the age subgroups. Although there were a few numerical differences regarding the incidence of the AE falls and dizziness between the age subgroups, both in the daridorexant and the placebo groups, there was no specific signal of increased incidence of falls or dizziness in the elderly treated with daridorexant vs those treated with placebo. This is supported by a lesser incidence rate of falls and dizziness in 50 mg vs 25 mg daridorexant group for both AE. Regarding the AE somnolence and fatigue, the same trend is observed in the elderly vs adults. Overall, for the most frequent AE of somnolence, dizziness, and fatigue, the incidence was slightly higher in the elderly at 25 mg compared to subjects < 65 years, this difference is however not seen in elderly subjects at 50 mg. In the SmPC, the following sentence is stated: «The adverse reaction profile in elderly subjects was consistent with younger subjects". This is acceptable. However, the experience in patients above the age of 75 years is very limited and this is reflected in the SmPC.

It seems that the Japanese subjects (ethnicity study) might be more sensitive to the effects of daridorexant (somnolence and other AE of interest such as sleep paralysis, sudden onset of sleep, and disturbance in attention were more frequently reported in Japanese subjects) compared to Caucasian subjects. After clarification, there is no precaution in the SmPC for this specific population.

In summary, no trend of specific safety concern has been highlighted in special populations, considering the age, the sex, the ethnicity, the region and the BMI. It seems that the Japanese subjects might be more sensitive to the effects of daridorexant compared to Caucasian subjects. This aspect has been clarified based on further data provided by the Applicant. There is a lack of data about the use of daridorexant during pregnancy and breastfeeding that does not allow to make a statement.

Discontinuation due to AES

Sixty-nine (69) subjects prematurely discontinued from studies 301, 302 and 303. Additional 9 subjects discontinued from phase 1 and phase 2 studies. A total of 76 discontinuations in phase 2 and phase 3 studies represents a rate of 4.5% of premature discontinuation which is rather low.

The proportion of subjects with at least 1 TEAE leading to premature discontinuation of studies 301 and 302 was low (from 1.0 to 3.2%). There was no dose relationship and the incidence of these AEs was numerically higher in the placebo group than in either daridorexant group.

In study 303, the proportion of subjects who discontinued treatment due to an AE was higher than in pivotal studies in each daridorexant group or placebo group (3.7% for 25 mg, 6.6% for 50 mg and 4.7% for placebo) except in the daridorexant 10 mg group (0.7%). Although a higher rate of discontinuation could be explained by the longer treatment exposure, the low rate of discontinuation observed in the 10 mg daridorexant group may be due to a lower occurrence of AE in this low-dose group.

No specific trend could be observed from these AE leading to discontinuation in any group as there was no dose relationship and the incidence of AE leading to discontinuation was numerically higher in the placebo groups of the pivotal studies than in the daridorexant groups.

2.6.10. Conclusions on clinical safety

A total of 1655 subjects with insomnia in phase 2 and phase 3 studies including the ongoing phase 3 study received at least one dose of daridorexant all doses combined, and 729 subjects received at least one dose of placebo. Of these 1655 subjects, 804 subjects received 25 mg, 369 subjects received 50 mg and 364 subjects received 10 mg.

The following clinical safety conclusions and concerns that have been clarified are summarized hereafter:

• The majority of ADRs were mild to moderate in intensity and there was no evidence of any dose relationship for either the frequency or the severity of ADRs. The ADR profile in the elderly was consistent with the profile in younger subjects. The applicant was requested to provide a respective justification/calculation as a process of estimation of frequency category for each ADR separately (i.e. "common" for all the ADRs). It should follow the guidance on how to estimate the frequency of ADR which is available within the EC document "A guideline on Summary of Product Characteristics (SmPC)", September 2009. The Applicant provided a brief explanation of the frequency categories assigned to the ADRs which are to be outlined in the section 4.8 of SmPC and respective part of the PIL. The data comes from the clinical trial incidences and leads to the frequency "common" in 5 ADRs and "uncommon" in 2 ADRs.

• A small increase in AEs of headache, somnolence, fatigue, dizziness, and nausea was observed for daridorexant compared to placebo, with no apparent dose dependence.

• No suicidal ideation or worsening of depression is highlighted. However as regards to the potential suicidal behaviour in high-risk patients (with a medical history of depression or other psychiatric disorders), this risk has been added as a safety concern in the RMP among the important potential risks.

• No cases of cataplexy and no cases of complex sleep behaviours (such as sleep walking / somnambulism, sleep driving, sleep talking, sleep eating, or sleep sex) were reported with daridorexant treatment. However, there were isolated cases of sleep paralysis and/or sleep-related hallucinations with daridorexant treatment, without dose dependency. However, although not frequent and not categorized as serious during the phase 2 and 3 studies, a few cases of sleep paralysis were encoded as severe and led to study discontinuation. This safety concern was not added in the RMP. Follow up this safety concern via routine pharmacovigilance (i.e., signal detection and adverse reaction reporting) as proposed by the Applicant is deemed sufficient.

• No next-morning residual effect was observed and there was no clinically significant trend of daytime sleepiness or increased somnolence. There was also no rebound insomnia when daridorexant is discontinued. No AEs indicating a withdrawal syndrome were observed while significant higher proportion of subjects with at least one risk symptom BWSQ item scored as severe (>20) at the end of treatment withdrawal period in the daridorexant group was observed as compared to placebo and clarified by the Applicant. There was no evidence of withdrawal symptoms upon drug discontinuation in clinical trials with daridorexant in subjects with insomnia.

• There was no increase in the risk of fall, accident or injury, in particular in elderly, considering that subjects > 65 years are of particular concern for these events. A caution in the SmPC has been added.

• A relative risk of abuse potential was suggested, based on the 'drug-liking' assessment in the HAP study (with no nonclinical signal). As regards to the potential for drug abuse, this risk has been added as a safety concern in the RMP among the important potential risks.

• Impairment of driving was shown at treatment initiation in healthy subjects, with disappearance of the effect after repeated doses. Clarifications regarding the methodology used in the study before have been provided. In addition, the SmPC statement has been adequately amended.

• No safety concerns were identified in moderate COPD subjects and in mild and moderate OSA subjects. Special statement are added in the SmPC for severe COPD and OSA related to the lack of data in these subjects.

• No dose reduction in patients with mild to severe renal impairment was recommended. There is insufficient knowledge about the use of daridorexant in subjects with severe hepatic impairment and a statement in the SmPC to not recommended daridorexant for this specific population has been added.

• No difference in the safety profile of daridorexant was identified in subgroups according to age, sex, race/ethnicity, region, or BMI that would influence the therapeutic dose. A precaution in Japanese subjects was not necessary. However studies are ongoing and the PI could be further updated if relevant

• No safety issues were identified during the preliminary results of the long-term study 303. The Applicant further provided data from this extension study and the number of subjects is around 100 subjects at 1 year for the recommended 50 mg daridorexant dose.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Potential for drug abuse Suicidal behaviour in high-risk patients (with a medical history of depression or other psychiatric disorders)
Missing information	Use in pregnant women Use in breastfeeding women Elderly > 75 years of age

2.7.2. Pharmacovigilance plan

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important potential risk: Potential for drug abuse	**Routine risk minimisation measures:** SmPC section 4.4 SmPC section 4.2 PIL section 2 Limited pack sizes	**Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire for AEs denoting potential drug abuse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None.	**Additional pharmacovigilance activities:** None.
Important potential risk: Suicidal behaviour in high-risk patients (with a medical history of depression or other psychiatric disorders)	**Routine risk minimisation measures:** SmPC section 4.4 SmPC section 4.2 PIL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None.	**Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire for AEs denoting suicidal behaviour **Additional pharmacovigilance activities:** None.
Missing information: Use in pregnant women	**Routine risk minimisation measures:** SmPC sections 4.6 and 5.3 PIL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None.	**Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** QUVIVIQ pregnancy registry
Missing information: Use in breastfeeding women	**Routine risk minimisation measures:** SmPC section 4.6 PIL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None.	**Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information: Use in patients > 75 years	**Routine risk minimisation measures:** SmPC section 4.4 SmPC section 4.2 PIL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None.	**Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

2.7.3. Conclusion

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

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 07 January 2022. The new EURD list entry will therefore use the {EBD} {IBD} to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, QUVIVIQ (daridorexant) is included in the additional monitoring list as it includes new active substance.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5, 2013), insomnia disorder is defined as "a predominant complaint of dissatisfaction with sleep quantity or quality with one (or more) of the following symptoms:

(i) difficulty initiating sleep,

(ii) difficulty maintaining sleep characterized by frequent awakenings or problems returning to sleep after awakenings,

(iii) early-morning awakening with inability to return to sleep.

The sleep disturbance causes clinically significant distress or impairment with detrimental effects on daytime functioning, including social, occupational, educational, academic, behavioral, or other important areas of functioning".

Similar diagnostic criteria for insomnia disorder were defined in the International Classification of Sleep Disorders. 3rd Edition (ICSD-3, 2014).

Insomnia is associated with an abnormal state of hyperarousal that overrides the normal control of sleep. Orexin is a central promotor of arousal and vigilance.

3.1.2. Available therapies and unmet medical need

According to treatment guidelines from the US and Europe, the first-line treatment is Insomnia-specific cognitive-behavioural therapy (CBT-i). Pharmacological intervention can be offered when CBT-i is not effective or not available.

Use of hypnotic drugs is currently mostly recommended for short-term treatment, or as a temporary adjunct to CBT-i, due to safety limitations.

Pharmacological treatment consists of benzodiazepines, non-benzodiazepine GABA-A receptor agonists, melatonin receptor agonists, and drugs that are administered in off-label use (e.g., sedating antidepressants, antihistamines).

In addition, several over-the-counter herbal medicines are used by people with insomnia.

3.1.3. Main clinical studies

The evidence of the efficacy of Quviviq (daridorexant) in the intended indication is based mainly on data from 2 pivotal phase 3 studies versus placebo (study 301 and study 302), supported by the interim results from one ongoing DB Phase 3 extension study (study 303).

Supportive data was obtained from two Phase 2 dose-finding studies one in adult subjects versus placebo with an active arm (zolpidem) (study 201) and one cross-over versus placebo in elderly (study 202).

3.2. Favourable effects

In the pivotal studies, the difference from placebo of the 50 mg dose on objective co-primary endpoints (WASO, LPS) is statistically significant at month 1 and month 3 (-18.3 [-23.9; -12.7] min, p-value <0.0001 for WASO; −11.7 [−16.3, −7.0] min, p-value <0.0001 for LPS). The difference from placebo of the 50 mg dose is also statistically significant on subjective secondary sTST endpoint at month 1 and month 3 (22.1 [14.4, 29.7] min, p-value <0.0001 at month 1). The effect observed at month 1 is similar to efficacy at month 3.

The efficacy of the 50 mg dose studied in one pivotal study on sleep awakenings, sleep latency and total sleep time seems clinically relevant. Indeed, after 3 months of daridorexant treatment at the 50 mg dose, patients sleep more than 6 hours on average per night, with a sleep latency of around 30 minutes and have around 1 hour of awakenings during the night.

Statistically significant difference over placebo was achieved for the 2 primary endpoints (WASO, LPS) at 25 mg in study 301 but failed for one of the primary endpoint (LPS) at 25 mg in study 302. The efficacy of 10 mg dose is not demonstrated.

Results by subgroups were consistent with the overall results. There was no apparent difference depending on the sex, age or region. In all demographic subgroups, the 50 mg dose provided a larger benefit than the 25 mg dose across almost all endpoints.

The long term study was a 40 weeks double-blind and placebo-controlled with efficacy exploratory subjective endpoints. Although an important placebo effect on subjective endpoints (sTST, sLSO, sWASO) was observed for patients treated with placebo, the effect seems maintained at 1 year for daridorexant 50 mg.

No next-morning residual effect was observed and there was no clinically significant trend of daytime sleepiness or increased somnolence. On the contrary, it was shown that the morning sleepiness, which could also be a consequence of insomnia, improved on daridorexant treatment, according to the results of the daily morning sleepiness VAS.

3.3. Uncertainties and limitations about favourable effects

EMA guideline recommends including an active comparator in phase 3 studies and this recommendation were not followed by the Applicant since the phase 3 studies did not include an active comparator. However, the addition of zolpidem as an active comparator in one of the pivotal studies during the first 4 weeks would have complicated results interpretation and make them unsuitable for inclusion in the primary analysis. Also, one phase 2 study (201) includes zolpidem as active comparator for validation assay.

EMA guideline recommends using subjective primary endpoints. Results should be supported by objective data. Those recommendation were not followed by the Applicant since the phase 3 studies used objective criteria (WASO, LPS) for primary endpoints and subjective criteria as secondary endpoints as this allowed them to comply with FDA requirements.

The objective assessment of awakenings during the night is not supported by subjective assessment. However, the total sleep time assessed subjectively follows the same trend that sleep duration assessed objectively with an acceptable observed dose effect at 50 mg. The choice of sTST as a key secondary endpoint with a well-controlled type 1 error is accepted by the CHMP to support the reassurance on efficacy.

The EMA guideline also recommends to include next-day daytime functioning as a co-primary endpoint in both studies. This was not followed by the Applicant. The Applicant justification related to the unavailable IDSIQ score at the time of phase 3 program discussion is partially endorsed. The impact on daytime functioning could also have been assessed by the ISI score which takes into account the impact on daytime functioning.

Based on pivotal studies results, 50 mg dose can be validated as efficient dose. However, this dose was only assessed in one pivotal study (301). It would have been appreciated to confirm the data observed at the 50 mg dose by another pivotal study performed with the same dose. The Applicant specifies that design of the 2 pivotal studies with only one study with the 50 mg dose was considered the most efficient design based on the knowledge at the time of the phase 3 program.

For the subjective secondary endpoint IDSIQ sleepiness domain score, the subjective effect on daytime sleepiness is statistically significant at 50 mg at month 1 and month 3. The mean difference to placebo at 50 mg is -1.8 [-2.5;-1] and -1.9 [-2.9;-0.9] at month 1 and month 3. The difference of 2 points on average on a graduated scale from 0 to 40 looks weak. The responder analysis on IDSIQ sleepiness domain with a 4 points or 8 points change were provided. Taking into account the 0-40 scale, the 8 points change could be considered as particularly clinically relevant. In study 301, at the 50 mg dose at 3 month, 37% of treated patients reported at least 8 points decrease at 3 months compared to 24.0% of responders in the placebo group. In the same study, the percentage of subjects showing a decrease from baseline at Month 3 of at least 4 points was 52.9% in the daridorexant 50 mg group, 50.0% in the 25 mg group and 44.4% in the placebo group. These results are not impressive. However, the impact on daytime functioning assessed by IDSIQ scores is supported by results observed on VAS daytime alertness and on VAS on ability to function. Same trend of improvement is observed through these tools leading to a positive impact of daridorexant at 50 mg per day on daytime functioning.

The patient complaints which are assessed by subjective measures (sTST, sWASO, sLSO) are important points to consider in insomnia. The values of subjective measures are lower with daridorexant than the objective values. The Applicant proposes a Pearson correlation analysis between objective (TST, WASO, LPS) and subjective endpoints (sTST, sWASO LSO). According to this analysis, there is a poor correlation between objective and subjective endpoints. The objective and subjective endpoints are different in nature and collection methods, this may partly explain the weak correlation of the parameters.

Subjects with insomnia associated with acute or unstable psychiatric disorders (e.g., depression, anxiety or dementia) were excluded from pivotal studies according to exclusion criteria. 6% to 8% patients with stable psychiatric comorbidities depending on the pivotal study were included. There are very few efficacy data on patients with psychiatric co-morbidities, whereas psychiatric comorbidities are often associated with insomnia. A warning has been added in section 4.4 of the SmPC.

Overall there are around 100 patients older than 75 years included in the phase III studies at different doses (54/930 in study 301 and 56/925 in study 302) however data on patients older than 75 years at 50 mg (19 patients in pivotal studies and 11 patients in phase 2 study) are limited. There are almost no patient older than 85 years (3/930 in study 301 and 1/925 in study 302). Based on data analysis over the full age range, the higher efficacy of the 50 mg dose on primary and secondary endpoints in patients aged from 65 to 75 years is considered as demonstrated and seems maintained in patients older than 75 years. Although there is no risk signal in elderly population at this time, caution should be used in this population.

3.4. Unfavourable effects

• A small increase in AEs of headache, somnolence, fatigue, dizziness, and nausea was observed for daridorexant compared to placebo, with no apparent dose dependence. Regarding the daytime somnolence and CNS-depressant effects, it was shown that fatigue and somnolence are the most frequent CNS-depressant AE, of mild or moderate intensity, in the daridorexant groups. These AE could be expected regarding the mechanism of action of the DORA (antagonism of the orexin receptors, stimulation of sleep-promoting effects).

• The concomitant administration of daridorexant and alcohol led to additive PD effect without any evidence of a synergic effect. As somnolence is the main reported AE in case of concomitant administration, alcohol consumption is therefore not recommended during treatment with daridorexant.

• Regarding the SAE, during the phase 1 to 3 studies, most were not treatment related or erroneously treatment related, with various medical histories or comorbidities underlying the occurrence of the SAE. There was not specific pattern of any system organ class or PT that could be highlighted from these SAE in any study treatment group, even if numerically most of the SAE (mainly related to orthopaedic injuries, cardiovascular disorders, infectious situations or cancer events) occurred in the 25 mg and 50 mg daridorexant groups. A few SAE led to discontinuation, mainly in relation to comorbidities since not treatment related. None of these SAE led to death.

3.5. Uncertainties and limitations about unfavourable effects

No cases of cataplexy and no cases of complex sleep behaviours (such as sleep walking / somnambulism, sleep driving, sleep talking, sleep eating, or sleep sex) were reported with daridorexant treatment. However, there were isolated cases of sleep paralysis and/or sleep-related hallucinations with daridorexant treatment, without dose dependency. Although not frequent and not categorized as serious during the phase 2 and 3 studies, a few cases of sleep paralysis were encoded as severe and led to study discontinuation. Considering the AESI sleep paralysis, some clarifications were provided in the SmPC, in particular that these events mainly occur during the first few weeks after treatment initiation. Following up on this safety concern via routine pharmacovigilance (i.e., signal detection and adverse reaction reporting) as proposed by the Applicant is deemed sufficient by the CHMP.

The AEs of suicidal ideation in Phase 3 studies were reported in 4 isolated cases, 2 in study 302 and 2 in study 303, equally distributed across daridorexant treatment and placebo groups (1 subject in each treatment group : 10 mg, 25 mg, 50 mg and placebo). Based on the C-SSRS scores assessment of the individual cases, and the pre-existing psychiatric disorders, and/or acute difficult circumstances (family stress, financial stress, illicit drug

use), there was no evidence of an increased risk of suicidal ideation or behaviour during treatment with daridorexant, as well as no dose-dependent trend. However, considering the potential seriousness of this AESI, this potential risk is added in the RMP which is supported by the CHMP.

A medical history within the psychiatric disorders SOC was reported in a total of 54 subjects (approximately 6%) in study 301 and 63 subjects (approximately 7%) in study 302. No AEs pertaining to depression or worsening of depression occurred in these subjects. The number of AEs denoting depression was rather low and balanced between treatment groups and study periods. There was no evidence of depression or worsening of depression during treatment with daridorexant, in particular in subjects with a medical history of psychiatric disorders, including depression. However, considering the potential seriousness of this AESI, this potential risk is added in the RMP under the safety concern "Suicidal behaviour in high-risk patients (with a medical history of depression or other psychiatric disorders)"which is supported by the CHMP.

An abuse potential for daridorexant was observed as compared to placebo and seems comparable to that of suvorexant (150 mg), and zolpidem (30 mg) at supratherapeutic doses (100 mg and 150 mg). The analysis of data from phase 3 studies did not permit to confirm the abuse risk of daridorexant for the target population of patients with insomnia under experimental conditions. The Applicant's proposal to add "drug abuse" safety concern as important potential risk on the RMP is supported as well as the warning in section 4.4 of the SmPC.

No dose reduction in patients with mild to severe renal impairment was recommended. There is insufficient knowledge about the use of daridorexant in subjects with severe hepatic impairment and a statement in the SmPC to not recommended daridorexant for this specific population has been added.

No safety data are available with daridorexant in pregnant women and in breastfeeding women. These safety concerns are added among the missing information in the RMP. Statements in the SmPC have been amended.

The experience in patients above the age of 75 years is very limited and this has been reflected in the SmPC.

3.6. Effects Table

Table X. Effects Table for [insert product name and indication] <(data cut-off: …)>.

Effect	Short Description	Unit	Difference to baseline	Difference to placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
WASO 50 mg Month 1	Duration of awakenings during the night at month 1 (min)	Least squares mean difference (95% CI)	−29.0 [−32.7, −25.3]	−22.8 [−28.0, −17.6]	< .0001* Statistically significant	Study 301
WASO 50 mg Month 3	Duration of awakenings during the night at month 1 (min)	Least squares mean difference (95% CI)	−29.4 [−33.4, −25.4]	−18.3 [−23.9, −12.7]	< .0001* Statistically significant	Study 301

Effect	Short Description	Unit	Difference to baseline	Difference to placebo	Uncertainties/ Strength of evidence	References
LPS 50 mg Month 1	Time in minutes to sleep onset at month 1 (min)	Least squares mean difference (95% CI)	−31.2 [−34.5, −27.9]	−11.4 [−16.0, −6.7]	< .0001* Statistically significant	Study 301
LPS 50 mg Month 3	Time in minutes to sleep onset at month 3 (min)	Least squares mean difference (95% CI)	−34.8 [−38.1, −31.5]	−11.7 [−16.3, −7.0]	< .0001* Statistically significant	Study 301
sTST 50 mg Month 1	Time spent being asleep reported by the patient at month 1 (min)	Least squares mean difference (95% CI)	43.6 [38.2, 49.1]	22.1 [14.4, 29.7]	< .0001* Statistically significant. The effect at month 1 is maintained at month 3.	Study 301
Unfavourable Effects						
headache	Incidence of headache	%	6	5	4	Headache is a common AE that occurred in at least 2% of subjects treated with daridorexant and more frequently (⩾ 1%) than in subjects who received placebo.	(1), (2), (3)
somnolence	Incidence of somnolence	%	2	3	2	Somnolence is a common AE that occurred in at least 2% of subjects treated with daridorexant and more frequently (⩾ 1%) than in subjects who received placebo.	(1), (2), (3)
dizziness	Incidence of dizziness	%	2	2	1	Dizziness is a common AE that occurred in at least 2% of subjects treated with daridorexant and more frequently (⩾ 1%) than in subjects who received placebo.	(1), (2), (3)
fatigue	Incidence of fatigue	%	2	3	2	Fatigue is a common AE that occurred in at least 2% of subjects treated with daridorexant and more frequently (⩾ 1%) than in subjects who received placebo.	(1), (2), (3)
nausea	Incidence of nausea	%	2	1	1	Nausea is a common AE that occurred in at least 2% of subjects treated with daridorexant and more frequently (⩾ 1%) than in subjects who received placebo.	(1), (2), (3)
sleep paralysis	Incidence of sleep paralysis	%	0.3	0.5	0	Important strength of evidence that this AE is treatment related since no case occurred in the placebo group	(1), (2), (3)
hallucination	Incidence of hallucination	%	0	0.8	0	Important strength of evidence that this AE is treatment related since no case occurred in the placebo group	(1), (2), (3)

Abbreviations:
Notes: (1): data from the 301 and/or 302 studies; (2): data from the 303 extension study; (3): data from the pooled safety dataset.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy package presented in this application establishes the efficacy of daridorexant in the treatment of adult patients with insomnia of moderate to severe intensity and insufficient sleep quantity during at least 3 months.

Insomnia is associated with an abnormal state of hyperarousal that overrides the normal control of sleep. Daridorexant is a specific and potent dual orexin receptor antagonist (DORA). Orexin neuropeptides (orexin A and orexin B) are central promotor of arousal and vigilance. It could therefore be hypothesized that daridorexant acts on sleep maintenance and on sleep latency in contrast with hypnotics such as benzodiazepines and z-drugs which act mainly on sleep latency.

The insomnia first-line treatment is cognitive-behavioural therapy (CBT). However, pharmacological intervention can be added when CBT is not effective or not available. At this time, use of hypnotic drugs is currently mostly recommended for short-term treatment due to safety limitations of benzodiazepines and z-drugs. There is an unmet medical need for patients with chronic insomnia.

The statistically significant difference over placebo is achieved for the 2 primary objective endpoints (WASO, LPS) at 50 mg in study 301. Efficacy data obtained from pivotal study 301 conducted in patients with moderate to severe insomnia demonstrated significant clinical superiority over placebo.

Clarifications were provided for efficacy data especially regarding the absence of active comparator, the use of objective endpoints as primary endpoints and daridorexant efficacy assessed by subjective endpoints which seems less important than when assessed by objective endpoints. The clinical relevance of sleep improvement is acceptable and the impact on daytime functioning seems positive although difficult to assess based on the selected IDSIQ score.

The safety profile of daridorexant is consistent with its mechanism of action (a specific and potent dual orexin receptor antagonist, acting on both orexin 1 and orexin 2 receptors and equipotent on both) and other DORA, suvorexant and lemborexant are already marketed in the USA.

The common adverse reactions of mild to moderate intensity are somnolence, dizziness, fatigue, headache and nausea which were observed more frequently in the daridorexant groups than in the placebo groups. The adverse reaction profile in elderly subjects was consistent with younger subjects. There was no evidence of a dose-relationship for the frequency or severity of adverse reactions at the recommended therapeutic dose.

A relative risk of abuse potential was suggested, based on the 'drug-liking' assessment in the HAP study (but with no nonclinical signal). The "drug abuse" safety concern has been added as an important potential risk on the RMP.

No safety issues were identified during the preliminary results of the long-term study 303. The Applicant further provided data from this extension study and the number of subjects is around 100 subjects at 1 year for the recommended 50 mg daridorexant dose. The provided long-term safety data are consistent with those observed during the first 3 months of treatment, and do not more represent a concern with regards to long-term potential risks, even in the absence of a recommended treatment duration.

3.7.2. Balance of benefits and risks

The use of daridorexant in treatment of patients with insomnia which is based on antagonist (DORA) of both orexin 1 (OX1) and orexin 2 (OX2) receptors is supported by favourable effects observed with the 50 mg dose.

The statistically significant difference over placebo was achieved for the 2 primary objective endpoints (WASO, LPS) at 50 mg in study 301. Efficacy data obtained from pivotal study 301 conducted in patients with moderate to severe insomnia and insufficient sleep quantity for at least 3 nights per week during at least 3 months demonstrated significant clinical superiority over placebo. From the efficacy perspective, the clinical development adequately supports the proposed indication at 50 mg. Available data could support the use of the 25 mg dose, when in judgement of the clinician a lower dose than 50 mg could be appropriate, for example in patients already treated with CNS depressant.

The agreed indication "*the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning*" reflects the characteristic of chronic insomnia.

The treatment should be as short as possible and the need to reassess the appropriateness of continued treatment within 3 months should be specified in the SmPC.

Overall, favourable effects outweigh the unfavourable effects.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall benefit/risk balance of QUVIVIQ is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of QUVIVIQ is favourable in the following indication(s):

For the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in

the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that daridorexant is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 24 February 2022.