EU-RISK MANAGEMENT PLAN FOR KYGEVVI (DOXECITINE AND DOXRIBTIMINE)

2G DOXECITINE AND 2G DOXRIBTIMINE POWDER FOR ORAL SOLUTION (SINGLE SACHET)

Version 1.0

Date: 30 Jan 2026 20260130-rmp-v1.0-rtn-016407

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ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 1.0

Data lock point for this RMP: 15 Mar 2024

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Rationale for submitting an updated RMP: Not applicable for initial marketing authorization application submission

Summary of significant changes in this RMP: Not applicable

Qualified Person for Pharmacovigilance (QPPV) name: Bart Teeuw

QPPV signature: Please see the electronic signature of the EEA QPPV or his deputy on the last page of this report.

LIST OF ABBREVIATIONS

AE	adverse event
α-OH-TMD	alpha-hydroxythymidine
BCRP	breast cancer resistance protein
CI	confidence interval
CYP	cytochrome P450
dC	deoxycytidine
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
dT	deoxythymidine
eGFR	estimated glomerular filtration rate
EPAR	European Public Assessment Report
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation
MATE	multidrug and toxic extrusion protein
MDDS	mitochondrial DNA depletion and deletion syndrome
mtDNA	mitochondrial DNA
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OAT	organic anion transporter
OATP	organic anion transporter polypeptide
OCT	organic cation transporter
PDE	permitted daily exposure
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PND	postnatal day
RMP	Risk Management Plan
SCE	sister chromatid exchange
SmPC	Summary of Product Characteristics
TK2	thymidine kinase 2
TK2d	thymidine kinase 2 deficiency

PART I PRODUCT(S) OVERVIEW

Table Part I–1: Product overview

Active substance(s)	Doxecitine and doxribtimine
Pharmacotherapeutic group(s)	Other alimentary tract and metabolism products, various alimentary tract and metabolism products, ATC code: A16AX29
Marketing Authorization Applicant	UCB Pharma S.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	KYGEVVI
Marketing authorization procedure	Centralised
Brief description of the product	**Chemical class:** 2 nucleoside synthetically-derived small molecules
	Summary of mode of action: The primary mechanism of action of doxecitine and doxribtimine is the incorporation of nucleosides deoxycytidine (dC) and deoxythymidine (dT) into skeletal muscle mitochondrial deoxyribonucleic acid (DNA) to restore mitochondrial DNA copy number and improve skeletal muscle function in patients with TK2d. Doxecitine and doxribtimine likely utilize residual TK2 activity as well as the cytosolic phosphorylation pathways such as thymidine kinase 1 and deoxycytidine kinase to increase mitochondrial DNA precursors deoxycytidine triphosphate and deoxythymidine triphosphate in the mitochondria.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	Module 1.3.1 SmPC, Labeling and Package Leaflet
Indication(s) in the EEA	Current: Doxecitine and doxribtimine is indicated for the treatment of pediatric and adult patients with genetically confirmed TK2d with an age of symptom onset on or before 12 years
	Proposed: Not applicable
Dosage in the EEA	Current: Dosing for KYGEVVI is based on weight of the patient; reassessment of weight should be performed by the prescribing physician. KYGEVVI is titrated and dosed based on individual patient tolerability, up to a maximum recommended

Table Part I–1: Product overview

	maintenance dose of 400mg/kg/day of doxecitine and 400mg/kg/day of doxribtimine. KYGEVVI should be administered every day in 3 equal doses with food.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: A white to off-white powder supplied in a single sachet containing 2g doxecitine and 2g doxribtimine for reconstitution in water as an oral solution
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC=Anatomical Therapeutic Chemical; dC=deoxycytidine; dT=deoxythymidine; EEA=European Economic Area; mtDNA=mitochondrial deoxyribonucleic acid; RMP=Risk Management Plan; SmPC=Summary of Product Characteristics; TK2d=thymidine kinase 2 deficiency

PART II SAFETY SPECIFICATION

Part II Module SI Epidemiology of the indication(s) and target population(s)

SI.1 Thymidine kinase 2 deficiency

SI.1.1 Incidence

Thymidine kinase 2 (TK2) deficiency (TK2d) is an ultra-rare mitochondrial autosomal recessive disorder, which was first identified and described in 2001 (Saada et al, 2001) in 4 children with different mutations resulting in severe myopathy, multiple mitochondrial respiratory chain defects, and decreased mitochondrial deoxyribonucleic acid (mtDNA) copy number in muscle. There is no incidence of TK2d published in the literature yet.

SI.1.2 Prevalence

In the Orpha.net directory, the estimated prevalence of the myopathic form of mitochondrial deoxyribonucleic acid (DNA) depletion and deletion syndrome (MDDS) (that is TK2d) is <1 in 1,000,000 (ORPHAcode: 254875; last accessed: September 2024). In a recent literature search conducted by the applicant in 2022, data indicate a prevalence of TK2d of 1.64 per 1,000,000 population (Ma et al, 2023). Published data suggest that the majority of patients with TK2d had childhood onset (84% had an age of onset of 0 to 4 years in Wang et al, 2018; and 84.4% had an age of onset of 0 to 12 years in Garone et al, 2018). The diagnosis of mitochondrial disorders has been extremely challenging, due to both the wide variability of disease presentation and the difficulty in determining the specific type of MDDS, low disease awareness, and limited access to genomic sequencing (Cohen et al, 2018). As a result, while TK2d is still very rare, the "true" prevalence and fatality rates of TK2d may exceed reported values, as reported patients do not include those who are undiagnosed or misdiagnosed. Overall, existing research on TK2d epidemiology is sparse, and understanding of the disease epidemiology is still evolving.

SI.1.3 Demographics of the population in TK2d

Thymidine kinase 2 deficiency is a phenotypically heterogeneous disease with an age of symptom onset ranging from birth to adulthood (Garone et al, 2018). Age of TK2d symptom onset has been recognized as a key prognostic factor for outcomes in TK2d. Two literature reviews, both published in 2018, summarize the clinical presentation, progression and outcomes associated with untreated TK2d defined clinical presentations and outcomes for subgroups based on age of onset (Garone et al, 2018; Wang et al, 2018). These reviews were published independently by separate academic groups, including both overlapping as well as unique patients. Both reviews come to similar conclusions regarding clinical presentation and known prognostic factors. For both reviews, the majority of patients evaluated were children (84% were 0 to 4 years at onset [Wang et al, 2018]; 84.4% were 0 to 12 years at onset [Garone et al, 2018]).

While the definition for the earliest age of onset groups may vary, there is general agreement that the late onset group is distinct and defined as having TK2d symptom onset greater than 12 years (Berardo et al, 2022; Domínguez-González et al, 2019b; Garone et al, 2018). Regardless of age of onset, TK2d is characterized by relentless disease progression and premature death (Berardo et al, 2022; Domínguez-González et al, 2019b; Garone et al, 2018).

Based on discussions with clinical investigators, international TK2d medical experts, and the current understanding of TK2d, UCB is using the following age of TK2d symptom onset categories to define study participant groups for purposes of efficacy analyses: ≤2 years, >2 to ≤12 years, and >12 years. These age of TK2d symptom onset categories reflect similarities that have been observed and reported in clinical presentation, disease course, and risk of morbidity and mortality. Among these subgroups based on age of TK2d symptom onset, the 2 youngest categories show clear similarities in loss of previously acquired developmental motor milestones or failure to acquire developmental motor milestones, impact on respiratory function, and impairment in feeding. Thus, the group with an age of TK2d symptom onset ≤12 years, representing the most vulnerable population in terms of morbidity and mortality of untreated disease, is proposed for the initial indication for doxecitine and doxribtimine as this group is at greatest risk given the lack of approved treatment options.

Thymidine kinase 2 deficiency is pan-ethnic with no obvious prevalence in any ethnicity, similar to most mitochondrial disorders (Wang et al, 2018).

SI.1.4 The main existing treatment options

There are no approved medicinal products indicated for treatment of TK2d, and treatment is limited to supportive care and, when needed, ventilatory and feeding support. The palliative care has remained largely unchanged since TK2d was first described in 2001 by Saada and colleagues and only addresses symptom management without substantially changing disease progression (Domínguez-González et al, 2019a; Garone et al, 2018; Saada et al, 2001).

SI.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Presentation and clinical course are similar in patients with an age of onset ≤2 years and >2 to ≤12 years. In general, both groups are characterized by initial childhood development of motor milestones, followed by loss of motor milestones. In patients with an age of TK2d symptom onset ≤2 years, the stages of normal development may not occur (ie, some are born with floppy baby syndrome) or have not proceeded very far prior to symptom onset, and patients may progress quickly to hypotonia; whereas in patients with an age of symptom onset >2 to ≤12 years, normal development may have proceeded further prior to a clear loss in motor milestones. In both groups, developmental motor milestones are rarely regained in the absence of treatment.

In addition to neuromuscular symptoms, patients have commonly reported respiratory difficulties, which can often result in a need for mechanical ventilation, and feeding problems (eg, dysphagia) with the need for gastrostomy tubes in some patients (Domínguez-González et al, 2019b; Garone et al, 2018; Wang et al, 2018). Central or peripheral nervous system manifestations including seizure, encephalopathy, cognitive impairment, hearing loss, and polyneuropathy have also been reported but are much less common (Lesko et al, 2010; Martí et al, 2010; Götz et al, 2008; Oskoui et al, 2006; Mancuso et al, 2002).

Premature death is seen in a majority of patients with TK2d, with an earlier age of TK2d symptom onset associated with a shorter latency between TK2d symptom onset and death. From the publication by Wang et al, 2018, 54% (38/70) of patients (all ages of TK2d symptom onset and with outcome data) died due to their disease; the average age of death was 40 months, and the median was 22 months (Wang et al, 2018). Analyses of mortality data from Garone et al,

2018 demonstrated that the median post-onset survival was 1.0 year (confidence interval [CI] 0.58 to 2.33 years) for patients with an age of TK2d symptom onset ≤1 year, at least 13 years for patients with an age of TK2d symptom onset >1 to <12 years, and 23 years (CI 10.0 to incomputable) for patients with an age of TK2d symptom onset ≥12 years (Garone et al, 2018); 27.2% of patients died from respiratory failure (Garone et al, 2018).

SI.1.6 Important co-morbidities

Although there are no co-morbidities per se, multisystem disease manifestations often occur in patients with mitochondrial disease, with various organ systems commonly involved including, but not limited to, cardiac, endocrine, brain, liver, kidney, and gastrointestinal systems (Berardo et al, 2022; Garone et al, 2018; Parikh et al, 2017).

Part II Module SII Nonclinical part of the safety specification

Doxecitine and doxribtimine is being developed as a nucleoside therapy for the treatment of pediatric and adult patients with genetically confirmed TK2d with an age of symptom onset on or before 12 years. Key safety findings from nonclinical studies and relevance to human usage are presented below and additional nonclinical study details are described in eCTD Section 2.6.2, Section 2.6.4, and Section 2.6.6.

SII.1 Toxicity

SII.1.1 Repeat-dose toxicity studies

Oral administration of doxecitine and doxribtimine was well tolerated when administered at doses up to 400mg/kg/day (200mg/kg/day doxecitine and 200mg/kg/day doxribtimine) once daily for 28 days in CByB6F1-Tg(HRAS)2Jic (rasH2 wt/wt) mice (MT1621-21-010), at doses up to 2000mg/kg/day (1000mg/kg/day doxecitine and 1000mg/kg/day doxribtimine) 3 times daily for 26 weeks in juvenile rats (MT1621-19-008) and 100mg/kg/day (50mg/kg/day doxecitine and 50mg/kg/day doxribtimine) once daily for 13 weeks in dogs (MT1621-19-029).

There were no doxecitine and doxribtimine-related clinical signs, no effects on ophthalmology, electrocardiography (dogs only), no effects on body weights or food consumptions, no hematology, coagulation, clinical chemistry, urinalysis (rats and dogs only), organ weights, macroscopic or microscopic analyses. No indication of emesis, diarrhea or increased liver enzymes was noted in these studies. The no observed adverse effect level (NOAEL) and the no observed effect level (NOEL) were the highest doses tested. The NOAEL of 400mg/kg/day in CByB6F1-Tg(HRAS)2Jic (rasH2 wt/wt) mice provided 39-fold for deoxycytidine (dC) and 94-fold for deoxythymidine (dT) margin of human exposure (AUC) at the clinical maintenance dose of 800mg/kg/day (400mg/kg/day doxecitine and 400mg/kg/day doxribtimine). The NOAEL of 2000mg/kg/day in the juvenile rats provided 2838-fold for dC and 1096-fold for dT margin of human exposure at the clinical maintenance dose. The NOEL of 100mg/kg/day in dogs provided a 589-fold for dC and 28-fold for dT margin of human exposure at the clinical maintenance dose.

Relevance to human: The test materials being endogenous in nature, and the well-known absorption/distribution through transporters and metabolism pathways that are generally conserved across species, administration of doxecitine and doxribtimine is expected to pose low risks in humans.

SII.1.2 Reproductive/developmental toxicity

Fertility and early embryonic development

Oral and 3 times daily administration of doxecitine and doxribtimine up to 2000mg/kg/day (1000mg/kg/day doxecitine and 1000mg/kg/day doxribtimine) in male and female rats before cohabitation, through mating and implantation was well tolerated (MT1621-19-024). There were no doxecitine and doxribtimine-related clinical signs or adverse effects on body weights, body weight gains, or food consumption, mating, fertility, reproductive organ weights, testicular histopathology or sperm parameters, or ovarian and uterine parameters (pre- and post-implantation loss) at any dose levels tested. Therefore, the NOAEL for both general and reproductive toxicity in males and females was the highest dose tested, 2000mg/kg/day (1000mg/kg/day doxecitine and 1000mg/kg/day doxribtimine) with oral and 3 times daily

administration (MT1621-19-024) with human exposure margins of between 2530- to 1867-fold for dC and 491- to 1083-fold for dT margin of human exposure at the clinical maintenance dose.

Relevance to human: Under the conditions of the study design, the nonclinical findings do not indicate direct or indirect harmful effects with respect to fertility.

Embryo-fetal development

Oral and 3 times daily administration of doxecitine and doxribtimine up to 2000mg/kg/day (1000mg/kg/day doxecitine and 1000mg/kg/day doxribtimine) to pregnant rats during the period of organogenesis did not produce any maternal or embryofetal toxicity (MT1621-19-027). The highest dose tested was associated with maternal plasma exposures approximately 1867-fold for dC and 491-fold for dT margin of human exposures at the clinical maintenance dose. Oral and 3 times daily administration of doxecitine and doxribtimine up to 2000mg/kg/day to pregnant rabbits during the period of organogenesis resulted in visceral malformations (distended aorta with associated narrow pulmonary trunk) and increased incidences of skeletal variations (misshapen sternebrae, incompletely ossified sternebrae, and incompletely ossified cervical centra) at the highest dose tested, which induced marked maternal toxicity (MT1621-19-016). The middle dose (600mg/kg/day [300mg/kg/day doxecitine and 300mg/kg/day doxribtimine]) was identified as a no-adverse-effect dose and was associated with maternal plasma exposures approximately 824-fold for dC and 141-fold for dT margin of human exposures at the clinical maintenance dose.

Relevance to human: Endogenous pyrimidine nucleosides are transported across the placenta by nucleoside transporters to help meet the fetal requirements for nucleosides (Knipp et al, 1999). Under the conditions of the study design, the study results do not indicate direct or indirect adverse event (AE) risks with respect to pregnancy, teratogenicity, embryonic/fetal development, or parturition in humans. The use of doxecitine and doxribtimine when planning for and during pregnancy may be considered if the clinical benefit outweighs the risk.

Peri- and postnatal development study

No peri- and postnatal development study has been conducted with doxecitine and doxribtimine at the time of this writing.

Juvenile toxicity study

Oral administration of doxecitine and doxribtimine was well tolerated when administered at doses up to 1000mg/kg/day (500mg/kg/day doxecitine and 500mg/kg/day doxribtimine) from postnatal day (PND) 7 through 70 (for 10 weeks) in juvenile rats (NCD4010). There were also no doxecitine and doxribtimine–related delayed effects at the end of a 21-day recovery period. During the dosing phase, nonadverse doxecitine and doxribtimine-related increases in absolute mean body weight and mean body weight gain were noted during the dosing phase for both sexes administered ≥300mg/kg/day, along with nonadverse doxecitine and doxribtimine-related increases in mean food consumption for males administered ≥300mg/kg/day.

No doxecitine and doxribtimine-related differences were noted in clinical observations; developmental landmarks and sexual maturation; reproductive capability or indices; neurobehavioral endpoints including locomotor activity, auditory startle, learning and memory, and functional observed battery evaluations; ophthalmology assessments; clinical pathology evaluations; macro and microscopic analyses; bone mineral density and content; and bone volume. Based on the lack of adverse findings during the dosing and recovery period, the NOAEL for juvenile toxicity was 1000mg/kg/day. The NOAEL of 1000mg/kg/day provided a 3072-fold for dC and 149-fold for dT margin of human exposure at the clinical maintenance dose.

Relevance to human: Based on these findings, administration of doxecitine and doxribtimine is expected to pose low risks in pediatric patients.

SII.1.3 Genotoxicity

Three in vitro and in vivo genotoxicity studies (MT1621-19-017, MT1621-19-015, and MT1621-19-018) were conducted in accordance with the International Council for Harmonisation (ICH) guideline S2 (R1). The genotoxicity battery shows that doxecitine and doxribtimine together are likely not genotoxic based on a weight of evidence.

The genotoxicity battery study designs used doxecitine and doxribtimine, rather than the individual components, to keep the pyrimidine precursor pools balanced. Imbalanced precursor nucleoside pools can affect DNA synthesis and replication fidelity (Mathews, 2006; Phear et al, 1987). For example, the results for the sister chromatid exchange (SCE) assay of dT were negative, equivocal, or positive with dose-dependent increases in SCEs (Marquardt et al, 1988; Perry, 1983; Bradley et al, 1981). However, Perry (1983) showed that this increase in SCE frequency was generally reversed with the addition of dC that essentially balanced the precursor nucleoside pools (Perry, 1983). In vitro, mitogenic stimulation in the chromosomal aberration assay can result in an increased number of nucleoside transporter binding sites that may contribute to nucleoside imbalance, and hence leading to a positive result in the test system (Kunz et al, 1994). Indeed, with doxecitine and doxribtimine, the in vitro reverse mutation Ames test in bacteria was negative (MT1621-19-017), while the in vitro metaphase chromosome aberration test was positive (MT1621-19-015). In the in vitro chromosomal aberration test, mitogenic stimulated cells upregulated the nucleoside transporter binding sites, which likely led to imbalanced nucleotide pools and hence the positive signal was observed in the study (MT1621-19-015). The in vivo micronucleus study in rats is a more relevant model for nucleoside evaluation, because in an in vivo evaluation the nucleosides remain balanced, and formation of nucleotides are regulated properly. The mammalian micronuclei study demonstrated nongenotoxic results in rats following oral administration of doxecitine and doxribtimine once daily at doses up to 2000mg/kg/day (1000mg/kg/day doxecitine and 1000mg/kg/day doxribtimine) for 2 days (MT1621-19-018). This negative result is consistent with proper balanced transport of nucleosides in vivo and the lack of any hyperplasia or tumors observed in the 13-week repeat-dose toxicity study in dogs (MT1621-19-029) and the 26-week repeat-dose toxicity study in juvenile rats (MT1621-19-008).

Relevance to human: Doxecitine and doxribtimine is likely nongenotoxic based on the weight of the evidence.

SII.1.4 Carcinogenicity

No carcinogenicity study has been conducted with doxecitine and doxribtimine at the time of this writing. Doxecitine and doxribtimine, as pyrimidine nucleosides, are not associated with a role in cancer development. Cell physiology parameters including metabolism pathways, concentration dependent enzyme regulation, and equilibrative transports all contribute to the overall support of in vivo-based weight of evidence that the potential carcinogenicity risk of doxecitine and doxribtimine is low. The histopathological (ie, tumorgenicity or hyperplasia), hormone, or immune modulation findings were not observed in the 26-week repeat dose toxicity study in juvenile rats at 2838-fold and 1096-fold margins of human exposure at the clinical maintenance dose for dC and dT, respectively (MT1621-19-008), and in the 13-week repeat dose toxicity study in dogs at 589-fold and 28-fold margins of human exposure at the clinical maintenance dose for dC and dT, respectively (MT1621-19-029).

Relevance to human: The carcinogenic risk of doxecitine and doxribtimine is low based on the weight of evidence.

SII.2 Safety pharmacology

SII.2.1 Cardiovascular system, including potential effect on the QT interval

No formal pharmacodynamic studies were conducted, the assessment of cardiovascular parameters was included in the 13-week repeat-dose toxicity study in dogs (MT1621-19-029). The cardiovascular effects in dogs administered up to 100mg/kg/day (50mg/kg/day doxecitine and 50mg/kg/day doxribtimine) orally once daily demonstrated that all electrocardiograms were qualitatively considered normal and no effect on the heart rate was observed.

Effects of doxecitine and doxribtimine on cardiac electrophysiology have not been determined in a formal clinical trial because doxecitine and doxribtimine are chemically identical to ubiquitous endogenous nucleosides. The range of plasma concentrations of dC and dT following oral administration of doxecitine and doxribtimine in patients with TK2d are in the range of circulating endogenous dC and dT concentrations reported in normal, healthy subjects.

Relevance to human: Based on these findings, the likelihood of doxecitine and doxribtimine producing QTc prolongation or other cardiac toxicities is considered to be low.

SII.2.2 Nervous and respiratory systems

No specific nervous or respiratory function assessments were conducted. However, in the proof-of-concept studies in either the *Tk2*-/- knock-out or *Tk2* H126N knock-in mutant mouse models, doxecitine and doxribtimine demonstrated pharmacologic effects and no doxecitine and doxribtimine-related toxic effects were observed at doses up to 1040mg/kg/day (520mg/kg/day doxecitine and 520mg/kg/day doxribtimine) with a once daily oral administration frequency from PND 4 onward.

The effect of oral administration of doxecitine and doxribtimine on neurobehavior and locomotor activities was assessed in TK2d mice. The treatment with doxecitine and doxribtimine from PND 4 onward improved locomotor activities as demonstrated in the following parameters: 1. Neuroscore evaluation for assessing motor and behavioral deficits; 2. Righting reflex test for assessing reflex to orient the body; 3. Rotarod test for assessing motor coordination and balance; 4. Balance test (ie, decreased latency to fall); 5. Open field test for assessing general activity with emphasis on locomotor activity and exploratory habit; and 6. Treadmill test for assessing distance travelled and tie time to exhaustion (MT1621-21-016). No doxecitine and doxribtimine-related toxicologic effects were noted in any of the assessments.

In addition, the effect of oral administration of doxecitine and doxribtimine at doses up to 1000mg/kg/day (500mg/kg/day doxecitine and 500mg/kg/day doxribtimine) on neurobehavior was evaluated in the 10-week juvenile toxicity study in rats (NCD4010). The neurobehavioral assessment included locomotor activity on PND 59 (±4 days) or PND 80 (±4 days), auditory startle on PND 62 (±4 days) or PND 83 (±4 days), learning and memory assessment on PND 65 (±4 days) and functional observation battery on PND 60 (±2 days) or PND 81 (±2 days). No doxecitine and doxribtimine-related effects were observed during the dosing or in the recovery period.

The respiratory function assessment was not possible in the TK2d mouse models due to the young age of animals (ie, PND 4 at the start of dose administration). Therefore, the respiratory effect was supported biochemically with increased mtDNA copy number in the diaphragm (MT1621-19-015). Increased mtDNA in the diaphragm is expected to improve respiratory function. No doxecitine and doxribtimine-related toxicologic effects were noted in the study.

In addition, no doxecitine and doxribtimine-related neurobehavioral alterations nor histopathological changes were observed in the brain or lungs of juvenile rats in the 26-week repeat dose toxicity study at 2838-fold and 1096-fold margins of human exposure at the clinical maintenance dose for dC and dT, respectively (MT1621-19-008), or in the 13-week repeat dose toxicity study in dogs at 589-fold and 28-fold margins of human exposure at the clinical maintenance dose for dC and dT, respectively (MT1621-19-029), or in the 10-week juvenile toxicity study in rats at 3072-fold for dC and 149-fold for dT margin of human exposure at the clinical maintenance dose (NCD4010).

Relevance to human: Based on these findings, the nervous or respiratory function risk of doxecitine and doxribtimine is considered low.

SII.2.3 Gastrointestinal system

No doxecitine and doxribtimine–related gastric retention or motility (eg, impaction or distended abdomen) nor histopathological changes in the gastrointestinal system were observed following oral administration at all dose levels in the 26-week repeat-dose toxicity study in the juvenile rats at 2838-fold and 1096-fold margins of human exposure at the clinical maintenance dose for dC and dT, respectively (MT1621-19-008), or in the 13-week repeat-dose toxicity study in dogs at 589-fold and 28-fold margins of human exposure at the clinical maintenance dose for dC and dT, respectively (MT1621-19-029), or in the 10-week juvenile toxicity study in rats at 3072-fold for dC and 149-fold for dT margin of human exposure at the clinical maintenance dose (NCD4010).

Relevance to human: Based on these findings, the gastrointestinal risk of doxecitine and doxribtimine is considered low.

SII.3 Other toxicity-related information or data

SII.3.1 Impurities

Previously distributed and current drug product contains an impurity of alpha-hydroxythymidine (α-OH-TMD) at levels up to approximately 10 times higher than the established permitted daily exposure (PDE) for α-OH-TMD (420µg/day or 15ppm). Alpha-hydroxythymidine is classified as a Class 2 known mutagen with unknown carcinogenic potential as per the 2023 ICH M7 classification (EMA/CHMP/ICH/83812/2013). Notably, the PDE for α-OH-TMD has been determined based on in silico analysis and literature studies using the impurity in isolation, while use of doxecitine and doxribtimine in TK2d patients provides at least 6500-fold excess of dT which is a significant margin to allow natural DNA error-repair function.

Nonclinical in vivo evidence of lack of genotoxicity, organ toxicity, and carcinogenic potential when α-OH-TMD was administered with dC and dT (or doxecitine and doxribtimine) were demonstrated in the toxicology studies with doxecitine and doxribtimine that included α-OH-TMD at up to 128ppm.The NOAELs in the 10-week juvenile toxicity study and 26-week (81 days exposures only) repeat dose toxicity study in rats were the highest dose of 1000 or 2000mg/kg/day doxecitine and doxribtimine (500 or 1000mg/kg/day doxribtimine), respectively, and provided margins of exposure, at the maintenance dose of 800mg/kg/day (400mg/kg/day doxecitine and 400mg/kg/day doxribtimine), of over 100- to 1000-fold for both dC and dT.

Relevance to human: Considering low incorporation of α-OH-TMD into DNA (Kahilainen et al, 1986; Matthes et al, 1979), rescue of cytotoxicity and mutagenicity in presence of dC and dT (ie, doxecitine and doxribtimine) (Li et al, 2020; Kahilainen et al, 1986; Kaufman, 1986), clinical exposure data, and available nonclinical in vivo data, the probability of genotoxicity caused by the α-OH-TMD impurity is considered extremely remote. With α-OH-TMD levels up to the highest observed levels in clinical batches manufactured to date, the impact of α-OH-TMD on the risk-benefit balance in this ultra rare disease with significant mortality remains negligible. Tumorigenicity due to presence of the α-OH-TMD impurity, in the vast excess of dT, is not considered a safety concern or new risk with clinical use of doxecitine and doxribtimine.

SII.3.2 Photoreactivity potential

The photoreactive potential of doxecitine and doxribtimine was evaluated per ICH S10 Photosafety Evaluation of Pharmaceuticals guidelines (STP/GA-QC-210928A). No absorption by doxecitine of wavelengths from 299nm to 700nm and by doxribtimine of wavelengths from 298nm to 700nm were apparent in methanol or water.

Relevance to human: These results indicate that the photoreactivity potential of doxecitine and doxribtimine is low.

SII.3.3 Photostability potential

The photostability of doxecitine and doxribtimine was assessed as recommended by the ICH Q1B guideline (SPS P039[7]-21-001-R[01]). Solid state doxecitine and doxribtimine stored at 25˚C was exposed to light providing an overall illumination of 1.2 and 2.4 million lux hours and an integrated near ultraviolet energy of 200 and 400watt h/m^2. No degradation was noted for doxecitine and doxribtimine. These results indicate that doxecitine and doxribtimine is photostable.

Relevance to human: These results indicate that the photostability risk of doxecitine and doxribtimine is considered low.

SII.3.4 Drug-drug interactions

Doxecitine and doxribtimine exhibits a low potential to perpetrate, or be subject to, pharmacokinetic (PK) interactions mediated by plasma protein binding displacements, cytochrome P450 (CYP) enzymes, and common drug transporters at clinically relevant concentrations. Protein binding is relatively low (<10%) in human plasma and independent of concentrations. Clinically relevant concentrations of doxecitine and doxribtimine show no direct or indirect inhibition nor induction of CYP enzymes in vitro, or of relevant solute and efflux transporters in vitro including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump, organic anion transporter polypeptide (OATP)B1, and OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, multidrug and toxic extrusion protein (MATE)1, and MATE2-K. Doxecitine and doxribtimine is metabolized by non-CYP enzymes specific to pyrimidine nucleosides. Results from in vitro assessments indicate that doxecitine and doxribtimine is not a substrate for P-gp, OAT1, OAT3, or OCT2. Deoxycytidine is unlikely to be a substrate of BCRP but dT is possibly a substrate of BCRP. Hence, PK of doxecitine and doxribtimine may be affected when co-administered with strong inhibitors or inducers of BCRP.

Relevance to human: The significance of potential PK drug-drug interactions (DDIs) mediated by BCRP in humans is unknown. Caution should be exercised when doxecitine and doxribtimine is co-administered with medicinal products that are strong inhibitors or inducers of BCRP. Additionally, some medicinal products may affect the enzymes and nucleoside transporters involved in the disposition of doxecitine and doxribtimine. Drugs that may induce, compete with, or directly inhibit the primary degradative enzymes (cytidine deaminase and thymidine phosphorylase) may affect the PK of doxecitine and doxribtimine. These potential perpetrators are mainly a small number of drugs in the antineoplastic, antiviral (nucleoside/nucleotide reverse transcriptase inhibitors), and anticoagulant/antiplatelet class. There is no specific experimental data in the program on these potential DDIs with oral doxecitine and doxribtimine. These potential atypical DDIs are anticipated to represent a small risk in patients with TK2d.

Part II Module SIII Clinical trial exposure

Table Part II–1 presents the study participant exposure to all formulations of study drug in TK2d clinical studies by duration. Note that the term study drug represents non-Good Manufacturing Practice (GMP) nucleotides deoxycytidine monophosphate/deoxythymidine monophosphate, non-GMP nucleosides dC/dT, or doxecitine and doxribtimine. Because the active moieties are the pyrimidine nucleosides dC and dT, regardless of formulation, the Sponsor considers that study participant experience with these treatments is relevant to the doxecitine and doxribtimine development program for TK2d and relevant for understanding the safety of doxecitine and doxribtimine. Data are pooled from retrospective studies MT-1621-101 and MT-1621-107, and open-label study TK0102.

Table Part II–1: Duration of exposure – all study participants

Cumulative for TK2d indication		
Duration of exposure	**Study participants (%)**	**Participant-years**
>0 months	67 (100)	
≥6 months	57 (85.1)	
≥12 months	55 (82.1)	
≥24 months	53 (79.1)	
≥36 months	52 (77.6)	
≥48 months	51 (76.1)	
≥60 months	45 (67.2)	
Total person time	-	345.0 participant-years

TK2d=thymidine kinase 2 deficiency
Data source: Integrated Summary of Safety Table 1.7.1 (data cutoff 15 Mar 2024)

Table Part II–2 presents duration of exposure to all formulations of study drug in study participants with an age of TK2d symptom onset ≤12 years of age. Data are pooled from MT-1621-101, TK0102, and MT-1621-107.

Table Part II–2: Duration of exposure – participants with age of TK2d symptom onset ≤12 years

Cumulative for TK2d indication		
Duration of exposure	**Study participants (%)**	**Participant-years**
>0 months	50 (100)	
≥6 months	45 (90.0)	
≥12 months	45 (90.0)	
≥24 months	44 (88.0)	
≥36 months	43 (86.0)	

Table Part II–2: Duration of exposure – participants with age of TK2d symptom onset ≤12 years

Cumulative for TK2d indication		
Duration of exposure	**Study participants (%)**	**Participant-years**
≥48 months	42 (84.0)	
≥60 months	36 (72.0)	
Total person time	-	283.0 participant-years

TK2d=thymidine kinase 2 deficiency
Data source: Table RMP 1.7.1.1 (data cutoff 15 Mar 2024)

Table Part II–3 presents the study participant exposure to all formulations of study drug in TK2d clinical studies by age group at first treatment and sex. Data are pooled from MT-1621-101, TK0102, and MT-1621-107.

Table Part II–3: Age group at first treatment and sex – all study participants

Age group	**Study participants**		**Participant-years**	
	Male	**Female**	**Male**	**Female**
≤2 years	P	P	PP	PP
>2 and ≤12 years	18	P	111.8	PP
>12 and <18 years	P	P	PP	PP
≥18 years	11	12	56.5	52.1
Total	38	29	207.8	137.2

Data source: Integrated Summary of Safety Table 1.7.3 (data cutoff 15 Mar 2024)

Table Part II–4 presents the study participant exposure to all formulations of study drug in TK2d clinical studies by age group at first treatment and sex in study participants with an age of TK2d symptom onset ≤12 years. Data are pooled from MT-1621-101, TK0102, and MT-1621-107.

Table Part II–4: Age group at first treatment and sex – participants with age of TK2d symptom onset ≤12 years

Age group	**Study participants**		**Participant-years**	
	Male	**Female**	**Male**	**Female**
≤2 years	P	P	PP	PP
>2 and ≤12 years	18	P	111.8	PP
>12 and <18 years	P	P	PP	PP
≥18 years	P	P	PP	PP
Total	32	18	192.4	90.5

TK2d=thymidine kinase 2 deficiency
Data source: Table RMP 1.7.3.1 (data cutoff 15 Mar 2024)

Table Part II–5 presents the study participant exposure to all formulations of study drug in TK2d clinical studies by dose. Data are pooled from MT-1621-101, TK0102, and MT-1621-107.

Table Part II–5: Exposure by dose of each individual API component – all study participants

Cumulative for the TK2d indication		
Dose of exposure[a]	**Study participants**	**Participant-years**
<200mg/kg/day	44	25.8
200 to ≤400mg/kg/day	67	314.4
>400mg/kg/day	P	PP

API=active pharmaceutical ingredient; CSR=clinical study report; TEAE=treatment-emergent adverse event; TK2d=thymidine kinase 2 deficiency

Note: At the start of the doxecitine and doxribtimine development program, dosing was presented as the amount of each API (see footnote a). However, during the development program, dosing nomenclature was updated to present dose as the total of doxecitine and doxribtimine combined, ie, 800mg/kg/day=400mg/kg/day doxecitine and 400mg/kg/day doxribtimine.

Note: Treatment durations with missing dose information were excluded.

Note: Dose category is based on doses received during studies; the target dose for all TK2d participants is 400mg/kg/day; doses <400mg/day were generally titration steps or due to a dose reduction.

[a] Doses are presented as the amount of each individual API (for example, 400mg/kg/day refers to 400mg/kg/day of doxecitine and 400mg/kg/day of doxribtimine).

Data source: Integrated Summary of Safety Table 1.7.2 (data cutoff 15 Mar 2024)

Table Part II–6 presents the study participant exposure to all formulations of study drug in TK2d clinical studies by dose in participants with an age of TK2d symptom onset ≤12 years. Data are pooled from MT-1621-101, TK0102, and MT-1621-107.

Table Part II–6: Exposure by dose of each individual API component - participants with age of TK2d symptom onset ≤12 years

Cumulative for the TK2d indication		
Dose of exposure[a]	**Study participants**	**Participant-years**
<200mg/kg/day	35	21.5
200 to ≤400mg/kg/day	50	256.8
>400mg/kg/day	P	PP

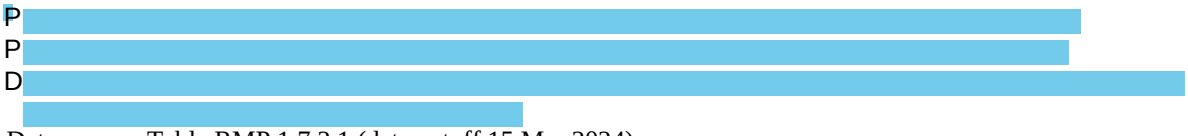
API=active pharmaceutical ingredient; CSR=clinical study report; TEAE=treatment-emergent adverse event; TK2d=thymidine kinase 2 deficiency

Note: At the start of the doxecitine and doxribtimine development program, dosing was presented as the amount of each API (see footnote a). However, during the development program, dosing nomenclature was updated to present dose as the total of doxecitine and doxribtimine combined, ie, 800mg/kg/day=400mg/kg/day doxecitine and 400mg/kg/day doxribtimine.

Note: Treatment durations with missing dose information were excluded.

Note: Dose category is based on doses received during studies; the target dose for all TK2d participants is 400mg/kg/day; doses <400mg/day were generally titration steps or due to a dose reduction.

[a] Doses are presented as the amount of each individual API (for example, 400mg/kg/day refers to 400mg/kg/day of doxecitine and 400mg/kg/day of doxribtimine).



Data source: Table RMP 1.7.2.1 (data cutoff 15 Mar 2024)

Table Part II–7 presents the study participant exposure to all formulations of study drug in TK2d clinical studies by ethnic origin. Data are pooled from MT-1621-101, TK0102, and MT-1621-107.

Table Part II–7: Exposure by ethnic origin – all study participants

Ethnic origin	Study participants	Participant-years
White	61	322.0
Asian	P	
Black or African American	P	
American Indian or Alaska Native	P	PP
Unknown	P	PP
Total	67	345.0

Data source: Integrated Summary of Safety Table 1.7.4 (data cutoff 15 Mar 2024)

Table Part II–8 presents the study participant exposure to all formulations of study drug in TK2d clinical studies by ethnic origin in study participants with an age of TK2d symptom onset ≤12 years. Data are pooled from MT-1621-101, TK0102, and MT-1621-107.

Table Part II–8: Exposure by ethnic origin – study participants with age of TK2d symptom onset ≤12 years

Ethnic origin	Study participants	Participant-years
White	44	260.0
Asian	P	
Black or African American	P	
American Indian or Alaska Native	P	
Unknown	P	
Total	50	283.0

TK2d=thymidine kinase 2 deficiency
Data source: Table RMP 1.7.4.1 (data cutoff 15 Mar 2024)

Part II Module SIV Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria in pivotal clinical studies within the development programme are discussed in Table Part II–9 below:

Table Part II–9: Exclusion criteria in pivotal clinical studies within the development programme

Hepatic impairment[a]	
Reason for exclusion	There is limited experience with the use of doxecitine and doxribtimine in patients with TK2d who have impaired hepatic function. Considering the potential for hepatic and extrahepatic metabolism of dC and dT, plasma concentrations of dC and dT may be affected following administration of doxecitine and doxribtimine in patients with moderate or severe hepatic impairment. However, based on the mode-of-action and pharmacokinetic and safety data, a future negative impact on benefit-risk is currently not expected.
Is it considered to be included as missing information	No
Pregnancy and breastfeeding[a]	
Reason for exclusion	The effect of pyrimidine nucleos(t)ides on pregnancy and breastfeeding has not been evaluated in humans. Animal data in both rat and rabbit do not indicate direct or indirect harmful effects with respect to reproductive toxicity at doses of up to 2000mg/kg/day in rats and 600mg/kg/day in rabbits (exposure margins compared to humans of 1867-fold for dC and 491-fold for dT in females and 2530-fold for dC and 1083-fold for dT in males at the NOAEL [2000mg/kg/day] in rats, and 824-fold for dC and 141-fold for dT at the NOAEL [600mg/kg/day] in rabbits). While endogenous pyrimidine nucleosides and nucleotides are present naturally in human milk, it is unknown whether doxecitine and doxribtimine are excreted in human milk.
Is it considered to be included as missing information	Yes

dC=deoxycytidine; dT=deoxythymidine; NOAEL=no observed adverse effect level; TK2d=thymidine kinase 2 deficiency

[a] Hepatic impairment and pregnancy and breastfeeding are exclusion criteria in TK0102 only.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table Part II–10 provides an example of overview of exposure in special population typically under-represented in clinical trial development programmes.

Table Part II–10: 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 relevant comorbidities: • Patients with renal impairment	16 study participants without TK2d but with renal impairment were included in renal impairment study MT-1621-106 (completed): A Phase 1, open-label, parallel study to characterize the pharmacokinetics and safety of a single oral dose of MT1621 in subjects with renal impairment matched to control healthy subjects. • 8 study participants with severe renal impairment: (eGFR ≥15 to ≤29mL/min/1.73m^2 using the CG or MDRD equation). • 8 study participants with moderate renal impairment: (eGFR ≥30 to ≤59mL/min/1.73m^2 using the CG or MDRD equation).
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Considering the ultra-rare disease population, patients with relevant comorbidities were not specifically excluded. With the exception of a limited number of patients with mild to moderate hepatic impairment (based on NCI-ODWG criteria), none participated in the clinical development programme.
Population with relevant different ethnic origin	See Table Part II–7
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme. Only study participants with confirmed genetic mutation(s) in the *TK2* gene were included.
Elderly (patients over 65 years of age)	There are limited data on the PK, safety, and efficacy of doxecitine and doxribtimine in study participants 65 years of age and older. Results from the population PK analysis in healthy study participants and study participants with TK2d revealed that age (in the range evaluated) had no significant effect on exposures to dC and dT.

Table Part II–10: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure

CG=Cockcroft-Gault; dC=deoxycytidine; dT=deoxythymidine; eGFR=estimated glomerular filtration rate; MDRD=Modification of Diet in Renal Disease; MT1621=doxecitine and doxribtimine; NCI-ODWG=National Cancer Institute-Organ Dysfunction Working Group; PK=pharmacokinetics; TK2=thymidine kinase 2; TK2d=thymidine kinase 2 deficiency

Part II Module SV Postauthorization experience

Doxecitine and doxribtimine is not currently marketed in any country, therefore this module is not applicable.

Part II Module SVI Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Based on the characteristics and target population of this drug, no evidence to suggest a potential for drug abuse or misuse is anticipated.

Part II 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

Table Part II–11: Risks not considered important and reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks not considered important	Justification for noninclusion in list of safety concerns
Diarrhea	Diarrhea is a nonimportant identified risk for doxecitine and doxribtimine which is not anticipated to affect the risk-benefit balance of the product or have implications for public health. While there is no obvious mechanistic link between doxecitine and doxribtimine and diarrhea, diarrhea has been reported as a frequent TEAE and appears to be dose-related. The majority of events of diarrhea have been mild to moderate in severity, occurred early after treatment initiation (<3 months, 37 of 50 participants [74.0%]), and generally have been self-limiting or have improved with dose reduction and longer duration of treatment at a lower dose, prior to escalating back to the target dose (of 133 events of diarrhea, 12% [16/133] required dose reduction with a median duration of 80 days [Q1,Q3=33.0, 201.5]). The median (Q1, Q3) duration of "diarrhoea" was 13.0 (3.0, 235.0) days. Diarrhea does not appear to be associated with weight loss. Neither does it appear to be correlated with lower systemic exposure to doxecitine and doxribtimine. PPD . As of the cutoff date for the submission, the participant has been treated with doxecitine and doxribtimine for over 12 years and no further events of diarrhea have been reported. There are no drug-related events of failure to thrive in the clinical program. Diarrhea may be managed according to routine patient management, including anti-diarrheals. Based on the severity of the diarrhea, the dose of doxecitine and doxribtimine should either be reduced, or temporarily withheld until the diarrhea improves or returns to baseline, and then resumed gradually (SmPC Section 4.2) to a tolerable dose level (SmPC Section 4.4). Diarrhea is included as a very common ADR (SmPC Section 4.8).

Table Part II–11: Risks not considered important and reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks not considered important	Justification for noninclusion in list of safety concerns
Abdominal pain (including abdominal pain upper)	Abdominal pain is a nonimportant identified risk for doxecitine and doxribtimine which is not anticipated to affect the risk-benefit balance of the product or have implications for public health. While there is no obvious mechanistic link between doxecitine and doxribtimine and abdominal pain, it is possible that the large volumes needed to be administered due to the low oral bioavailability of pyrimidine nucleos(t)ides may trigger abdominal pain in some patients. The severity of events of abdominal pain (including abdominal pain upper) in clinical studies has ranged from mild to severe. The majority of events have been self-limiting. The median (Q1, Q3) duration of "abdominal pain (including abdominal pain upper)" was 1.5 (1.0, 4.0) days. As of the cutoff date for the submission, PPD . The event was not related to study drug in the opinion of the Investigator, no change in dosing occurred, and the outcome was resolved at the time of study completion. Abdominal pain (including abdominal pain upper) is included as a very common ADR (SmPC Section 4.8).
Vomiting	Vomiting is a nonimportant identified risk for doxecitine and doxribtimine which is not anticipated to affect the risk-benefit balance of the product or have implications for public health. There is no obvious mechanistic link between doxecitine and doxribtimine and vomiting. However, the large volumes that need to be administered due to the low oral bioavailability of pyrimidine nucleos(t)ides may trigger vomiting in some patients. In addition, palatability, which is considered unfavorable from a patient perspective, could potentially influence vomiting through mechanisms involving dysgeusia, feelings of disgust, or reflexive gag responses. The majority of events of vomiting in clinical studies have been mild in intensity and self-limiting. The median (Q1, Q3) duration of "vomiting" was 2.0 (1.0, 3.0) days. As of the cutoff date for the submission, there have been 2 serious events of vomiting. PPD . The event was not related to treatment in the opinion of the Investigator, no change in dosing occurred, and the outcome was resolved at the time of the interim CSR. PPD . Vomiting is included as a very common ADR (SmPC Section 4.8).

ADR=adverse drug reaction; CSR=clinical study report; dCMP=deoxycytidine monophosphate; dTMP=deoxythymidine monophosphate; RMP=Risk Management Plan; SmPC=Summary of Product Characteristics; TEAE=treatment-emergent adverse event

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table Part II–12: Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks:	
None	
Important potential risks:	
Liver dysfunction	
Risk-benefit impact	Elevations of ALT and AST have been frequently reported amongst participants with TK2d treated in the clinical studies MT-1621-101 and TK0102. No distinct pattern in the type of elevation (consistent or episodic) nor specific time frame of occurrence was observed. The median (Q1, Q3) duration of "alanine aminotransferase increased" and "aspartate aminotransferase increased" was 142.5 (64.0, 222.0) days and 197.0 (58.5, 379.0) days, respectively. Observed increases in transaminases have not been associated with clinically confirmed liver injury, and as such no impact on the risk-benefit profile has been identified from clinical studies with doxecitine and doxribtimine. From a mechanism of action point of view there is no obvious link between doxecitine and doxribtimine and liver enzyme elevations. Patients with TK2d, however, may have pre-existing liver enzyme elevations to varying degrees (Berardo et al, 2022; Wang et al, 2018), and potential treatment-related exacerbations of clinical relevance (eg, liver dysfunction/failure), though not observed in clinical studies, cannot be fully excluded to date.
Missing information	
Long-term safety in patients with TK2d symptom onset ≤2 years and symptom onset >2 to ≤12 years	
Risk-benefit impact	At least 18 of 32 participants with TK2d symptom onset ≤2 years and at least 14 of 18 participants with TK2d symptom onset >2 and ≤12 years have been exposed to doxecitine and doxribtimine for ≥5 years. Although this degree of exposure in an ultra-rare disease with considerable mortality offers sufficient follow-up duration, it represents only a subset of the total 67 treated patients and does not meet the conventional standard of at least 100 patients treated for a minimum of 12 months. Longer term follow-up of a larger group of treated patients could compensate for the small sample size. Potential risks associated with long-term treatment with doxecitine and doxribtimine in a larger patient population remain unknown.

Table Part II–12: Risks considered important for inclusion in the list of safety concerns in the RMP

Use during pregnancy and breastfeeding	
Risk-benefit impact	The effect of pyrimidine nucleos(t)ides on pregnancy and breastfeeding has not been evaluated in humans and is therefore considered missing information. While endogenous pyrimidine nucleosides and nucleotides are present naturally in human milk, it is unknown whether doxecitine and doxribtimine are excreted in human milk. Endogenous pyrimidine nucleosides are transported across the placenta by placental nucleoside transporters to help meet the fetal requirements for nucleosides (Knipp et al, 1999). It is therefore anticipated that a fetus would be exposed to doxecitine and doxribtimine. Animal data in both rat and rabbit do not indicate direct or indirect harmful effects with respect to reproductive toxicity at doses of up to 2000mg/kg/day in rats and 600mg/kg/day in rabbits (exposure margins compared to humans of 1867-fold for dC and 491-fold for dT in females and 2530-fold for dC and 1083-fold for dT in males at the NOAEL [2000mg/kg/day] in rats, and 824-fold for dC and 141-fold for dT at the NOAEL [600mg/kg/day] in rabbits).

ALT=alanine aminotransferase; AST=aspartate aminotransferase; dC=deoxycytidine; dT=deoxythymidine; NOAEL=no observed adverse effect level; RMP=Risk Management Plan; TK2d=thymidine kinase 2 deficiency

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

This section is not applicable since this is the initial Risk Management Plan (RMP) for doxecitine and doxribtimine.

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

Characterization of risks was performed using pooled data from all study participants in MT-1621-101, TK0102, and MT-1621-107.

Important identified risks

None.

Important potential risks

Important potential risks with doxecitine and doxribtimine are characterized in Table Part II–13.

Table Part II–13: Important potential risk: Liver dysfunction

Potential mechanisms	The primary mechanism of action of doxecitine and doxribtimine is incorporation of the deoxynucleosides dC and dT into mtDNA to increase mtDNA copy number in target tissue, including skeletal muscle. Mechanistically, there is no obvious link between doxecitine and doxribtimine and liver enzyme elevations. Patients with TK2d may have pre-existing liver enzyme elevations to varying degrees (Berardo et al, 2022; Wang et al, 2018), which may be related to their TK2d (either potentially through a mitochondria-related effect on the liver and/or disease-related muscle injury). Potential treatment-related exacerbations of clinical relevance (eg, liver dysfunction/failure), though not observed in clinical studies, cannot be fully excluded to date. Other possible causes of liver injury should be evaluated prior to initiating treatment with doxecitine and doxribtimine.
Evidence source(s) and strength of evidence	Elevations in transaminases have been frequently reported amongst the participants with TK2d treated with doxecitine and doxribtimine in the clinical studies MT-1621-101 and TK0102.
Characterization of the risk	Frequency: In the clinical development studies MT-1621-101 and TK0102, a total of 22/50 participants with TK2d (44.0%) experienced events within the drug-related hepatic disorders comprehensive search SMQ. The most frequently reported events in the SMQ were ALT increased (14 of 50 participants [28.0%]) and AST increased (11 of 50 participants [22.0%]). Severity: The observed elevations in transaminases have been nonserious and asymptomatic with no distinct pattern (consistent vs episodic elevation). There have been no reports of hepatic failure, jaundice, liver injury, or Hy's Law during treatment with doxecitine and doxribtimine. Reversibility: Transaminase elevations are generally reversible with dose unchanged or with drug discontinuation; 2 study participants with elevated liver enzymes discontinued after experiencing positive de/-rechallenge. Most participants (92 to 96%) with elevated AST/ALT at Baseline had last post-Baseline AST/ALT values that were of equal or lower grade than the Baseline grade, suggesting a stabilization and/or improvement of AST/ALT levels while on treatment.
Characterization of the risk (cont.)	Absolute risk: TK2d itself can be associated with transaminase elevation either potentially through a mitochondria-related effect on the liver and/or disease-related muscle injury. Elevated liver enzymes (Berardo et al, 2022; Wang et al, 2018) are among the 10 most frequently reported symptoms of patients with TK2d, having been reported in up to 82% of patients (Wang et al, 2018). Long-term outcome/impact on quality of life: No long-term effect is expected after return of transaminase levels to normal levels.
Risk factors and risk groups	Patients with TK2d may have pre-existing liver enzyme elevations to varying degrees.
Preventability	Transaminase levels should be checked prior to initiation of treatment, and changes in liver function monitored periodically during treatment with doxecitine and doxribtimine and according to routine patient management.

Table Part II–13: Important potential risk: Liver dysfunction

Impact on risk-benefit balance of the product	The elevations in transaminases that have been observed in patients with TK2d receiving doxecitine and doxribtimine treatment have been asymptomatic and nonserious. They have been incorporated in the risk-benefit assessment with the overall risk-benefit balance remaining positive. Routine and additional pharmacovigilance activities are in place to monitor this risk (see Table Part III–1).
Public health impact	The elevations in transaminases that have been observed in patients with TK2d receiving doxecitine and doxribtimine treatment have been asymptomatic and nonserious; therefore, the potential public health impact is considered low.

MedDRA=Medical Dictionary for Regulatory Activities; mtDNA=mitochondrial deoxyribonucleic acid; SMQ=Standardised MedDRA Query; SOC=system organ class; TK2d=thymidine kinase 2 deficiency
Data source: Integrated Summary of Safety (data cutoff 15 Mar 2024) Table 2.4.3 and Table 2.5.1

SVII.3.2 Presentation of the missing information

Long-term safety in patients with TK2d symptom onset ≤2 years and symptom onset >2 to ≤12 years

Evidence source**:**

At least 18 of 32 participants with TK2d symptom onset ≤2 years and at least 14 of 18 participants with TK2d symptom onset >2 and ≤12 years have been exposed to doxecitine and doxribtimine for ≥5 years. Although this degree of exposure in an ultra-rare disease with considerable mortality offers sufficient follow-up duration, it represents only a subset of the total 67 treated patients and does not meet the conventional standard of at least 100 patients treated for a minimum of 12 months.

Population in need of further characterization:

Potential risks associated with long-term treatment with doxecitine and doxribtimine in a larger patient population remain unknown.

Use during pregnancy and breastfeeding

Evidence source:

The effect of pyrimidine nucleos(t)ides on pregnancy and breastfeeding has not been evaluated in humans. Animal data do not indicate direct or indirect harmful effects with respect to reproductive toxicity at doses up to 2000mg/kg/day in rats and 600mg/kg/day in rabbits.

Population in need of further characterization:

While endogenous pyrimidine nucleosides and nucleotides are present naturally in human milk, the safety and efficacy of doxecitine and doxribtimine in pregnant or breastfeeding women are not established.

Part II Module SVIII Summary of the safety concerns

Table Part II–14: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Liver dysfunction
Missing information	Long-term safety in patients with TK2d symptom onset ≤2 years and symptom onset >2 to ≤12 years
	Use during pregnancy and breastfeeding

TK2d=thymidine kinase 2 deficiency

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for safety concerns: None
- Other forms of routine pharmacovigilance activities: In addition to AE reporting and standard signal detection practices, there will be continued surveillance for AEs of interest in post-marketing safety data and throughout the ongoing studies in the doxecitine and doxribtimine development program.

III.2 Additional pharmacovigilance activities

III.2.1 Post-authorization safety study TK0109

Study short name and title:

A post-authorization noninterventional study to describe safety and clinical outcomes of doxecitine and doxribtimine treatment in patients with thymidine kinase 2 deficiency (TK2d) with age of symptom onset on or before 12 years

Primary objective

- To describe the safety of doxecitine and doxribtimine (KYGEVVI) in the treatment of patients with genetically confirmed TK2d with an age of symptom onset on or before 12 years (including patients with TK2d symptom onset ≤2 years and patients with TK2d symptom onset >2 to ≤12 years).
- To describe the frequencies of (serious) adverse drug reactions and (serious) AEs leading to discontinuation or interruption.
- To describe safety topics of interest, including treatment-emergent liver dysfunction, diarrhea, vomiting, and abdominal pain (including abdominal pain upper) among TK2d patients.

Secondary objectives

- To describe clinical outcomes for the targeted study population, including developmental motor milestones as well as ventilatory and feeding support, during the course of the study. Additional secondary outcomes are to describe activities of daily living and health-related quality of life of patients and caregivers.
- To describe pregnancy and birth outcomes in TK2d pregnant women exposed to doxecitine and doxribtimine, and infant outcomes up to the first year of life.

Study design:

Post-authorization, noninterventional study

Study population:

Pediatric and adult patients with genetically confirmed TK2d with an age of symptom onset on or before 12 years who are currently receiving prescription doxecitine and doxribtimine (KYGEVVI) will be eligible to enroll in this study.

Approximately 50 to 80 patients globally are anticipated to enroll in the study during the 3-year enrollment period.

Milestones:

Protocol submission: within 6 months of marketing authorization in Europe

Intermediate report: annually

For further details please see EU-RMP Part VII Annex 3 for the study concept document.

III.3 Summary Table of additional Pharmacovigilance activities

The summary of ongoing and planned additional pharmacovigilance activities is provided in Table Part III–1.

Table Part III–1: Ongoing and planned additional Pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
TK0109 - A post-authorization noninterventional study Planned	To describe the safety and clinical outcomes of doxecitine and doxribtimine treatment	Important potential risk: Liver dysfunction Missing information: Long-term safety in patients with TK2d symptom onset ≤2 years and symptom onset >2 to ≤12 years; use during pregnancy and breastfeeding	Protocol submission	Within 6 months of marketing authorization in Europe
			Intermediate report	Annually

TK2d=thymidine kinase 2 deficiency

PART IV PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed post-authorization efficacy studies that are conditions of the marketing authorisation or that are specific obligations for doxecitine and doxribtimine.

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 Routine Risk Minimization Measures

Description of routine risk minimization measures by safety concern is presented in Table Part V–1.

Table Part V–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
None	
Important potential risks	
Liver dysfunction	**Routine risk communication**: SmPC Section 4.4 (Special warnings and precautions for use) **Routine risk minimization activities recommending specific clinical measures to address the risk**: Transaminase levels should be checked prior to initiation of treatment, and changes in liver function monitored periodically during treatment with KYGEVVI and according to routine patient management. SmPC Section 4.4 (Special warnings and precautions for use) **Other routine risk minimization measures beyond the Product Information:** KYGEVVI is intended for use with the instructions and supervision of specialist healthcare professionals experienced in the management of patients with mitochondrial disorders (SmPC Section 4.2 [Posology and method of administration]) PL Section 3 (How to take KYGEVVI)

Table Part V–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Missing information	
Long-term safety in patients with TK2d symptom onset ≤2 years and symptom onset >2 to ≤12 years	**Routine risk communication:** The frequencies of adverse reactions are based on pooled data from clinical studies (MT-1621-101 and TK0102) in 50 patients who were exposed to KYGEVVI for a median of 78.2 months (min 4, max 157 months), at a median maintenance dose of 387.2mg/kg/day of doxecitine and 387.2mg/kg/day of doxribtimine (min 170, max 400mg/kg/day) (SmPC Section 4.8 [Undesirable effects]) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Use during pregnancy and breastfeeding	**Routine risk communication**: SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) PL Section 2 (What you need to know before you use KYGEVVI) **Routine risk minimization activities recommending specific clinical measures to address the risk**: SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) PL Section 2 (What you need to know before you use KYGEVVI) **Other routine risk minimization measures beyond the Product Information:** KYGEVVI is intended for use with the instructions and supervision of specialist healthcare professionals experienced in the management of patients with mitochondrial disorders (SmPC Section 4.2 [Posology and method of administration]) PL Section 3 (How to take KYGEVVI)

PL=patient information leaflet; SmPC=summary of product characteristics; TK2d=thymidine kinase 2 deficiency

V.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Section V.1 are sufficient to manage the safety concerns of the medicinal product. Additional risk minimization measures are not considered necessary.

V.3 Summary of risk minimization measures

Table Part V–2 provides a summary table of pharmacovigilance activities and risk minimization activities by safety concern.

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important potential risk		
Liver dysfunction	**Routine risk minimization measures:** KYGEVVI is intended for use with the instructions and supervision of specialist healthcare professionals experienced in the management of patients with mitochondrial disorders SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.4 (Special warnings and precautions for use) PL Section 3 (How to take KYGEVVI) **Additional risk minimization measures:** None	**Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detections:** None **Additional Pharmacovigilance activities:** Post authorization safety study TK0109
Missing Information		
Long-term safety in patients with TK2d symptom onset ≤2 years and symptom onset >2 to ≤12 years	**Routine risk minimization measures:** KYGEVVI is intended for use with the instructions and supervision of specialist healthcare professionals experienced in the management of patients with mitochondrial disorders (SmPC Section 4.2 Posology and method of administration) PL Section 3 (How to take KYGEVVI) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Post authorization safety study TK0109
Use during pregnancy and breastfeeding	**Routine risk minimization measures:** KYGEVVI is intended for use with the instructions and supervision of specialist healthcare professionals experienced in the management of patients with mitochondrial disorders (SmPC Section 4.2 [Posology and method of administration]) SmPC Section 4.6 (Fertility, Pregnancy, and Lactation)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Post authorization safety study TK0109

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
	PL Section 2 (What you need to know before you take KYGEVVI) PL Section 3 (How to take KYGEVVI) **Additional risk minimization measures:** None	

PL=patient information leaflet; SmPC=summary of product characteristics; TK2d=thymidine kinase 2 deficiency

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR KYGEVVI

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

KYGEVVI's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how KYGEVVI should be used.

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

Important new concerns or changes to the current ones will be included in updates of KYGEVVI's RMP.

I The medicine and what it is used for

KYGEVVI is authorized for the treatment of pediatric and adult patients with genetically confirmed thymidine kinase 2 deficiency with an age of symptom onset on or before 12 years (see SmPC for the full indication). It contains doxecitine and doxribtimine as the active substances and it is given orally. If the patient is unable to swallow, the prescribed dose of KYGEVVI can be administered via a feeding tube.

Further information about the evaluation of KYGEVVI's benefits can be found in KYGEVVI's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/kygevvi

II Risks associated with the medicine and activities to minimize or further characterise the risks

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

Measures to minimize 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization 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*.

If important information that may affect the safe use of KYGEVVI is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of KYGEVVI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered/taken. 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 KYGEVVI. 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.

List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	Liver dysfunction
Missing information	Long-term safety in patients with TK2d symptom onset ≤2 years and symptom onset >2 to ≤12 years Use during pregnancy and breastfeeding

TK2d=thymidine kinase 2 deficiency

II.B Summary of important risks

There are no important identified risks for doxecitine and doxribtimine. A summary of important potential risks is provided in the below table.

Summary of important potential risks

Important potential risk: Liver dysfunction	
Evidence for linking the risk to the medicine	Elevations in transaminases have been frequently reported amongst the participants with TK2d treated with doxecitine and doxribtimine in the clinical studies MT-1621-101 and TK0102. There is no obvious link between the mechanism of action of doxecitine and doxribtimine and liver enzyme elevations. Potential treatment-related exacerbations of clinical relevance (eg, liver dysfunction/failure), though not observed in clinical studies, cannot be fully excluded to date.
Risk factors and risk groups	Patients with TK2d may have pre-existing liver enzyme elevations to varying degrees (Berardo et al, 2022; Wang et al, 2018).

Summary of important potential risks

Important potential risk: Liver dysfunction	
Risk minimization measures	Routine risk minimization measures: Product labeling Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post authorization safety study TK0109 See Section II.C of this summary for an overview of the post-authorisation development plan.

TK2d=thymidine kinase 2 deficiency

A summary of missing information is provided in the below table.

Summary of missing information

Missing information: Long-term safety in patients with TK2d symptom onset ≤2 years and symptom onset >2 to ≤12 years	
Risk minimization measures	Routine risk minimization measures: Product labeling Additional risk minimization measures: None
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: Post authorization safety study TK0109 See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use during pregnancy and breastfeeding	
Risk minimization measures	Routine risk minimization measures: Product labelling Additional risk minimization measures: None
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: Post authorization safety study TK0109 See Section II.C of this summary for an overview of the post-authorisation development plan.

TK2d=thymidine kinase 2 deficiency

II.C Postauthorization development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study (TK0109) is a condition of the marketing authorisation:

Study short name: A post-authorization noninterventional study to describe safety and clinical outcomes of doxecitine and doxribtimine treatment in patients with thymidine kinase 2 deficiency (TK2d) with age of symptom onset on or before 12 years.

Purpose of the study:

Primary objective

- To describe the safety of doxecitine and doxribtimine (KYGEVVI) in the treatment of patients with genetically confirmed TK2d with an age of symptom onset on or before 12 years (including patients with TK2d symptom onset ≤2 years and patients with TK2d symptom onset >2 to ≤12 years.
- To describe the frequencies of (serious) adverse drug reactions and (serious) AEs leading to discontinuation or interruption.
- To describe safety topics of interest, including treatment-emergent liver dysfunction, diarrhea, vomiting, and abdominal pain (including abdominal pain upper) among TK2d patients.

Secondary objectives

- To describe clinical outcomes for the targeted study population, including developmental motor milestones as well as ventilatory and feeding support, during the course of the study. Additional secondary outcomes are to describe activities of daily living and health-related quality of life of patients and caregivers.
- To describe pregnancy and birth outcomes in TK2d pregnant women exposed to doxecitine and doxribtimine, and infant outcomes up to the first year of life.

II.C.2 Other studies in post-authorisation development plan

There are no other studies required for KYGEVVI.

PART VII ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable.