EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP)

Active substance (International Nonproprietary Name or common name)	Tovorafenib (IPN60310)
Pharmaco-therapeutic group (Anatomical Therapeutic Chemical (ATC) Code):	L01EC04
Name of Marketing Authorisation Holder (MAH) or Applicant:	Ipsen Pharma
Number of medicinal products to which this Risk Management Plan (RMP) refers:	1
Product concerned (brand name):	Ojemda

Data lock point for this RMP: 13 August 2024
Version Number: 1.0
Date of final sign off: 27 February 2026

Rationale for submitting an updated RMP: Not Applicable, as this is the first approved version of the EU RMP.

Qualified Person for Pharmacovigilance (QPPV) name:
Frédérique Korn

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation QPPV. The electronic signature is available on file.

[redacted]

Administrative information on the Risk Management Plan (RMP)

Table 1 Summary of Significant Changes in this RMP

Part	Module/Annex	Significant changes in this RMP*
Part I Product Overview		Not Applicable
Part II Safety Specification	**Module SI** Epidemiology of the Indication(s) and Target Population(s)	Not Applicable
	Module SII Nonclinical Part of the Safety Specification	Not Applicable
	Module SIII Clinical Trial Exposure	Not Applicable
	Module SIV Populations Not Studied in Clinical Trials	Not Applicable
	Module SV Post-authorisation Experience	Not Applicable
	Module SVI Additional European Union (EU) Requirements for the Safety Specification	Not Applicable
	Module SVII Identified and Potential Risks	Not Applicable
	Module SVIII Summary of the Safety Concerns	Not Applicable
Part III Pharmacovigilance Plan (Including Post-authorisation Safety Studies)		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)		Not Applicable
Part VI Summary of the RMP		Not Applicable
Part VII Annexes	Annex 1 EudraVigilance Interface	Not Applicable
	Annex 2 Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme	Not Applicable
	Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan	Not Applicable

Part	Module/Annex	Significant changes in this RMP*
	Annex 4 Specific Adverse Drug Reaction Follow-Up Forms	Not Applicable
	Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV	Not Applicable
	Annex 6 Details of proposed Additional Risk Minimisation Activities (If applicable)	Not Applicable
	Annex 7 Other Supporting Data (Including Referenced Material)	Not Applicable
	Annex 8 Summary of Changes to the RMP Over Time	Not Applicable

Abbreviations: EU=European Union; RMP= risk management plan.

*All changes are Not Applicable as this is the first approved EU RMP for tovorafenib.

Other RMP versions under evaluation:

There are no other RMP versions under evaluation.

Details of the currently approved RMP:

Table 2 Details of the Currently Approved RMP

Version number	1.0
Approved with procedure	EMEA/H/C/0006140 - Initial MAA
Date of approval (opinion date)	26 February 2026

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LIST OF ABBREVIATIONS

Abbreviation	Wording definition
AE	Adverse event
AESI	Adverse event of special interest
BRAF	V-Raf murine sarcoma viral oncogene homolog B
CBR	Clinical benefit rate
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
COG-V/C	Children's oncology group-vincristine/carboplatin
CR	Complete response
CRAF	V-Raf murine sarcoma viral oncogene homolog C
CYP	Cytochrome P450
DOR	Duration of response
EFS	Event-free survival
EOT	End of treatment
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GD	Gestation day
HRQoL	Health-related quality of life
IRC	Independent Review Committee
LTFU	Long-term follow-up
MAPK	Mitogen activated protein kinase
MEK	Mitogen activated protein kinase kinase
MR	Minor response
mTORC	Mammalian target of rapamycin complex
NF1	Neurofibromatosis type 1
ORR	Overall/Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
pLGG	Paediatric low-grade gliomas
PSUR	Periodic safety update reports
RAF	Rapidly accelerated fibrosarcoma
RANO-HGG	Response assessment in neuro-oncology-high-grade glioma
RANO-LGG	Response assessment in neuro-oncology-low grade glioma
RAPNO	Response assessment in paediatric neuro-oncology
RMP	Risk management plan
SIOPe-LGG-V/C	International society for paediatric oncology-low-grade glioma vincristine/carboplatin
SmPC	Summary of product characteristics
SoC	Standard of care
TTR	Time to response
US	United States
UV	Ultraviolet
VABS	Vineland adaptive behaviour composite scales
VBL	Vinblastine

PART I: PRODUCT OVERVIEW

Table 3 Product Overview

Active substance(s) (International Non-proprietary Name (INN) or common name)	Tovorafenib
Pharmacotherapeutic group(s) (ATC Code)	L01EC04
Marketing authorisation applicant	Ipsen Pharma
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ojemda
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Tovorafenib is an oral, potent, Type II RAF inhibitor of mutant BRAF V600E, wild-type BRAF and wild-type CRAF kinases with in vitro IC_{50} values of 7.1, 10.1 and 0.7 nM, respectively.
	Summary of mode of action Tovorafenib is a Type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases, with in vitro IC_{50} values of 7.1, 10.1, and 0.7 nM, respectively. Tovorafenib exhibited antitumour activity in cultured cells and xenograft tumour models harbouring BRAF V600E and V600D mutations. Tovorafenib also exhibited antitumour activity in a xenograft tumour model harbouring a BRAF fusion, without inducing paradoxical activation of the MAPK pathway as observed with Type I BRAF inhibitors.
	Important information about its composition No important information available.
Hyperlink to the Product Information	Ojemda® Product Information (Module 1.3.1)
Indication in the EEA	**Current**: Ojemda is indicated as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (pLGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies.
	Proposed: Not applicable.
Dosage in the EEA	**Current**: Recommended dose is 380 mg/m^2 orally once weekly (not to exceed 600 mg) according to body surface area to be taken with or without food.
	Proposed: Not applicable.
Pharmaceutical form and strengths	**Current**: 100 mg immediate release tablet and oral suspension (25 mg/mL, supplied as a powder for oral suspension).
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: ATC=anatomical therapeutic chemical; BRAF=v-raf murine sarcoma viral oncogene homolog B; CRAF=v-raf murine sarcoma viral oncogene homolog C; EEA=European economic area; EU=European Union; IC_{50}=half maximal inhibitory concentration; INN=International nonproprietary name; pLGG=paediatric low-grade glioma; MAPK=mitogen-activated protein kinase; RAF=rapidly accelerated fibrosarcoma; RMP=risk management plan.

PART II: SAFETY SPECIFICATION

Part II: Module SI – Epidemiology of the Indication(s) and Target Population(s)

Ojemda is indicated as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (pLGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies.

Incidence:

Paediatric low-grade gliomas and glioneuronal tumours (subsequently referred to as pLGG) represent the most frequently encountered brain tumours accounting for nearly 30% of paediatric central nervous system (CNS) neoplasms overall [1]. As noted above, BRAF alterations are the most common oncogenic factors in low-grade paediatric gliomas and are present in up to 70% of low-grade paediatric gliomas [2,3,4].

Primary CNS tumours in children are rare events, with an age-standardised incidence rate of 2.1 per 100,000 individuals aged 0 to 19 years in European Union (27) (EU-27) (Cancer Today database, 2022). It was assumed based on the assumption that low-grade glioma represents 30% of CNS neoplasms, the incidence of pLGG was 0.63 per 100,000 individuals aged 0 to 19 years. And that 70% of them have BRAF alterations, the incidence was 0.44 per 100,000 individuals aged 0 to 19 years.

Cancers of the brain and the CNS are the most frequently diagnosed solid malignant tumours in children, with an incidence of 5.21 per 100,000 in individuals aged 0 to 25 years [5].

Of those, pLGG constitute the most common brain tumours, with an incidence of 1.3 to 2.1 per 100,000 in the United States (US) [6,4]. In 2021, the total annual incidence of pLGG among individuals aged under 25 years in the US was estimated at ~2600 [7,8]. Paediatric LGG occurs mainly in children and young adults with a peak incidence in the 5 to 9-year-old range [9]. There are about 150 cases of childhood low-grade gliomas a year in the United Kingdom [10]. They can occur anywhere within the CNS, including the cerebellum (15%–25%), cerebral hemisphere (10%–15%), optic pathway (5%), spinal cord (5%), or brain stem (2%–4%) [9]. The precise incidence of low-grade gliomas is a shifting target since adopting 2016 World Health Organisation CNS classification among tumour registries is just beginning. Based on the studies using the previous classification, the incidence of Grade 2 oligodendrogliomas is 0.25, for astrocytomas is 0.51, and for mixed glioma is 0.20 per 100,000 per year in the US [11]. Low-grade gliomas occur more commonly in the younger age group between 20 and 40 years [12]. The peak incidence for oligodendrogliomas is 40 to 45 years, whereas for astrocytomas, considering all mutation types, is 30 to 40 years [11]. Most rapidly accelerated fibrosarcoma (RAF) alterations are seen in children and younger adults. The older adult's low-grade gliomas tend not to have RAF alterations but more isocitrate dehydrogenase 1 and alpha-thalassemia/mental retardation, X-linked [13].

Prevalence:

For the years between 2016 and 2020, the 5-year prevalence counts for glioma in the European Economic Area ranged from 32,758 to 52,413 cases, based on the assumption that glioma represents 25% to 40% of all brain/CNS tumours, respectively, and corresponding prevalence rates range from 0.7 to 1.2 per 10,000 persons. Even 10-year prevalence estimates, using the more robust assumption that glioma represents 40% of all brain/CNS tumours, results in a prevalence rate of only 2.3 per 10,000 persons [2,3,4].

Among individuals aged 0-18 years, the complete prevalence of BRAF-altered low-grade glioma subtypes in the US in 2019 was 7813 cases. Among those aged 19 years and older, the complete prevalence of BRAF-altered low-grade glioma subtypes in the US in 2019 was 21,584 cases. The complete prevalence of all BRAF-altered low-grade glioma subtypes for all ages in the US in 2019 was 29,398 cases.

Demographics of the population in the authorised indication:

Patients 6 months of age and older.

Like most brain tumours, the cause of low-grade gliomas is unknown in most cases. However, some are associated with a genetic condition called neurofibromatosis type 1 (NF1) (NHS 2024). There are no known causes of gliomas, and the risk factors favouring the development are poorly understood.

Therapeutic irradiation is the only major environmental factor increasing the risk of all brain tumours, including low-grade gliomas [14]. Low-grade gliomas are slightly more common in males [11].

The main existing treatment options:

Paediatric low-grade gliomas are treated through a combination of approaches tailored to each patient's needs. Surgery is often the first step, with complete resection being the most favourable predictor of patient outcome. For approximately one-half of patients, this single surgical approach is curative [15]. However, complete resection is not always feasible, especially for highly infiltrative or deep-seated tumours which have a high-risk of functional impact if the tumour were completely removed.

For patients whose disease recurs after surgery or for whom surgery was not an option, chemotherapy is commonly used in first-line therapy, especially in younger children, to avoid the long-term effects of radiation. There are no approved chemotherapy regimens for paediatric low-grade glioma, but carboplatin and vincristine is a widely used combination [16,17] as well as single agent vinblastine [18].

Targeted therapies, such as BRAF and mitogen activated protein kinase kinase (MEK) inhibitors, are increasingly used for tumours with specific genetic mutations. Recently, the combination of dabrafenib plus trametinib recently received US Food and Drug Administration (FDA) approval (November 2023) and European Medicines Agency approval (January 2024) for the treatment of paediatric patients 1 year of age and older with low-grade glioma harbouring a BRAF V600E mutation who require systemic therapy [19,20]. For patients with relapsed or recurrent paediatric low-grade glioma (those with BRAF fusions or those without BRAF alterations), there were no approved agents and there is no established standard of care. The combination of dabrafenib plus trametinib may be used for those patients with low-grade glioma harbouring a BRAF V600E mutation. Chemotherapy may be attempted again, or a targeted therapy may be offered [21].

Radiotherapy is typically reserved as a last resort, particularly for older peadiatric patients in the salvage setting, as radiation has been associated with cognitive decline, endocrine deficiencies, secondary malignancies/malignant transformation, vascular damage, and growth abnormalities in survivors of paediatric brain tumours [22].

In some cases, careful observation without immediate intervention is recommended, particularly if the tumour is not causing significant symptoms. Treatment choices depend on clinical presentation, tumour location, operability, histology and molecular profile. An observation-only approach is appropriate in asymptomatic patients without evidence of tumour growth.

Natural history of the paediatric low-grade glioma condition in the untreated population, including mortality and morbidity:

Paediatric low-grade glioma can be diagnosed in patients of all ages, with a median age between 6.7 and 10.2 years [23, 24]. The prognosis for pLGG is generally favourable, with an overall survival (OS) rate of 85 to 96% at 10 years [25,26,27] and, in contrast to adult low-grade gliomas, rarely undergo malignant transformation [28].

Even pLGGs are histologically benign tumours can be associated with substantial adverse effects on health, including but not limited to significant morbidity and even life-threatening consequences as a result of their capacity to occupy space within the cranium and exert effects of local infiltration [29]. Many patients suffer profound tumour- and treatment-associated morbidity, including cognitive, physical, neurological, and endocrinological deficits, leading to disability, reduced quality of life, and poorer socioeconomic outcomes [30,31]. The chances for cure in children with relapsed or refractory pLGG are minimal, which illustrates an unmet medical need for innovative treatment strategies in this population. Paediatric low-grade gliomas typically become quiescent, or senescent, as patients enter the third decade of life, underscoring the need for treatments which control tumour growth while reducing long-lasting side effects that may compromise the quality of life and quality of survivorship [25,26,27].

Paediatric low-grade gliomas in contrast to adult low-grade gliomas, rarely undergo malignant transformation [28]. However, even histologically benign tumours can be associated with significant morbidity or be life-threatening because of their space-occupying effects within the cranium and effects of local infiltration [29]. Spontaneous regression has not been widely reported in the literature. Of the factors that have been suggested as positive associations for potential tumour regression, the association with neurofibromatosis type 1 (NF1) has been more widely reported [25,32].

Important comorbidities:

For children with low-grade gliomas, both the tumour and the required treatment(s) can result in varying degrees of cognitive, physical, neurologic, and endocrinologic deficits, such as vision, seizures, growth delay, hypothyroid, delayed or early onset puberty. Adult survivors of paediatric low-grade glioma are at increased risk for long-term disabilities, such as visual or motor impairment, neurocognitive impairment, and lower socioeconomic status [30,31], and for those who require or receive radiation therapy, an increased risk of secondary neoplasms and stroke [33,34].

Part II: Module SII – Nonclinical Part of the Safety Specification

Key safety findings from nonclinical studies and relevance to human usage:

Table 4 Summary of Key Findings from Nonclinical Studies

Study type	Key finding(s)	Relevance to human usage
Acute or repeat-dose toxicity	Initial repeat-dose toxicity studies demonstrated a QD regimen of tovorafenib was not tolerated in rats and monkeys, as mortality was observed in 14-day non-GLP daily oral gavage dosing studies in female rats (≥500 mg/kg/day) and monkeys (≥3 mg/kg/day). Slight accumulation of tovorafenib was noted with daily dosing in both species. Subsequent dose range-finding studies were performed with Q2D, Q3D, and/or QW regimens, which demonstrated improved tolerability of tovorafenib when administered less frequently. Tovorafenib was tolerated in 4-week GLP studies in rats and monkeys at doses up to 500 and 30 mg/kg Q2D, respectively (the highest doses tested) and in 3-month GLP toxicity studies at doses up to 500 mg/kg Q2D in rats, 20 mg/kg Q2D in male monkeys, and 3 mg/kg Q2D in female monkeys.	The pivotal GLP toxicology studies were conducted with a Q2D regimen, which is more frequent than the QW clinical regimen of 600 mg or 420 g/m^2 (in paediatric patients) tovorafenib due to differences in half-life. The US approved paediatric dose is 380 mg/m^2 QW (maximum of 600 mg) which is now used in ongoing clinical studies instead of 420 mg/m^2.
Reproductive/ developmental toxicity	A preliminary embryo-foetal development study was conducted in rats. Tovorafenib administered daily from gestation Day 7 to 17 at doses ≥37.5 mg/kg resulted in 100% resorption of fetuses in rats. Therefore, there were no fetuses available for evaluation. In a fertility and early embryonic development study in female rats, tovorafenib decreased the number of pregnancies, corpora lutea and live embryos, as well as increased post-implantation losses at doses as low as 37.5 mg/kg/day (approximately 0.8-fold the human exposure at the recommended dose based on AUC). In male rats, there were no tovorafenib-related effects on any mating or fertility or sperm (motility and density) parameters and reproductive organs.	Women of childbearing potential should be cautioned about the adverse and possibly lethal effects of tovorafenib on a conceptus/foetus. Males should not impregnate.

Study type	Key finding(s)	Relevance to human usage
	In repeat- dose toxicology studies in rats of up to three months duration, in male rats, tovorafenib reduced weights of epididymis and testes, which correlated with reversible tubular degeneration/atrophy of the testes and reduced epididymal sperm at approximately 0.3-fold the human exposure at the recommended dose based on AUC.	
Genotoxicity	Tovorafenib was negative in both a non-GLP screening and GLP Ames bacterial reverse mutation assay, indicating that tovorafenib is not mutagenic. Tovorafenib was negative in the rat bone marrow micronucleus assay at doses up to 2000 mg/kg. Tovorafenib was also negative for inducing chromosomal aberrations in cultured human lymphocytes without metabolic activation (all concentrations) and was negative with metabolic activation (S9) at ≤172 mcg/mL (initial assay) and ≤150 mcg/mL (confirmatory assay). Tovorafenib was positive in the chromosomal aberration assay in the presence of S9 at 200 and 245 mcg/mL, both of which showed some precipitation in the cultures.	It is unlikely that a single positive result at only two concentrations in the presence of a drug precipitate is biologically relevant.
Carcinogenicity	Tovorafenib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Tovorafenib was not genotoxic in cultured human lymphocytes without metabolic activation. Tovorafenib induced chromosomal aberrations in cultured human lymphocytes with metabolic activation at a single concentration in vitro. Tovorafenib was not genotoxic in an in vivo rat bone marrow micronucleus assay. Tovorafenib was not carcinogenic in a 26-week study in transgenic mice at exposures approximately 0.6-fold the human exposure (AUC) at the recommended human dose.	No risk has been identified.
Safety pharmacology	In an in vitro pharmacological hERG assay, the IC_{50} for hERG channel inhibition was 8.9 µM tovorafenib (free drug concentration). In the hERG Lite assay, no inhibition of hERG channel trafficking to the cell membrane was observed at concentrations up to 30 µM. Single oral administration of tovorafenib to rats at doses up to and including 1500 mg/kg did not alter CNS activity or	Based on the C_{max} observed at the clinical dose of 600 mg QW, the potential risk for hERG inhibition is considered low. Overall, the in vitro and in vivo cardiovascular safety pharmacology data support a low risk for cardiovascular liabilities.

Study type	Key finding(s)	Relevance to human usage
	change excitability reactions and was not associated with any adverse changes to respiratory parameters, including respiratory rates, tidal volumes, or minute volumes. Autonomic nervous system parameters, sensorimotor reactions, neuromuscular function, and body temperature were not significantly altered after administration of tovorafenib. The NOAEL was 1500 mg/kg orally administered tovorafenib. In a non-GLP study in telemetered dogs, increased HR (up to ~50 bpm); diastolic arterial pressure, SAP, and mean arterial pressure (up to 60 mmHg); and body temperature (up to 3°C) were seen in dogs at 25 mg/kg (increased HR only) and 125 mg/kg. The potential effects of tovorafenib on the cardiovascular system were evaluated in a GLP study in cynomolgus monkeys. Single oral gavage administration of tovorafenib to telemetered monkeys (3/sex/group) at doses up to and including 60 mg/kg was not associated with any adverse changes to cardiovascular parameters, including HR, electrocardiogram intervals, core body temperature, and blood pressure. Mild increases (within normal ranges) in HR at 10, 30, and 60 mg/kg and blood pressure (SAP and mean arterial pressure) at 60 mg/kg were noted in monkeys.	
Other - Phototoxicity	The photo absorption spectrum for tovorafenib exhibits a peak at 302 nm, which is within the zone of concern for photo safety (i.e., 290 to 700 nm). The QWBA assessment in male LE rats after single oral gavage administration of [^{14}C] tovorafenib demonstrated that [^{14}C] tovorafenib derived radioactivity was present in melanin-containing tissues (e.g. skin pigmented and eye uveal tract). Concentrations in pigmented skin were notably higher than concentrations observed in nonpigmented skin.	Based on these findings and the safety profile assessment, routine pharmacovigilance activities are deemed sufficient for characterisation of this risk.

Abbreviations: AUC=area under the curve; bpm=beats per minute; C_{max}=maximum plasma concentration; CNS=central nervous system; GLP=good laboratory practice; hERG=human ether à go go–related gene; HR=heart rate; IC_{50}=half-maximal inhibitory concentration; LE=Long-Evans; NOAEL=no observed adverse effect level; Q2D=every second day; Q3D=every third day; QD=every day, QW=every week; QWBA=quantitative whole body autoradiography; SAP=systolic arterial pressure; US=United States.

Part II: Module SIII – Clinical Trial Exposure

The completed clinical trials contributing exposure information include:

- C28001: An open-label, phase I, dose escalation study of MLN2480 in patients with relapsed or refractory solid tumours followed by a dose expansion phase in patients with metastatic melanoma.

- C28002: A multi-arm, open-label, phase Ib study of MLN2480 (an oral A-, B-, and v-raf murine sarcoma viral oncogene homolog C (CRAF) inhibitor) in combination with MLN0128 (an oral mammalian target of rapamycin complex (mTORC) 1/2 Inhibitor), or alisertib (an oral Aurora A kinase inhibitor), or paclitaxel, in adult patients with advanced nonhaematologic malignancies.
- QSC205140: A two-part, phase I study to evaluate the taste profile and relative bioavailability assessment of novel DAY101 paediatric suspension formulations compared with the DAY101 tablet formulation and a food effect assessment of the DAY101 tablet formulation in healthy subjects.
- DAY101-103: A phase I, open-label study of the absorption, metabolism, and excretion of [^{14}C]-DAY101 following a single oral dose in healthy male subjects.

The ongoing clinical trials, conducted by business partner Day One Biopharmaceuticals, Inc. (Day One) (Ipsen and Day One will be collectively called as the sponsor) contributing exposure information with a data lock point of 13 August 2024, include:

- DAY101-001/PNOC026: FIREFLY-1: A phase II, open-label, multicenter study to evaluate the safety and efficacy of the oral pan-RAF inhibitor DAY101 in paediatric patients with BRAF-altered, recurrent or progressive LGG and advanced solid tumours.
- DAY101-102a: A phase II, subprotocol of DAY101 monotherapy for patients with recurrent, progressive, or refractory solid tumours with mitogen activated protein kinase (MAPK) pathway aberrations.
- DAY101-102b: A phase Ib/2, subprotocol of DAY101 in combination with pimasertib for patients with recurrent, progressive, or refractory solid tumours and MAPK pathway aberrations.

Table 5 through Table 11 presented data by all exposures (all indication), patients with LGGs, patients with solid tumours, and healthy participants, where applicable data is available per trial population. Studies with LGGs are in paediatrics and studies in solid tumours and healthy participants are in adults.

Table 5 Duration of Exposure

Duration of exposure		
Cumulative for all indications	**Patients**	**Person time (months)**
≥6 months	160	3106.14
≥12 months	123	2794.12
≥18 months	98	2415.21
≥24 months	37	1032.38
Total	459	3670.31
Patients with Low-grade Glioma		
≥6 months	119	2553.99
≥12 months	108	2454.18
≥18 months	92	2211.88
≥24 months	33	874.35
Total	137	2609.61
Patients with Solid Tumours		
≥6 months	41	552.15
≥12 months	15	339.94
≥18 months	6	203.33
≥24 months	4	158.03
Total	303	1043.94
Healthy Participants		
≥6 months	0	0
≥12 months	0	0
≥18 months	0	0
≥24 months	0	0
Total	19	16.76

Table 6 Age Group and Gender

Cumulative for all indications				
Age group	**Patients**		**Person time (months)**	
	Male	**Female**	**Male**	**Female**
0 months to <2 years	2	1	41.23	22.05
2 years to <6 years	16	11	343.00	259.48
6 years to <12 years	35	32	694.28	581.39
12 years to <18 years	21	19	330.65	266.22
18 years to <65 years	94	104	325.85	406.90
≥65 years	67	57	146.14	253.14
Total	235	224	1881.13	1789.18
Patients with low-grade glioma				
0 months to <2 years	2	1	41.23	22.05
2 years to <6 years	16	11	343.00	259.48
6 years to <12 years	35	31	694.28	580.90
12 years to <18 years	18	17	318.36	261.49
18 years to <65 years	2	4	36.34	52.50
≥65 years	0	0	0	0
Total	73	64	1433.20	1176.41
Patients with solid tumours				
0 months to <2 years	0	0	0	0
2 years to <6 years	0	0	0	0
6 years to <12 years	0	1	0	0.49
12 years to <18 years	3	2	12.29	4.73
18 years to <65 years	79	94	280.80	346.35
≥65 years	67	57	146.14	253.14
Total	149	154	439.23	604.71
Healthy participants				
0 months to <2 years	0	0	0	0
2 years to <6 years	0	0	0	0
6 years to <12 years	0	0	0	0
12 years to <18 years	0	0	0	0
18 years to <65 years	13	6	8.71	8.05
≥65 years	0	0	0	0
Total	13	6	8.71	8.05

Table 7 Exposure by Starting Dose in mg – Dosed Every Second Day

Dose of exposure	Patients	Person time (months)
Patients with solid tumours		
20 mg Q2D	4	7.79
40 mg Q2D	3	3.58
80 mg Q2D	3	2.79
135 mg Q2D	3	4.17
200 mg Q2D	94	367.47
280 mg Q2D	7	36.73
Total	114	422.54

Abbreviation: Q2D=every second day.

Table 8 Exposure by Starting Dose in mg – Dosed Weekly

Dose of exposure	Patients	Person time (months)
Patients with solid tumours		
200 mg QW	9	44.09

Dose of exposure	Patients	Person time (months)
300 mg QW	1	3.48
400 mg QW	48	132.67
500 mg QW	9	13.47
600 mg QW	80	295.00
800 mg QW	4	6.340
Total	151	495.05

Abbreviation: QW=every week.

Table 9 Dose Calculated for Body Surface Area – Dosed Weekly

Dose of exposure	Patients	Person time (months)
All participants		
380 mg/m^2	0	0
420 mg/m^2	143	2627.12
Total	143	2627.12
Patients with low-grade glioma		
380 mg/m^2	0	0
420 mg/m^2	137	2609.61
Total	137	2609.61
Patients with solid tumours		
380 mg/m^2	0	0
420 mg/m^2	6	17.51
Total	6	17.51

Table 10 Exposure with Other Doses

Dose of exposure	Patients	Person time (months)
All participants		
100 mg single dose	7	0.23
300 mg max dose	12	16.53
100 mg QOD	19	70.37
160 mg QOD	10	31.64
200 mg QOD	3	6.83
Total	51	125.60
Patients with solid tumours		
100 mg QOD	19	70.37
160 mg QOD	10	31.64
200 mg QOD	3	6.83
Total	32	108.85
Healthy participants		
100 mg single dose	7	0.23
300 mg max dose	12	16.53
Total	19	16.76

Abbreviations: max=maximum; QOD=every other day.

Table 11 Ethnic Origin

Ethnic origin	Patients	Person time (months)
All indications		
White	353	2554.23
Black or African American	18	70.80
Asian	23	240.20
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Island	0	0
Multiple	4	57.72
Other	14	186.91
Not reported	47	560.46
Total	459	3670.31

Ethnic origin	Patients	Person time (months)
All indications		
Patients with low-grade glioma		
White	87	1693.37
Black or African American	3	52.73
Asian	10	177.94
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Island	0	0
Multiple	3	53.78
Other	8	146.50
Not reported	26	485.29
Total	137	2609.61
Patients with solid tumours		
White	252	847.01
Black or African American	10	15.15
Asian	13	62.26
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Island	0	0
Multiple	1	3.94
Other	6	40.41
Not reported	21	75.17
Total	303	1043.94
Healthy participants		
White	14	13.83
Black or African American	5	2.92
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Island	0	0
Multiple	0	0
Other	0	0
Not reported	0	0
Total	19	16.76

Part II: Module SIV – Populations Not Studied in Clinical Trials

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

Table 12 Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion criteria	Reason for exclusion	Missing information (Yes/No)	Rationale
Tumour with previously known or expected to be activating molecular alteration(s) (e. g. histone mutation, IDH1/2 mutations, FGFR mutations or fusions, MYBL alterations, NF1 somatic or germline mutations).	No expected therapeutic benefit from tovorafenib.	No	No expected therapeutic benefit from tovorafenib.
Known or suspected diagnosis of NF1 via genetic testing or current diagnostic criteria.	Tovorafenib may promote tumour growth in patients with NF1 tumours.	No	No expected therapeutic benefit from tovorafenib and potential for harm. Included in Warnings and Precautions in prescribing information. Off-label use in NF1 associated tumours is a non-important potential risk.

Exclusion criteria	Reason for exclusion	Missing information (Yes/No)	Rationale
History or current evidence of CSR, RVO, or ophthalmopathy present at baseline that would be considered a risk factor for CSR or RVO.	Increased risk of ophthalmologic toxicity.	No	Ophthalmologic events are a non-important potential risk.
Nausea and vomiting NCI CTCAE v5.0 Grade ≥2, malabsorption requiring supplementation, or significant bowel or stomach resection.	Preclude adequate absorption of tovorafenib.	No	Only oral or enteral formulations are available.
Clinically significant skin toxicity.	Increased risk of severe skin toxicity.	No	Rash is a non-important identified risk.
Concomitant medications that are strong or moderate inhibitors or inducers of CYP2C8 within 14 days before initiation of therapy. Concomitant medications that are substrates of BCRP with a narrow therapeutic index within 14 days before initiation of therapy.	Potential drug-drug interaction.	No	Planned pharmacokinetic studies are considered part of the clinical development programme and not additional PV activities. Therefore, drug-drug interaction will be monitored via routine PV activities.
Patients with severe hepatic impairment.	Routine exclusion criteria in early clinical trials.	No	Patients with paediatric LGG are generally not expected to have moderate to severe hepatic impairment and the benefit-risk of patients with moderate to severe hepatic impairment is not expected to be different than for those patients with paediatric LGG and normal hepatic function based on the current preclinical and clinical data.
Patients with severe renal impairment.	Routine exclusion criteria in early clinical trials.	No	Patients with paediatric LGG are generally not expected to have severe renal impairment and the benefit-risk of patients with severe renal impairment is not expected to be different than for those patients with paediatric LGG and normal renal function based on the current preclinical and clinical data.

Abbreviations: BCRP=breast cancer resistance protein; CSR=central serous retinopathy; CTCAE=common terminology criteria for adverse events; CYP2C8=cytochrome P450 2C8; FGFR=fibroblast growth factor receptor; IDH=isocitrate dehydrogenase; LGG=low-grade glioma; MYBL=myeloblastosis oncogene-like; NCI=National Cancer Institute; NF1=neurofibromatosis type 1; PV=pharmacovigilance; RVO=retinal vein occlusion.

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, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

Table 13 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical trial development programme.
Breastfeeding women	Not included in the clinical trial development programme.
Patients with relevant comorbidities/comedication[a]: • Patients with hepatic impairment	Mild (bilirubin ≤ULN, and AST>ULN or bilirubin >1.0×ULN to ≤1.5×ULN, and AST of any value); n=52. Moderate (bilirubin >1.5×ULN to ≤3×ULN, and AST of any value); n=1.
• Patients with renal impairment	Mild (eGFR (mL/min/1.73 m^2) 60-89; or CrCl (mL/min) 60-89); n=108. Moderate (eGFR (mL/min/1.73 m^2) 30-59; or CrCl (mL/min) 30-59); n=21.
• Patients with cardiovascular impairment	• Not included in the clinical development programme.
• Immunocompromised patients	• Not included in the clinical development programme.
• Patients with a disease severity different from inclusion criteria in clinical trials	• Not included in the clinical development programme.
Population with relevant different ethnic origin[b]	Asian/Black/Multiple/Other=37 White=258 Hispanic=34
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical trial development programme.
Other: patients <6 months of age	Not included in the clinical development programme; (n=3).

Abbreviations: AST=aspartate aminotransferase; CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; ULN=upper limit of normal.

a C28001, C28002, QSC20514 and FIREFLY-1 (data cutoff date: 22 December 2022).

b Asian/Black/Multiple versus White were analysed under Race. Not Hispanic versus Hispanic were analysed under Ethnicity.

Part II: Module SV – Post-authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1. Method used to calculate exposure

Exposure is based on filled starting dose prescriptions during the period from product launch to 22 July 2024. Age calculations are based on birth year. Expanded access programmes are not included in the calculations, however, named patient programmes are included.

SV.1.2. Exposure

Since the first launch of tovorafenib up to 22 July 2024, a total of three adults >25 years of age were exposed in the named patient programme in France. Table 14 through Table 18 provides the number of patients exposed through postmarketed tovorafenib in the US through 22 July 2024.

Table 14 Postmarketing Exposure by Age Group

Age group	Persons
0 to <2 years	3
2 years to <6 years	12
6 years to <12 years	29
12 years to <16 years	13
16 years to ≤25 years	15
>25 years	23
Total	95

Table 15 Postmarketing Exposure by Sex

Sex	Persons
Male	44
Female	44
Unknown	7
Total	95

Table 16 Postmarketing Exposure by Formulation

Formulation	Persons
Tablet	67
Powder for Oral Suspension	28
Total	95

Table 17 Postmarketing Exposure Calculated for Body Surface Area at Starting Dose

Dose of exposure	Persons
380 mg/m^2	95

Table 18 Postmarketing Exposure by Country

Country	Persons
United States	95

Part II: Module SVI – Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

There has been no evidence of psychological or physical dependence, or withdrawal or rebound effects in nonclinical or clinical studies or in postmarketing reports.

There is no conceivable reason or easy method of administration for use for illegal purposes. The potential for misuse for illegal purposes is considered non-existent.

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Constipation, Diarrhoea, Dry skin, Oedema, Epistaxis, Fatigue, Hair colour changes, Headache, Nausea, Paronychia, Pruritus, Pyrexia, Stomatitis, Vomiting, Weight decreased.

Adverse 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 (e.g. actions being part of standard clinical practice where the product is authorised):

- Decreased lymphocytes, Hypophosphatemia, Increased alanine transaminase, Increased aspartate aminotransaminase, Increased bilirubin, Increased creatinine phosphokinase levels, Increased lactate dehydrogenase, Low haemoglobin/Anaemia, Rash, Photosensitivity

Known risks that do not impact the risk-benefit profile:

- None

Other reasons for considering the risks not important:

- Medication error – Surveillance for packaging related errors with tablet dosing ongoing will be carried out by the sponsor.
- Off-label use in NF1 associated tumours – Evidence of BRAF alteration prior to initiation of treatment and controlled distribution of medicinal product.
- Ophthalmologic events – Similar in class effect medications approved for use in pLGG (such as dabrafenib and trametinib) include “Visual Impairment” in their warnings and precautions - specifically for retinal pigment epithelial detachment and retinal vein occlusion. To date, no retinopathy or corneal events have been observed with tovorafenib treatment. Tovorafenib has not produced events consistent with typical MEK inhibitor adverse drug reactions (such as serous retinopathy, chorioretinopathy, or similar retinal findings), nor has it caused events consistent with Type-1 BRAF adverse drug reactions (like uveitis or iridocyclitis). The visual changes observed appear more consistent with the underlying disease itself, as pLGG most often affects the optic nerve and surrounding structures. Despite these findings, ophthalmologic events will continue to be subject to routine safety surveillance.
- Secondary primary malignancies (nonhaematologic) – Similar in class effect medications approved for use in pLGG such as dabrafenib and trametinib have the term ‘New Malignancies’ included in warnings and precautions. To date, there are no cases of secondary primary malignancies reported in subjects treated with tovorafenib in the clinical development programme. Tovorafenib does not result in paradoxical activation of MAPK signalling in BRAF wild-type tissues, a mechanism that has been associated with tumorigenesis in other RAF inhibitors which is a likely explanation for this absence of cases. The biological mechanism of action of tovorafenib (a selective type II RAF inhibitor) does not suggest genotoxic potential or a mechanistic basis for secondary malignancies. Preclinical studies, including toxicology assessments and genotoxicity studies, have not demonstrated carcinogenicity or mutagenicity. Secondary primary malignancies will continue to be monitored through routine safety surveillance. Additionally, ongoing clinical studies will maintain follow-up assessments to evaluate this potential outcome in study participants.
- Ventricular Premature Beats (VPBs) – Events have been captured in exposed population with no evidence for risk of adverse clinical consequences. Cardiac events will be subject to routine pharmacovigilance surveillance.
- Embryo-foetal toxicity – Embryo-foetal toxicity has been observed in non-clinical trials in rodents but not in primates. Considering the young population and the SmPC recommendations, very few cases of pregnancy/embryo-foetal toxicity are expected to occur and thus, it is questionable if a PAS study will be feasible to further characterise this risk. Consequently, Embryo-foetal toxicity will be included as an important potential risk in the PSUR safety concerns only.

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

The risks included in the safety concerns as important identified risks, important potential risks or missing information are discussed in this section.

Important Identified Risks:

The identified risks considered important for inclusion as a safety concern in the RMP are presented in Table 19.

Table 19 Important Identified Risks

Important identified risk	Risk-benefit impact
Growth Retardation	Risk-benefit impact: Event may lead to discontinuation of treatment. Treatment with tovorafenib is associated with slowing of linear growth at the level of the growth plate. Observations of decrease in growth velocity have not been associated with disruption of systemic signals for growth nor any evidence of impact on bone integrity, advanced bone age, or premature closure of growth plates. In patients who discontinued treatment with tovorafenib, growth velocity recovered. Given the known issues with growth in children with cancer regardless of treatments and the reversible potential of the adverse reaction, the benefit-risk is assessed as acceptable in this treatment population [35].
Intratumoral Haemorrhage [a]	Risk-benefit impact: Tumour haemorrhage is known to occur in 8 to 20% of patients with pilocytic astrocytomas. While spontaneous tumour haemorrhages are known to occur commonly in high-grade gliomas [36], intratumoral haemorrhage is also reported to occur in low-grade pilocytic astrocytomas in 8 to 20% of cases [37,38,39,40]. Several factors such as tumour vascularity, prior radiation and age at first radiation can contribute to the risk of intratumoral haemorrhage [36,38]. Other factors which were prevalent in the FIREFLY-1 study among patients who experienced tumour haemorrhage were several lines of prior therapies including bevacizumab, multiple prior surgical resections, cystic tumour morphology and disseminated/leptomeningeal tumour spread. Although symptomatic tumour haemorrhage did not occur in FIREFLY-1 at rates higher than expected based on the existing literature, monitoring of tumour haemorrhage is warranted given the potential for severe clinical outcomes. Events may lead to reduction or discontinuation of the treatment. Fatal events of tumour haemorrhage have occurred in the setting of disease progression.

a Intratumoral haemorrhage (includes intracranial tumour haemorrhage).

Important Potential Risks:

The potential risks considered important for inclusion as a safety concern in the RMP are presented in Table 20.

Table 20 Important Potential Risks

Important potential risk	Risk-benefit impact
Decreased Fertility Risk	In nonclinical toxicology studies, abnormalities in vaginal and ovarian histopathology were observed in female rats but not in female monkeys. In a fertility and early embryonic development study in mature rats, there were tovorafenib -related effects on fertility parameters which were evident in fewer pregnancies, corpora lutea, implantation sites and live embryos in treated females administered tovorafenib until GD 6. At the end of the recovery period, the effects in males were reversed or reversing. In female rats reversible increased thickness of the vaginal mucosa, increased size and/or numbers of corpora haemorrhagicum and haemorrhage, and non-reversible cystic follicles, decreased corpora lutea, and interstitial cell hyperplasia were observed in ovaries at approximately 0.4-fold the human exposure at the recommended dose based on AUC. No impact on pregnancies or fertility parameters was observed for treated males mated with untreated females. In repeat- dose toxicology studies in rats of up to three months duration, in male rats, tovorafenib reduced weights of epididymis and testes, which correlated with reversible tubular degeneration/atrophy of the testes and reduced epididymal sperm at approximately 0.3-fold the human exposure at the recommended dose based on AUC. Risk-benefit impact: There is no relevant clinical experience with tovorafenib on fertility in humans and potential decreased fertility risk. Given the limited data and the potential impact on the benefit-risk balance, the risk of decreased fertility is considered as an important potential risk.

Abbreviations: AUC=area under the curve; GD=gestational day.

Missing information:

The missing information considered important for inclusion as a safety concern in the RMP are presented in Table 21.

Table 21 Missing Information

Missing information	Risk-benefit impact
Long-term Safety	Risk-benefit impact: There is currently no long-term safety data (patient exposure for up to five years) available on use of tovorafenib.

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

Not applicable since this is the first RMP for the product.

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

Table 22 Important Identified Risks: Growth retardation

Growth retardation **MedDRA PTs:** Growth failure, Growth retardation, Growth disorder, Failure to thrive, Growth hormone deficiency	
Potential mechanisms:	Tovorafenib is a type II RAF inhibitor with potent (IC_{50}=0.7 nM) activity against CRAF, in addition to activity against BRAF [41,42,43,44]. C-rapidly accelerated fibrosarcoma is the predominant RAF isoform expressed in hypertrophic chondrocytes [45]. Chondrocyte-specific CRAF ablation in genetically engineered mouse models reduced the rate of apoptosis in the hypertrophic chondrocyte layer, thereby reducing the rate of new bone formation and indicated that CRAF plays an important role in growth plate maturation [41,45,46]. Pharmacologic inhibition of CRAF is hypothesised to cause a reversible decrease in growth velocity, potentially validating the genetically engineered mouse model studies [47].
Evidence source(s) and strength of evidence:	Paediatric patients treated with tovorafenib in study FIREFLY-1 tended to have lower than expected annualised growth velocity relative to normative curves in age- and gender-matched children without cancer. Patients' height percentiles tended to decrease overtime when plotted on the US Centres for Disease Control and Prevention normative growth charts.
Characterisation of the risk:	In study FIREFLY-1, a decrease in growth velocity was observed, resulting in changes from baseline in height Z-scores over the course of treatment. The median height percentile at baseline was 43.1 (range: 0 to 99.99) corresponding to a median Z-score of -0.2 (minimum -4.53, maximum 3.85). Among patients on treatment through Cycle 13 (12 months; N=107 evaluable for height), the median change from baseline in height percentile was -14, corresponding to a change in Z-score of -0.6. Among patients on treatment through Cycle 19 (~18 months; n=95 evaluable for height), the median change from baseline in height percentile was –20.3, corresponding to a change in Z-score of 0.9. Reduction in percentile and Z-score over time on treatment was slightly higher among patients 2 to <6 years of age, although this assessment is limited by small subgroup sample size. Among patients with bone age assessment performed, there was no evidence of advancement of bone age or premature growth plate closure. No abnormal fractures, osteopenia, or other bone-related complications have been reported. Four patients in FIREFLY-1 discontinued tovorafenib due to decreased growth velocity. Of patients in trial FIREFLY-1 who were followed after discontinuation or completion of tovorafenib therapy, there was recovery of growth velocity and subsequent increase in Z-scores, including achievement of full catch-up growth.
Risk factors and risk groups:	Patients ≤18 years of age.
Preventability:	Patient height should be monitored during treatment with tovorafenib and tracked on age and gender based normative curves per local standard of care to inform patient/caregiver and prescriber decisions about continuation of therapy based on benefit-risk to the patient.
Impact on the risk-benefit balance of the product:	Decreased growth velocity is considered an AESI in patients ≤18 years of age. Decrease in growth velocity appears to be reversible upon tovorafenib discontinuation. Bone age and height will be measured in DAY101-002: LOGGIC/FIREFLY-2 study. No additional risk minimisation measures are deemed necessary.
Public health impact:	No significant public health impact for patients with suspected decrease in growth velocity, monitor growth routinely during and following discontinuation of treatment with tovorafenib.

Abbreviations: AESI=adverse event of special interest; BRAF=B-rapidly accelerated fibrosarcoma; CRAF=C-rapidly accelerated fibrosarcoma; IC50=half maximal inhibitory concentration; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; RAF=rapidly accelerated fibrosarcoma; US=United States.

Growth retardation **MedDRA PTs:** Growth failure, Growth retardation, Growth disorder, Failure to thrive, Growth hormone deficiency

Table 23 Important Identified Risks: Intratumoral haemorrhage

Intratumoral haemorrhage **MedDRA PTs**: Haemorrhages (SMQ) (Broad) Haemorrhagic central nervous system vascular conditions (SMQ) (Narrow)	
Potential mechanisms:	Intratumoral haemorrhage is associated with paediatric low-grade glioma and other CNS tumours in children. The mechanisms of intratumoral haemorrhage remain unclear but include tumour necrosis, rupture of tumour blood vessels and invasion of parenchymal blood vessels by tumour [48].
Evidence source(s) and strength of evidence:	While spontaneous tumour hemorrhages' are known to occur commonly in high grade gliomas [36], intratumoral haemorrhage is also reported to occur in low-grade pilocytic astrocytomas in 8 to 20% of cases [37,38,39,40].
Characterisation of the risk:	Intratumoral haemorrhage (includes term intracranial tumour haemorrhage) was reported in 20 (14.6%) patients, all in patients with paediatric low-grade glioma; 10/20 patients (7.3% of patients overall) had Grade 1 events that were asymptomatic and identified on routine study magnetic resonance imaging, 4/20 (2.9% of patients overall) had Grade 2 events, and 6/20 (4.4% of patients overall) had Grade 3 or higher events, including one fatal event. Four patients, three with Grade 1 asymptomatic event and one with a Grade 3 event, discontinued treatment due to the tumour haemorrhage. There were no other discontinuations for any other haemorrhage associated events. Among the 15 patients who continued treatment after the event onset, two were treated with corticosteroids only, five required surgical procedures for shunt revision and eight required no medical or surgical interventions.
Risk factors and risk groups:	Review of all reported events of intratumoral haemorrhage in referenced clinical studies was consistent in frequency and severity with the natural history of pilocytic astrocytomas in this population [36,37,38,39,40,49]. Several factors such as tumour vascularity, prior radiation and age at first radiation can contribute to the risk of intratumoral haemorrhage [36,38]. Case series to date have been limited to identification of spontaneous tumour haemorrhage either at the time of resection, as a presenting characteristic, or prior to any surgical intervention on the tumour. While some risk factors are identified among the literature, there are no case series exploring the prevalence of tumour haemorrhage among patients with relapsed or refractory paediatric low-grade glioma, particularly those who are as heavily pretreated as the FIREFLY-1 population. Important recognised risks predisposing this high-risk population to intratumoral haemorrhage include having had one or more tumour resections, non-pilocytic histology, leptomeningeal or disseminated disease and treatment with multiple therapeutic regimens including vascular endothelial growth factor receptor inhibitors.
Preventability:	Advise patients and caregivers of the known risk of haemorrhage in patients with paediatric low-grade glioma. Monitor for signs and symptoms of haemorrhage and evaluate as clinically indicated. These actions should be considered standard of care in the clinical management of patients with paediatric low-grade glioma.
Impact on the risk-benefit balance of the product:	The risk-benefit balance continues to be favourable. Events of severe haemorrhage and any intratumoral haemorrhage are considered AESIs given the rate of tumour haemorrhage in the natural history of low-grade glioma as cited in the literature. No additional risk minimisation measures are deemed necessary. Warnings and precautions include language in the Product Information.

Intratumoral haemorrhage **MedDRA PTs**: Haemorrhages (SMQ) (Broad) Haemorrhagic central nervous system vascular conditions (SMQ) (Narrow)	
Public health impact:	The rate of tumour haemorrhage in this heavily pretreated population with relapse remains within expected range for the natural history of the disease. The potential impact on public health is expected to be low.

Abbreviations: AESI=adverse event of special interest; CNS=central nervous system; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SMQ=standardised MedDRA Query.

Table 24 Important Potential Risks: Decreased fertility risk

Decreased **fertility risk** **MedDRA Search:** Fertility disorders SMQ (Broad)	
Potential mechanisms:	In nonclinical toxicology studies, abnormalities in vaginal and ovarian histopathology were observed in female rats but not in female monkeys. In a fertility and early embryonic development study in mature rats treated until GD 6, there were tovorafenib-related effects on fertility parameters which were evident in fewer pregnancies, corpora lutea, implantation sites, and live embryos. In repeat- dose toxicology studies in rats of up to three months duration, in male rats, tovorafenib reduced weights of epididymis and testes, which correlated with reversible tubular degeneration/atrophy of the testes and reduced epididymal sperm at approximately 0.3-fold the human exposure at the recommended dose based on AUC.
Evidence source(s) and strength of evidence:	In a fertility and early development study in mature rats, female rats were administered the vehicle control article or tovorafenib beginning 14 days before cohabitation with untreated males, during cohabitation, and continuing until GD 6. In treated female rats mated with untreated males, there were tovorafenib-related effects on female fertility parameters which were evident as fewer pregnancies, corpora lutea, implantation sites, and live embryos. Ovarian weights and numbers of oestrous cycles were unaffected and there were no macroscopic abnormalities observed at necropsy evaluation at any dose level. Male rats dosed once daily beginning 29 days before cohabitation with untreated females, during cohabitation and continuing through the day before euthanasia for a minimum of 49 doses had no negative effects on male fertility parameters or the ability to impregnate females.
Characterisation of the risk:	No decreased fertility risk has been observed to date.
Risk factors and risk groups:	Males and females of reproductive potential.
Preventability:	Advise males and females of reproductive potential of the potential risk for impaired fertility with tovorafenib.
Impact on the risk-benefit balance of the product:	Patients in study DAY101-002: LOGGIC/FIREFLY-2 will have gonadal function monitored during treatment and in long-term follow-up to assess for long-term effects of tovorafenib on fertility separate from direct toxic effects on the foetus or embryo.
Public health impact:	Given the size of the patient population, the public health impact is expected to be low.

Abbreviation: AUC=area under the curve; GD=Gestational day; MedDRA=Medical Dictionary for Regulatory Activities; SMQ=standardised MedDRA Query.

SVII.3.2. Presentation of the Missing Information

Table 25 Missing Information: Long-term Safety

Long-term safety **MedDRA search:** Rhabdomyolysis/myopathy (SMQ) Broad Ventricular tachyarrhythmias (SMQ) Narrow MedDRA PTs: Growth failure, Growth retardation, Growth disorder, Failure to thrive, Growth hormone deficiency Haemorrhages (SMQ) Broad Hemorrhagic central nervous system vascular conditions (SMQ) Narrow Non-haematological malignant tumours (SMQ) Narrow Eye Disorders SOC, excluding the high-level group terms of "Congenital eye disorders (excluding glaucoma)", "Ocular neoplasms", and "Ocular neuromuscular disorders" Haematopoietic erythropenia (SMQ) Broad Pregnancy and neonatal topics (SMQ) Fertility disorders (SMQ) Broad	
Evidence source:	It is currently not known if the safety profile will be different in the long-term use (up to five years) population. Anticipated risk/consequence of the missing information: Given the duration of exposure to tovorafenib in clinical trials and postmarketing setting, additional data is needed. Long-term Extension Phase (DAY101-001: FIREFLY 1) Patients in Arm 1 and Arm 2 (low-grade glioma) will enter the 36-month long-term extension phase after the last patient enrolled in Arm 1 completes 26 cycles of treatment. Patients in Arm 3 will enter long-term extension after completion of 26 cycles of treatment. During the long-term extension phase, patients will either continue on tovorafenib or opt to enter a "drug holiday" discontinuation period after completion of 26 cycles of treatment. Patients will continue to undergo routine periodic radiographic evaluations per protocol-defined timelines during treatment and the drug holiday discontinuation period. Patients on drug holiday may be re-treated with tovorafenib if there is clinical or radiographic evidence of disease progression as documented by the investigator. Impact on the benefit-risk balance of the product: Potential limitation on length of tovorafenib treatment duration.

Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SMQ=standardised MedDRA Query; SOC=system organ class.

Part II: Module SVIII – Summary of the Safety Concerns

Table 26 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Growth retardation • Intratumoral haemorrhage
Important potential risks	• Decreased fertility risk
Missing information	• Long-term safety

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific adverse reaction follow-up questionnaires:

None

Other forms of routine pharmacovigilance activities:

Individual and regular cumulative reviews of relevant Standardised Medical Dictionary for Regulatory Activities Queries for each AESI category, from both the global safety database and clinical trial database.

III.2 Additional Pharmacovigilance Activities

None

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 27 Summary of Ongoing and Planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

CIPN=chemotherapy-induced peripheral neuropathy; EFS=event-free survival; IRC=Independent review committee; OPG=optic pathway glioma; ORR=overall response rate; OS=overall survival; PFS=progression free survival; RAF=rapidly accelerated fibrosarcoma; RAPNO=response assessment in paediatric neuro-oncology; SoC=standard of care; VABS=Vineland adaptive behaviour composite scales.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Completion of ongoing studies DAY101-002: LOGGIC/FIREFLY-2 are planned to confirm efficacy objectives of postmarketing requirements.

Table 28 Planned and Ongoing Post-authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
DAY101-002: LOGGIC/FIREFLY-2: A Phase III, Randomised, International Multicenter Trial of DAY101 Monotherapy Versus Standard of Care Chemotherapy in Patients with Paediatric	To compare the ORR, PFS, EFS assessed per RAPNO criteria by IRC of tovorafenib monotherapy versus standard of care chemotherapy in patients with paediatric low-grade glioma harbouring an	Verify and describe the clinical benefit of tovorafenib through assessment of ORR as a primary endpoint and PFS and DOR, as determined by blinded IRC, as key secondary endpoints.	Interim analysis report	30 April 2028

Low-Grade Glioma Harbouring an Activating RAF Alteration Requiring First-Line Systemic Therapy. Ongoing	activating RAF alteration requiring first-line systemic therapy. To compare the OS of tovorafenib monotherapy versus standard of care chemotherapy. As secondary objective, to compare the safety and tolerability of tovorafenib monotherapy versus SoC chemotherapy to address the following safety concerns: growth retardation, intratumoral haemorrhage, decreased fertility risk and long-term safety.		Final clinical study report	30 April 2032
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

Abbreviations: BRAF=B-rapidly accelerated fibrosarcoma; DOR=duration of response; EFS=event-free survival; IRC=independent review committee; ORR=objective response rate; OS=overall survival; PFS=progression free survival; RAF=rapidly accelerated fibrosarcoma; RAPNO=response assessment in paediatric neuro-oncology.

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

V.1 Routine Risk Minimisation Measures

Table 29 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Growth retardation	Routine risk communication: SmPC Sections 4.4 and 4.8. PL Sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation regarding monitoring growth routinely during and following discontinuation of treatment with tovorafenib is included in SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

Safety concern	Routine risk minimisation activities
Intratumoral haemorrhage	Routine risk communication: SmPC Sections 4.4 and 4.8. PL Section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Monitor for signs and symptoms of haemorrhage, including tumour haemorrhage and evaluate as clinically indicated. Withhold and resume at reduced dose upon improvement, or permanently discontinue based on severity (see Section 4.2). Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Important potential risks	
Decreased fertility risk	Routine risk communication: SmPC Sections 4.4, 4.6 and 5.3. PL Section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Missing information	
Long-term safety	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None

Abbreviations: PL=package leaflet; SmPC=summary of product characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 30 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Growth retardation	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8. PL Sections 2 and 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Intratumoral haemorrhage	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8. PL Section 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None
Important potential risks		
Decreased fertility risk	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3. PL Section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information		
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Abbreviations: PL=package leaflet; SmPC=summary of product characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for tovorafenib

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

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

This summary of the RMP for tovorafenib should be read in the 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 (EPAR).

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

I. The Medicine and What is it Used for

Tovorafenib is authorised for treatment of patients 6 months of age and older with paediatric low-grade glioma harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies. Tovorafenib is the active substance and it is given orally.

Further information about the evaluation of tovorafenib's benefits can be found in EPAR, including in its plain-language summary, available on the European Medicines Agency website under the medicine's webpage Medicines European Medicines Agency (europa.eu).

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of tovorafenib, together with measures to minimise such risks and the proposed studies for learning more about tovorafenib'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 (e.g. 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 reports (PSUR) 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 tovorafenib is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of tovorafenib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely 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 tovorafenib. 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 (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information

Important identified risks	• Growth retardation • Intratumoral haemorrhage
Important potential risks	• Decreased fertility risk
Missing information	• Long-term safety

II.B Summary of Important Risks

Important identified risk, Important potential risk and Missing information

Important identified risk: Growth retardation	
Evidence for linking the risk to the medicine	Paediatric patients treated with tovorafenib in study FIRFELY-1 tended to have lower than expected annualised growth velocity relative to normative curves in age- and gender-matched children without cancer. Patients' height percentiles tended to decrease overtime when plotted on the US Centres for Disease Control and Prevention normative growth charts. As of the data cutoff date, 61 (44.5%) patients in Arms 1 and 2 of FIREFLY-1 from 24 different study sites have reported TEAEs of decrease in growth velocity. Three (2.2%) patients had dose reduction, seven (5.1%) patients had dose interruption, and four (2.9%) patients permanently discontinued tovorafenib treatment due to decrease in growth velocity. Forty-five (32.8%) patients had decrease in growth velocity considered CTCAE Grade 3, and 1 (0.7%) patient had CTCAE Grade 4. In Arms 1 and 2 of the FIREFLY-1, the most commonly reported Grade ≥3 TEAE in children was growth retardation (32.1% patients). The growth retardation was one of the most commonly reported treatment related SAEs reported in nine patients. Decrease in growth velocity (PT: Growth retardation) was more commonly reported as serious and treatment related among younger patients (14.8%, 6.1%, 3.8%, and 0% among patients ages 2 to <6 years, 6 to <12 years, 12 to <16 years and 16 to ≤25 years, respectively). Four patients withdrew from the study as a result of growth retardation. Three patients had

	TEAEs of growth retardation leading to dose reduction. Six patients had TEAEs of growth retardation leading to dose interruption.
Risk factors and risk groups	Patients ≤18 years of age.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL section 4
Additional pharmacovigilance activities	None
Important identified risk: Intratumoral haemorrhage	
Evidence for linking the risk to the medicine	While spontaneous tumour haemorrhages are known to occur commonly in high grade gliomas [36], intratumoral haemorrhage is also reported to occur in low-grade pilocytic astrocytomas in 8 to 20% of cases [37,38,39,40]. As of the clinical cutoff date, 20 (14.6%) patients in Arms 1 and 2 of FIREFLY-1 have reported events meeting search criteria for intratumoral haemorrhage. No patients had dose reduction, five (3.6%) patients had dose interruption and four (2.9%) patients, including three patients with Grade 1 intratumoral haemorrhage, permanently discontinued tovorafenib treatment due to intratumoral haemorrhage events. Two (1.5%) patients had maximum CTCAE Grade 3 serious events, of which one was considered treatment related (leading to interruption and ultimately discontinuation of tovorafenib) and the other as not related (with no change in study treatment). Three (2.2%) subjects (including the subject with the event of subdural haemorrhage) had maximum CTCAE Grade 4 serious events and one subject had a fatal (Grade 5) event. The fatal case involved a 14-year-old subject in Arm 2 who had a serious TEAE of Grade 4 tumour haemorrhage on Day 226, which worsened to Grade 5 on Day 239, 21 days after the last dose of tovorafenib. The event was noted by the investigator to be attributable to disease progression and considered not related to tovorafenib treatment.
Risk factors and risk groups	Review of all reported events found them to be consistent in frequency and severity with the natural history of pilocytic astrocytomas in this population [36,37, 38, 39,40,49]. Several factors such as tumour vascularity, prior radiation, and age at first radiation can contribute to the risk of intratumoral haemorrhage [36,38]. Case series to date have been limited to identification of spontaneous tumour haemorrhage either at the time of resection, as a presenting characteristic, or prior to any surgical intervention on the tumour. While some risk factors are identified among the literature, there are no case series exploring the prevalence of tumour haemorrhage among patients with relapsed or refractory paediatric low-grade glioma, particularly those who are as heavily pretreated as the FIREFLY-1 population. Important recognised risks predisposing this high-risk population to intratumoral haemorrhage include having had one or more tumour resections, non-pilocytic histology, leptomeningeal or disseminated disease, and treatment with multiple therapeutic regimens including vascular endothelial growth factor receptor inhibitors.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL section 4.

Additional pharmacovigilance activities	None
Important potential risk: Decreased fertility risk	
Evidence for linking the risk to the medicine	In a fertility and early development study in mature rats, female rats were administered the vehicle control article or tovorafenib beginning 14 days before cohabitation with untreated males, during cohabitation, and continuing until gestation Day 6. In treated female rats mated with untreated males, there were tovorafenib-related effects on female fertility parameters which were evident as fewer pregnancies, corpora lutea, implantation sites, and live embryos. For male rats treated until Day 64, fewer pregnancies, corpora lutea, implantation sites, live embryos and increased post-implantation loss occurred at all doses. Ovarian weights and numbers of estrous cycles were unaffected and there were no macroscopic abnormalities observed at necropsy evaluation at any dose level. In repeat- dose toxicology studies in rats of up to three months duration, in male rats, tovorafenib reduced weights of epididymis and testes, which correlated with reversible tubular degeneration/atrophy of the testes and reduced epididymal sperm at approximately 0.3-fold the human exposure at the recommended dose based on AUC.
Risk factors and risk groups	Males and females of reproductive potential
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.6 and 5.3. PL section 2.
Additional pharmacovigilance activities	None
Missing information: Long-term safety	
Risk minimisation measures	None
Additional pharmacovigilance activities	None

Abbreviations: AUC=area under the curve; CTCAE=common terminology criteria for adverse events; PL=package leaflet; PT=preferred term; RAF=rapidly accelerated fibrosarcoma; SAE=serious adverse event; SmPC=summary of product characteristics; TEAE=treatment-emergent adverse event; US=United States.

II.C Post-authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation in European Union (EU)

The following study is a condition of the marketing authorisation:

DAY101-002: LOGGIC/FIREFLY-2

Study short name and title:

A Phase III, Randomised, International Multicenter Trial of DAY101 Monotherapy Versus Standard of Care Chemotherapy in Patients with Paediatric Low-Grade Glioma Harbouring an Activating RAF Alteration Requiring First-Line Systemic Therapy

Purpose of the Study:

To compare the ORR, event-free survival, assessed per response assessment in paediatric neuro-oncology criteria by IRC of tovorafenib monotherapy versus standard of care chemotherapy in patients with paediatric LGG harbouring an activating RAF alteration requiring first-line systemic therapy.

To compare the OS of tovorafenib monotherapy versus standard of care chemotherapy.

LTFU period that includes a 30-day safety follow-up visit. Upon completion of the treatment phase (including EOT visit), ongoing safety, disease stability/progression, survival status, and subsequent anticancer therapies will be assessed in the LTFU period. For each patient, study participation is up to five years, inclusive of the Treatment phase and a LTFU period.

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

There are no other studies required for tovorafenib.

PART VII: ANNEXES

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Annex 1 - EudraVigilance Interface

Not applicable.

Annex 2 - Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme

There are no planned, ongoing nor completed pharmacovigilance studies for tovorafenib.

Annex 3 - Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

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Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

Not applicable.

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP.

Not applicable.

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority.

Approved protocols:

Not applicable.

Final protocols not reviewed or not approved:

Not applicable.

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 5 - Protocols for Proposed and Ongoing Studies in RMP Part IV

DAY101-002: LOGGIC/FIREFLY-2:

Study title:

A phase III, randomised, international multicenter trial of DAY101 monotherapy versus standard of care chemotherapy in patients with paediatric low-grade glioma harbouring an activating RAF alteration requiring first-line systemic therapy.

Rationale and study objectives:

- To compare the ORR assessed per RAPNO criteria by IRC of tovorafenib monotherapy versus SoC chemotherapy in patients with paediatric low-grade glioma harbouring an activating RAF alteration requiring first-line systemic therapy.
- To compare the PFS assessed by IRC of tovorafenib monotherapy versus SoC chemotherapy per RAPNO criteria.
- To compare the EFS assessed by IRC of tovorafenib monotherapy versus SoC chemotherapy per RAPNO criteria.
- To compare the OS of tovorafenib monotherapy versus SoC chemotherapy.
- To compare the safety and tolerability of tovorafenib monotherapy versus SoC chemotherapy.
- To compare changes in growth and development of tovorafenib monotherapy versus standard of care chemotherapy.
- To compare the efficacy and safety of individual standard of care chemotherapy regimens versus tovorafenib monotherapy for up to five years.

Endpoints:

- ORR, per RAPNO criteria, defined as the proportion of patients with overall confirmed response of CR, PR, or MR.
- PFS per RAPNO criteria, defined as time from randomisation to PD or death from any cause, whichever comes first.
- EFS per RAPNO criteria, defined as time from randomisation to PD, death from any cause, or initiation of any new anticancer therapy, whichever comes first.
- OS, defined as time from randomisation up to death from any cause.
- Type, frequency and severity of AEs and vital signs and laboratory abnormalities.
- Changes in neurological function and adaptive behaviour using VABS.
- Visual function outcomes in optic pathway glioma patients.
- ORR, CBR, TTR, PFS, EFS, and DOR by IRC per RANO-HGG and RANO-LGG criteria.
- HRQoL using PROMIS® assessment.
- Measured by changes in body length, weight, epiphyseal growth plate closure, and Tanner staging.

Study design:

This study consists of a screening phase, a treatment phase that includes an EOT visit, and a LTFU period that includes a 30-day safety follow-up visit. Upon completion of the treatment phase (including EOT visit), ongoing safety, disease stability/progression, survival status, and subsequent anticancer therapies will be assessed in the LTFU period. For each patient, study participation is up to 5 years, inclusive of the Treatment phase and a LTFU period.

Arm 1 (tovorafenib): treatment cycles will repeat every 28 days in the absence of disease progression. Patients will continue tovorafenib until any of the following occurs: disease progression, unacceptable toxicity, withdrawal of consent to treatment, or end of study.

Arm 2 (Investigator's Choice of SoC Chemotherapy): patients will receive one of 3 SoC chemotherapy options selected by the treating investigator: COG-V/C regimen, SIOPe-LGG-V/C regimen, or VBL regimen. The choice of SoC chemotherapy regimen will be selected prior to patient randomisation. Treatment will continue until completion of therapy or until any of the following occurs: disease

progression based on RANO-LGG criteria, unacceptable toxicity, withdrawal of consent to treatment, or end of study.

Patients who discontinue treatment due to disease progression will have (1) radiographic evidence of PD based on RANO-LGG, as determined by the Investigator and confirmed by the IRC, or (2) clinical progression based on RANO-LGG criteria determined by the Investigator. Investigators are encouraged to discuss cases of clinical progression and early radiographic progression without clinical symptom with the sponsor Medical Monitor prior to treatment discontinuation or initiation of a different form of treatment for the malignancy. Patients may continue therapy beyond PD.

Study population:

Less than 25 years of age with LGG with known activating RAF alteration.

Milestones:

MILESTONE	PLANNED DATE
Final clinical study report	30 April 2032

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

None.

Annex 7 - Other Supporting Data (Including Referenced Material)

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Annex 8 - Summary of Changes to the Risk Management Plan Over Time

Version	Approval date Procedure	Change
1.0	26 February 2026 EMEA/H/C/0006140	Initial Risk Management Plan