EU Risk Management Plan (Version 1.0)

Global Patient Safety
Signatory information is available on request.
Initial EU Risk Management Plan electronically approved by Lilly on date provided below.

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EU Risk Management Plan for Flortaucipir ^{18}F

RMP version to be assessed as part of the application: 1.0

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Rationale for submitting an updated RMP: This updated EU RMP is submitted as part of the response to Committee for Medicinal Products for Human Use 2nd Day-180 list of outstanding issues.

Summary of significant changes in this RMP: Not applicable.

Other RMP versions under evaluation: None

Details of the currently approved RMP: Not applicable

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

Table of Content

Table of Contents

Table **Page**

List of Abbreviations

Terms	Definition
AD	Alzheimer's disease
CI	confidence interval
CNS	central nervous system
ECG	electrocardiogram
hERG	human ether- á-go-go-related (gene)
HR	hazard ratio
IC_{50}	concentration of drug required for 50% inhibition
MCI	mild cognitive impairment
MHD	maximum human dose
NOEL	no-observed-effect level
PET	positron emission tomography
PY	patient-years
QTc	corrected QT interval
QTcF	corrected QT interval (Fridericia method)
RMP	risk management plan

Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Flortaucipir F18/ Flortaucipir ^{18}F
Pharmacotherapeutic group(s) (ATC Code)	Diagnostic Radiopharmaceutical (V09AX)
Marketing authorisation applicant	Eli Lilly Nederland B.V
Medicinal products to which this RMP refers	^{18}F Flortaucipir
Invented name(s) in the EEA	Tauvid
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Flortaucipir is a radiopharmaceutical diagnostic agent. The drug substance flortaucipir ^{18}F is intended to be administered by a single human IV injection at a level of 370 MBq (containing no more than 20 µg of flortaucipir [^{18}F]). The radioactive isotope of the agent is fluorine-18, which decays by positron emission with a half-life of 110 minutes.
	Summary of mode of action: Flortaucipir ^{18}F is a molecule that binds with high affinity and selectivity to aggregated tau pathology (but not normal, monomeric tau) in ex vivo human brain sections. Flortaucipir ^{18}F may be useful as a radioactive diagnostic agent for positron emission tomography imaging of the brain to assess tau pathology in adult patients who are being evaluated for AD and other related neurological diseases.
	Important information about its composition: Flortaucipir ^{18}F is chemically synthesised. • **Formulation 1**: 10% (v/v) ethanol in 0.9% sodium chloride injection. • **Formulation 2**: 10% v/v ethanol, up to 0.05% dibasic sodium phosphate, up to 1.5 mM hydrochloric acid in 0.9% sodium chloride aqueous solution.
Hyperlink to the Product Information	The proposed PI is included in eCTD sequence 1.3.1.
Indication(s) in the EEA	**Proposed:** For PET imaging of the brain to assess the neocortical distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for AD. Flortaucipir (^{18}F) is an adjunct to clinical and other diagnostic evaluations.
Dosage in the EEA	**Proposed:** Single IV dose is 370 MBq (10 mCi) of flortaucipir (^{18}F) in a dose volume of ≤10 mL for an adult weighing 70 kg.

Pharmaceutical form(s) and strengths	**Proposed:** 15 mL multi-dose vial containing a clear, colourless injectable solution at the following flortaucipir ^{18}F strengths: • 800 ± 80 MBq/mL at End of Synthesis • 1900 ± 190 MBq/mL at End of Synthesis
Product Overview Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC = anatomical therapeutic chemical; AD = Alzheimer's disease; eCTD = electronic common technical document; INN = international non-proprietary names; IV = intravenous; PI = package insert; RMP = risk management plan; SmPC = summary of medicinal product characteristics.

Part II: Safety Specification

Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Alzheimer's Disease and Mild Cognitive Impairment

Flortaucipir ^{18}F is a radioactive diagnostic agent for PET imaging of the brain to assess the neocortical distribution of aggregated tau in adult patients who are being evaluated for AD.

Given that flortaucipir is indicated to assist with AD diagnosis, patients receiving flortaucipir will likely be experiencing cognitive impairment. Therefore, for this epidemiology section, patients diagnosed with MCI are described.

SI.1.1 Incidence

Incidence estimates of MCI vary widely. In a recent age-specific systematic review of 7 population-based MCI studies from the Americas, Europe, and Australia, incidence rates were examined using 5-year age categories (Gillis et al. 2019). Meta-analysis resulted in MCI incidence of 22.5 (95% CI: 5.1, 51.4) per 1000 PYs for ages 75 to 79 years, 40.9 (95% CI: 7.7, 97.5) per 1000 PYs for ages 80 to 84 years, and 60.1 (95% CI: 6.7, 159.0) per 1000 PYs for ages 85 years and older (Gillis et al. 2019).

Globally, the incidence of MCI ranges from 21.5 per 1000 PYs in individuals aged 65 to 84 years and older to 104.6 per 1000 PYs in those aged 70 to 90 years (Brodaty et al. 2013; Roberts and Knopman 2013). In European studies, rates of overall MCI ranged between 21.5 per 1000 PYs and 76.8 per 1000 PYs, while incidence rates in the US have been reported to be as high as 63.6 per 1000 PYs in people aged 70 years and older (Roberts and Knopman 2013).

SI.1.2 Prevalence

Prevalence estimates for MCI across Europe, North America, and Asia ranged from as low as 3.0% in those aged 55 years and older (China) to 42% in individuals 65 years and older (France); in the US, MCI prevalence in those aged 65 years and older ranged between 18.8% and 28.3% (Ward et al. 2012).

In a meta-analysis of 11 studies in 9 Latin American countries, estimates for the prevalence of MCI ranged from 6.8% to 25.5% and the pooled prevalence of MCI across the 8 included studies revealed a prevalence of 14.95% (95% CI: 6.81%, 25.52%) (Ribeiro et al. 2021). Estimates differed by age and education, with oldest and lower-educated adults presenting higher MCI prevalence.

In a systematic review of 78 articles of MCI prevalence in low-and middle-income countries, mostly from China (n=55 studies), the prevalence of MCI ranged from 6.1% to 30.4% (McGrattan et al. 2020).

While age has a significant impact on prevalence range, study methods and classification of MCI should also be considered. When definitions of MCI were harmonised across 11 studies, spanning across the US, Europe, Asia, and Australia, and eligible patients were limited to 60

years of age and older and without overt dementia, prevalence of MCI was between 6% and 12% (Sachdev et al. 2015).

SI.1.3 Demographics of the Population in the Indication and Risk Factors for the Disease

Demographic risk factors for MCI include increased age (Prince et al. 2015) and lower educational attainment (Livingston et al. 2020). Gender differences are unclear (Petersen et al. 2018). Risk of MCI is also associated with health (for example, cardio-metabolic disease) and lifestyle (for example, social isolation, smoking, diet, and physical activity) factors (McGrattan et al. 2020).

Older age was found to be significantly associated with incident total MCI (Luck et al. 2010). Using results from 11 epidemiological studies, Sachdev et al. (2015) found that prevalence of MCI increased with increasing age, though the pattern across age groups differed between men and women and across the definitions of cognitive impairment used.

Overall, Sachdev et al. (2015) did not find any significant gender differences in the prevalence of MCI. Additionally, a meta-analysis found no statistically significant gender differences in the incidence of MCI (Au et al. 2017).

Among a community-based longitudinal study of participants with MCI (mean age 78.7 years), the 3-year decline in cognitive function was significantly higher in African Americans when compared with non-African Americans (Lee et al. 2012). In addition, the prevalence of MCI was lower in those with higher education, despite the neuropsychological test results having been corrected for education (Sachdev et al. 2015).

Among low-and middle-income countries, both modifiable and non-modifiable risks factors were identified for MCI: socio-demographic risk factors included increased age, sex (usually, but not always, female), and low educational attainment (McGrattan et al. 2020). Modifiable health and lifestyle risk factor included, but were not limited to, smoking, presence of cardiovascular related diseases, social contact, occupation, physical activity, and dietary related factors (McGrattan et al. 2020).

In a meta-analysis of 46 longitudinal studies, subjective cognitive decline was associated with increased risk of developing MCI (HR = 1.73, 95% CI: 1.18, 2.52; Odds Ratio = 1.83, 95% CI: 1.56, 2.16) (Pike et al. 2020).

SI.1.4 Main Existing Treatment Options

Flortaucipir ^{18}F is not a therapeutic agent, but rather is used to help establish a diagnosis of AD in patients with cognitive impairment. Flortaucipir ^{18}F is an adjunct to other diagnostic evaluations. There are no approved alternative imaging agents for assessing the neocortical distribution of the aggregated tau of AD in adult patients who are being evaluated for AD and other causes of cognitive decline.

SI.1.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

Progression of cognitive impairment over time varies tremendously among patients. Some patients with MCI progress to dementia or AD precipitately after diagnosis, whereas a substantial proportion of patients do not develop dementia or AD even after a prolonged period of up to 10 years (Liao et al. 2016). The annual rate at which MCI progresses to dementia varies between 8% and 15% per year (Peterson 2016).

Patients with MCI have less favourable survival rates than elderly people without MCI (Contador et al. 2014). When compared with cognitively normal individuals, patients with MCI had higher significant risk of mortality in the long-term, with only the amnestic multiple domain MCI being significant at the short term of 5 years (Contador et al. 2014). Across studies, the mortality HR for MCI when compared to that of cognitive normal controls ranged from 1.13 to 2.03 (Vassilaki et al. 2015; Santabarbara et al. 2016).

SI.1.6 Important Co-morbidities

MCI is associated with many somatic disorders and modifiable risk factors. MCI has biologically plausible associations with hypertension, diabetes mellitus, and hyperlipidaemia (Etgen et al. 2011).

Important Co-morbidity Prevalence in Mild Cognitive Impairment by Disease Category	
Category	
Cholesterol Levels	
Hypercholesterolemia	27.1% - 59.0% (Artero et al. 2008; Lipnicki et al. 2017)
Hypolipidemia	25.2% (Lipnicki et al. 2017)
Cardiovascular Conditions	
Cardiovascular disease/disorders	38.4% (Moretti et al. 2013)
Hypertension	23.6% - 92.4% (Ganguli et al. 2013; Lipnicki et al. 2017)
Coronary artery disease	13.2% - 49.2% (Solfrizzi et al. 2004; Singh et al. 2013)
Atrial fibrillation	4.8% - 18.5% (Pankratz et al. 2015; Lipnicki et al. 2017)
Congestive heart failure	2.87% - 13% (Pankratz et al. 2015; Snowden et al. 2015)
Myocardial infarction	5.3% - 16% (Ellis et al. 2009; Pankratz et al. 2015)
Stroke	2.76% - 34.3% (Ganguli et al. 2013; Lipnicki et al. 2017)
Transient ischaemic attack	8.73% (Ganguli et al. 2013)
Cerebrovascular disease	9.9% - 18.2% (Stump et al. 2001; Li et al. 2013)
Atherosclerotic vascular disease	5.6% (Stump et al. 2001)
Diabetes	10.5% - 85.9% (Ellis et al. 2009; Ganguli et al. 2013)
Psychiatric	
Depression	2.4% - 25.3% (Artero et al. 2008; Pink et al. 2015)
Anxiety	7.5% - 24% (Pankratz et al. 2015; Santabarbara et al. 2016)
Rheumatic Diseases	
Arthritis	25.1% - 55.7% (Stump et al. 2001; Sachdev et al. 2012)
Osteoarthritis	18.9% (Li et al. 2013)
Malignancy	8.0% - 15% (Stump et al. 2001; Ellis et al. 2009)
Sleep Disturbances	
Insomnia	19.6% (Kim et al. 2017)
Falls	35% (Seijo-Martinez et al. 2016)

Patients with MCI frequently experience age-related co-morbidities and therefore many are treated with polypharmacy. Among a European cohort of patients in Development of screening guidelines and diagnostic criteria for pre-dementia AD, a multi-centre study, most patients (85.7%, n = 754) were taking at least 1 medication. On average, patients with MCI take 3 medications for the prevention or treatment of an average of 2 medical conditions (Tsolaki et al. 2016). As per Tsolaki et al. (2016), the most prevalent types of medications were

- cardiovascular drugs (62%)
- anti-depressants (16.8%)
- sedatives (14.6%)
- thyroid drugs (10%)
- statins (9.6%), and
- anti-diabetic drugs (7.6%).

Among a sub-sample of participants in the Sydney Memory and Ageing Study (Sachdev et al. 2012), patients with MCI reported use of medications for co-morbid diseases at baseline as follows:

- anti-hypertensives (61.1%)
- hypolipidaemic medications (48%)
- anti-depressants (9.8%)
- hypoglycaemic medications (8.8%), and
- anti-anxiety agents (6.1%).

Module SII – Nonclinical Part of the Safety Specification

SII.1 Toxicity

Animal studies to assess the carcinogenicity or reproductive toxicity potential of ^{18}F have not been conducted. Non-radioactive flortaucipir showed the potential for genotoxicity in in vitro bacterial reverse mutation assay (Ames test) and chromosomal aberration assays. However, when potential in vivo genotoxicity of flortaucipir was evaluated in a rat micronucleus study, non-radioactive flortaucipir did not increase the number of micronucleated polychromatic erythrocytes at the highest achievable dose level (1600 µg/kg/day for 2 days). This dose is greater than 750x (allometrically scaled) and 4800x (mg/kg) the intended MHD, and there is no evidence for risk to human subjects at the proposed microdose. Pre-clinical toxicity studies of non-radioactive flortaucipir showed a good safety profile with no observable effects at high multiples of the intended MHD.

SII.2 Safety Pharmacology

SII.2.1. Assessment of Binding Potential to Central Nervous System Relevant Receptors, Channels, and Transporters

AV-1451 (flortaucipir) was assessed in competitive binding or functional assays against a panel of 72 of the most common CNS targets. With the exception of 5 targets (norepinephrine transporter, monoamine transporter - VMAT2, polyamine site on the glutamate receptor, µ-opiate receptor, and acetylcholinesterase), less than 50% inhibition of specific binding or function was observed at an AV-1451 concentration of 10 µM. The IC_{50} of AV-1451 was determined to be 2.2 µM for the norepinephrine transporter, 0.4 µM for the monoamine transporter, and 2.7 µM for the glutamate receptor. Acetylcholinesterase activity was inhibited by 27% at 1 µM and binding at the µ-opiate receptor was inhibited by 31% at 1 µM and by 12% at 0.1 µM of AV-1451. The functional IC_{50} for AV-1451 towards monoamine oxidase A was found to be 0.57 µM, while monoamine oxidase B activity was inhibited by 17%. The MHD of AV-1451 of 20 µg results in a maximum plasma concentration of approximately 15 nM (assuming dose is restricted to the blood volume [approximately 5.2 L in an adult human]) and a maximum brain concentration of 4 nM (assuming maximum peak brain levels of 7.0% injected dose). Since the maximum peak brain concentration is at least 100x less than the IC_{50} for any of these targets, the potential for adverse CNS effects due to inhibition of these CNS targets is low.

SII.2.2. Effects of AV-1451 on Cloned hERG Potassium Channels in HEK293

AV-1451 was positive in the hERG assay, with an IC_{50} of 0.26 µM. If the AV-1451 hERG channel IC_{50} is converted to a ng/mL concentration (68 ng/mL) and compared to the maximum theoretical AV-1451 peak plasma concentration in a subject given a 20-µg dose (3.8 ng/mL), the safety margin is at least 18-fold. This calculation assumes a worst-case scenario that 100% of the drug is unbound and that the volume of distribution is restricted to the blood volume (about 5.2 L in an adult human). The safety margin increases to approximately 340-fold when accounting for plasma protein binding ($f_{u\text{-}human}$ 0.053). Additionally, an in vivo cardiovascular safety study was

conducted in Beagle dogs and concluded that there is no specific risk for QT prolongation at the intended clinical dose.

SII.2.3. Central Nervous System Safety Pharmacology Evaluation of AV-1451 in Rats

Neurological function was assessed in 40 male rats randomly assigned to 5 groups (8 rats/group) given a single intravenous bolus dose of the vehicle control article or 50, 100, or 200 µg/kg AV-1451 at a dose volume of 4 mL/kg. No AV-1451-related effects were observed on mortality; clinical observations; or the home cage, hand-held, open-field, or elicited behaviour components of the modified Irwin battery up to 24 hours post-dose. Administration of the positive control article (30 mg/kg chlorpromazine hydrochloride by oral gavage) confirmed the sensitivity of the modified Irwin assessment. Therefore, with respect to neurological assessment, the NOEL of AV-1451 in rats is at least 200 µg/kg (100x (allometrically scaled) and 600x (mg/kg) MHD), the highest dose tested. Thus, ^{18}F-AV-1451 is not expected to induce CNS effects in humans.

SII.2.4. Cardiovascular Safety Pharmacology Evaluation of AV-1451 in Dogs

Cardiovascular safety pharmacology assessments were performed as part of the repeat-dose toxicology study in dogs. Cardiovascular safety results are summarised below.

Heart rate was elevated 1 through 2.5 hours post-dose on Day 29 of the dosing phase in females given 30 µg/kg/dose, although the effect was not clinically significant. When compared with controls, the increase in mean heart rate in females given 30 µg/kg/dose was up to 30 beats per minute (34%) at 1-hour post-dose and was not apparent after 2.5 hours post-dose. This finding is not considered clinically important. No effect on mean heart rate was noted on Day 1 of the dosing phase in females given 5, 15, 30, or 60 µg/kg/dose (up to 100x (allometrically scaled) and 180x (mg/kg) MHD) or on Day 29 in females given 5 or 15 µg/kg/dose (up to 25x (allometrically scaled) and 45x (mg/kg) MHD).

No effect on heart rate was noted on Day 1 (up to 100x (allometrically scaled) 180x (mg/kg) MHD) or Day 29 (up to 50x (allometrically scaled) and 90x (mg/kg) MHD) of the dosing phase in males given any dosage of AV-1451.

No AV-1451-related changes in PR interval, QRS duration, QT interval, or QTc were observed on Day 1 of the dosing phase in animals given 5, 15, 30, or 60 µg/kg/dose (up to 100x (allometrically scaled) and 180x (mg/kg) MHD) or on Day 29 of the dosing phase in Beagle dogs given 5, 15, or 30 µg/kg/dose (up to 50x (allometrically scaled) and 90x (mg/kg) MHD, allometrically scaled). No rhythm abnormalities or qualitative ECG changes were attributed to AV-1451 during qualitative assessment of the ECGs.

The NOEL for males and no-observed-adverse-effect level for females were determined to be 100x (allometrically scaled) and 180x (mg/kg) MHD on Day 1 and 50x (allometrically scaled) and 90x (mg/kg) MHD on Day 29. In summary, ^{18}F-AV-1451 is not expected to prolong the QT interval or have any untoward cardiovascular effects at the intended clinical dose.

Module SIII - Clinical Trial Exposure

Table SIII.1. Exposure

Number of Flortaucipir Doses	Number of Subjects
1 dose	3022
2 doses	1023
3 doses	552
>3 doses	55

Table SIII.2. Age Group and Gender

Age Group	Number of Subjects
<65 years	648
≥65 years	4003
unknown	1
Total	**4652**
Gender Group	**Number of Subjects**
Males	2322
Females	2330
Total	**4652**

Table SIII.3. Mean Flortaucipir Dose by Imaging Visit

Dose of Exposure	Flortaucipir Dose (MBq)	Flortaucipir Mass Dose (µg)
Imaging visit #1 (n = 4652)	348.94	1.174 (n=908)[a]
Imaging visit #2 (n = 1630)	329.61	0.784 (n=345)[a]
Imaging visit #3 (n = 607)	326.94	0.997 (n=151)[a]

Abbreviation: n = number of administrations (a subject will be counted more than once if the subject was enrolled in multiple studies and received flortaucipir in those studies).

[a] Mass dose was not recorded for all subjects.

Table SIII.4. Ethnic Origin

Race	Number of Patients
Non-White	513
White	4107
Not reported	32
Total	**4652**

Ethnic Origin	Number of Patients
Hispanic or Latino	224
Not Hispanic	4305
Not reported	123
Total	**4652**

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Clinically significant hepatic disease

Reason for exclusion: Flortaucipir (^{18}F) is excreted partially through the hepatobiliary system and patients with hepatic impairment have the potential for increased radiation exposure.

Is it considered to be included as missing information?: No.

Rationale: Patients with hepatic impairment have the potential for prolonged radiation exposure; however, radioactive decay of ^{18}F ($t_{1/2}$ = 109.77 minutes) is independent of physiologic flortaucipir elimination and would be 98% decayed at 10 hours regardless of hepatic function. Flortaucipir (^{18}F) is intended for a one-time administration which eliminates any risk of drug accumulation with repeated dosing in these patients. There are no data to suggest that clinically significant hepatic disease imposes a greater variety, frequency, or severity of adverse events in these patients.

Clinically significant renal disease

Reason for exclusion: Flortaucipir (^{18}F) is excreted partially through the renal system, and patients with renal impairment have the potential for increased radiation exposure.

Is it considered to be included as missing information?: No.

Rationale: Patients with renal impairment have the potential for prolonged radiation exposure; however, radioactive decay of ^{18}F ($t_{1/2}$ = 109.77 minutes) is independent of physiologic flortaucipir elimination and would be 98% decayed at 10 hours regardless of renal function. Flortaucipir (^{18}F) is intended for a one-time administration, which eliminates any risk of drug accumulation with repeated dosing in these patients. There are no data to suggest that clinically significant renal disease imposes a greater variety, frequency, or severity of adverse events in these patients.

Clinically significant cerebrovascular disease

Reason for exclusion: Ischaemic damage can result in reduced perfusion and reduced tracer uptake in the area of infarct. Subjects with magnetic resonance imaging evidence of multiple infarcts, sufficient to support a diagnosis of mixed or cerebrovascular aetiology of cognitive deficit, were excluded from early phase trials, and subjects with major structural loss of brain matter were excluded from the pivotal trial.

Is it considered to be included as missing information?: No.

Rationale: There are no data to suggest that clinically significant cerebrovascular disease imposes a greater variety, frequency, or severity of adverse events in these patients.

Current clinically significant cardiovascular disease or clinically significant abnormalities on screening ECG (including, but not limited to, QTc >450 msec) or known risk factors for torsade de pointes.

Reason for exclusion: Flortaucipir was positive in the in vitro hERG assay. However, the cardiovascular assessments performed during the dog toxicology studies showed no evidence that flortaucipir prolongs the QT interval at high multiples of relevant clinical doses, and therefore, risk of QT prolongation was not included in the risk profile.

Is it considered to be included as missing information?: No.

Rationale: Flortaucipir was positive in the hERG assay, with an IC_{50} of 0.26 µM. If the flortaucipir hERG channel IC_{50} is converted to a ng/mL concentration (68 ng/mL) and compared to the maximum theoretical flortaucipir peak plasma concentration in a subject given a 20-µg dose (3.8 ng/mL), the safety margin is at least 18-fold. This calculation assumes a worst-case scenario that 100% of the drug is unbound and that the volume of distribution is restricted to the blood volume (about 5.2 L in an adult human). The safety margin increases to approximately 340-fold when accounting for plasma protein binding ($f_{u\text{-}human}$ 0.053).

Cardiovascular safety pharmacology assessments were performed as part of the repeat-dose toxicology study in dogs. No flortaucipir -related changes in PR interval, QRS duration, QT interval, or QTc interval were observed on Day 1 of the dosing phase in animals given 5, 15, 30, or 60 µg/kg/dose (up to 100x (allometrically scaled) and 180x (mg/kg) MHD) or on Day 29 of the dosing phase in Beagle dogs given 5, 15, or 30 µg/kg/dose (up to 50x (allometrically scaled) and 90x (mg/kg) MHD). No rhythm abnormalities or qualitative ECG changes were attributed to flortaucipir during qualitative assessment of the ECGs.

The NOEL for males and no-observed-adverse-effect level for females was determined to be 100x (allometrically scaled) and 180x (mg/kg) MHD on Day 1 and 50x (allometrically scaled) and 90x (mg/kg) MHD on Day 29. In summary, flortaucipir is not expected to prolong the QT interval or have any untoward cardiovascular effects at the intended clinical dose.

Clinical trial data indicate a mean change from baseline in QT interval duration (Fridericia correction method; QTcF) of 5.14 msec (± 12.09 msec; standard deviation) at approximately 90 to 120 minutes post-infusion for 785 measurements. While the absence of placebo or active compound comparator groups limits interpretation of these findings, it is noted that the mean 5.14 msec increase in QTcF approximates the regulatory threshold of concern (5 msec); however, the upper limit of the 90% CI (equivalent to a 1-tailed 95% CI) was 5.85 msec, which is well below the 10 msec threshold of concern. No study subjects demonstrated a QTcF interval >500 msec or an increase of 60 msec or greater above baseline values.

Scatterplots of QTcF change from pre-dose values versus flortaucipir mass dose failed to demonstrate statistically significant correlations at either the immediate post-dose or end of scan time points.

No statistically significant differences in mean change from baseline for QTcF were identified for subjects with a history of cardiac rhythm disturbance when compared to subjects without

such a history, nor were any significant differences observed when subjects receiving concomitant medications known to influence QT interval duration were compared with subjects not receiving such medications. The small numbers of scans for these comparisons (n = 40 for history of rhythm disturbance and n = 36 for subjects with concomitant QT-influencing medications) may limit the statistical power of any comparisons.

It is further noted that no treatment-emergent adverse events related to QT interval prolongation or ventricular arrhythmias were reported in study patients.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The flortaucipir clinical development programme is unlikely to fully detect rare adverse reactions due to the size of the clinical trial safety population (N = 4652). Adverse events possibly related to prolonged or cumulative exposure would be difficult to identify since subjects enrolled in clinical trials received 1 to 3 or more individual doses of flortaucipir over a period of several years. This limited and infrequent pattern of flortaucipir dose exposure matches the expected use of the radiopharmaceutical in the clinical setting.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with hepatic impairment Patients with renal impairment Immunocompromised patients	Patients with pre-existing hepatic impairment were not specifically included in the clinical development programme; however, 112 subjects with pre-existing hepatic impairment have been identified in the safety population. Patients with pre-existing renal impairment were not specifically included in the clinical development programme; however, 271 subjects with pre-existing renal impairment have been identified in the safety population. Immunocompromised patients were not included in the clinical development programme.
Obese patients (BMI >32 kg/m^2)	n = 311[a]
Patients with a disease severity different from inclusion criteria in clinical trials	Patients with varying levels of cognition (ranging from cognitively normal, through mild cognitive impairment, to moderate dementia) have been included in the flortaucipir development programme.
Population with relevant different ethnic origin	Patients of different ethnic backgrounds were included in the flortaucipir development programme.
Subpopulations carrying relevant genetic polymorphisms	Subpopulations carrying known and relevant genetic polymorphisms (other than the ApoE gene) were not included in clinical trials. ApoE4 genotyping: • Carrier, n = 839 • Non-carrier, n = 830 • Unknown, n = 2983

Abbreviations: ApoE4 = apolipoprotein E ε4 allele; BMI = body mass index; n = number of subjects in each category (unknown includes subjects with missing ApoE).

[a] Flortaucipir ^{18}F was administered as individual dose(s). Any attempt at conversion to person-time basis is not clinically meaningful.

Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Worldwide doses of flortaucipir in the post-marketing environment for the cumulative period ending 31 December 2023 have been collected. Post-marketing exposure is considered to be the sum of

- commercial doses (sales and vouchers), and
- doses purchased for clinical trials sponsored by third-party pharmaceutical companies or investigators (non-Lilly).

SV.1.2 Exposure

Cumulatively, it is estimated that approximately 6470 patients have been exposed to flortaucipir worldwide through 31 December 2023. To date, 257 commercial doses of flortaucipir have been distributed in the US.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

Flortaucipir ^{18}F has no known pharmacological activity and has very low binding affinity to all CNS receptors that have been tested in pre-clinical screening assays. It is intended to be administered only by appropriately trained medical staff within a controlled health care environment. The type and small amount of radioactivity in the product is also unlikely to have any potential for misuse for illegal purposes. It is considered therefore that there is no potential for misuse for illegal purposes.

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The following adverse drug reactions have not been designated as risks because there are no data to indicate they persist beyond the immediate post-exposure period and they have not been demonstrated to impose a relevant risk of adverse outcomes to the patient. These events, namely, injection site pain, headache, blood pressure increased, and dysgeusia, are deemed to not adversely influence the benefit-risk balance of flortaucipir.

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated): PET scan imaging using flortaucipir carries a hypothetical risk of error in image interpretation, as does radiologic imaging utilising other diagnostic radiopharmaceuticals. The risk of image interpretation error resulting in inappropriate clinical management is mitigated by flortaucipir's adjunct role, representing only 1 aspect of diagnostic assessment.

Adverse drug reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated: None.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers: None.

Known risks that do not impact the risk-benefit profile: None.

Other reasons for considering the risks not important: Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk

There are no important identified risks for flortaucipir.

Important Potential Risk:.

There are no important potential risks for flortaucipir.

Missing Information:

There is no missing information for flortaucipir.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable as this is the initial submission in the EU.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk:

There are no important identified risks for flortaucipir.

Important Potential Risk:

There are no important potential risks for flortaucipir.

SVII.3.2 Presentation of the Missing Information

There is no missing information for flortaucipir.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None

III.2 Additional Pharmacovigilance Activities

None

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
Not applicable	-	-	-	-
			-	-
Category 2 - Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable	-	-	-	-
Category 3 - Required additional pharmacovigilance activities				
Not applicable	-	-	-	

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
None	Not applicable

V.2 Additional Risk Minimisation Measures

None.

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
None	Not applicable	Not applicable

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Tauvid™ (Flortaucipir)

This is a summary of the RMP for Tauvid. The RMP details important risks of Tauvid, how these risks can be minimised, and how more information will be obtained about Tauvid's risks and uncertainties (missing information).

Tauvid's summary of product characteristics and its package leaflet give essential information to health care professionals and patients on how Tauvid should be used.

This summary of the RMP for Tauvid should be read in context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report.

Important new concerns will be included in updates of Tauvid's RMP.

I - The Medicine and What It is Used for

Tauvid is a radiopharmaceutical diagnostic agent authorised for PET imaging of the brain to assess the neocortical distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for AD. Flortaucipir is an adjunct to clinical and other diagnostic evaluations (see summary of product characteristics for the full indication). It contains flortaucipir as the active substance and is given intravenously.

Further information about the evaluation of Tauvid's benefits can be found in Tauvid's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Tauvid, together with measures to minimise such risks and the proposed studies for learning more about Tauvid's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size: the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status: the way a medicine is supplied to the patient (for example., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Tauvid are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tauvid.

Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (for example, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

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II.B Summary of Important Risks

There are currently no important identified risks, important potential risks, or missing information for Tauvid.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Tauvid.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no other studies required for Tauvid.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the Form
None	-

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable