26 February 2026
EMA/67438/2026
Committee for Medicinal Products for Human Use (CHMP)

CHMP Assessment report

Ojemda

International non-proprietary name: tovorafenib

Procedure No. EMEA/H/C/006140/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AEMPS	Agency of Medicines and Medical Devices (Spain)
AESI	Adverse events of special interest
AGV	Annualized growth velocity
ALT	Alanine aminotransferase
AO	Aldehyde oxidase
API	Active pharmaceutical ingredient
ASD	Amorphous solid dispersion
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-168}	Area under the plasma concentration-time curve from time zero to 168 hours
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
AUC0-∞	Area under the plasma-concentration time curve from time 0 extrapolated to infinity
AUC_{0-inf}	Area under the plasma concentration-time curve from time extrapolated to infinity
AUC_{0-last}	Area under the plasma concentration-time curve from time zero to the last measurable concentration
AUC0-xx	Area under the plasma-concentration time curve from time 0 to time "xx" hours postdose
AUCss	Area under the plasma concentration-time curve at steady state
BCRP	Breast cancer resistance protein
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
BIW	Twice a week
BRAF	v-raf murine sarcoma viral oncogene homolog B
BSA	Body surface area
Caco-2	Human colonic adenocarcinoma cell line
CAN	Copy number alterations
CBR	Clinical benefit rate
CDx	Companion Diagnostic
CE	Conformité Européene
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum observed plasma concentration

Abbreviation	Definition
C_{min}	Minimum observed plasma concentration
CNS	Central nervous system
CPK	creatine phosphokinase
CR	Complete response
CRAF	v-raf murine sarcoma viral oncogene homolog C
CSR	Clinical study report
CTA	Clinical trial assay
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
EFD	Embryo-fetal development
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
E-R	Exposure-Response
ERK	Extracellular signal-regulated kinase
EU	European Union
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FISH	Fluorescent *in situ* hybridization
FLAIR	Fluid attenuated inversion recovery
FMI	Foundation Medicine, Inc
GD	Gestation Day
GLP	Good Laboratory Practice
hERG	Human ether- à -go-go related gene
HGG	High-grade glioma
IC50	Concentration required for 50% inhibition
ICH	International Conference on Harmonisation
IND	Investigational new drug
Indels	Insertion and deletion alternations
IRC	Independent Radiology Review Committee
ITH	Intra-tumoral hemorrhage
IV	Intravenous
IVDD	*In vitro* Devices Directive
IVDR	*In vitro* Devices Regulation
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
LGG	Low-grade glioma

Abbreviation	Definition
LoB	Limit of blank
LoD	Limit of detection
MAPK	Mitogen-activated protein kinase
MedDRA	Medical dictionary for regulatory activities
MEK	Mitogen-activated protein kinase
MR	Minor response
MRI	Magnetic resonance imaging
NaCMC	sodium carboxymethylcellulose
NDA	New drug application
NF1	Neurofibromatosis type 1
NGS	Next-generation sequencing
NOAEL	No-observed-adverse-effect level
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
ORR	Overall response rate
OS	Overall survival
PBPK	Physiological-based pharmacokinetics
PCEs	Polychromatic erythrocytes
PCR	Polymerase chain reaction
PD	Progressive disease
PD	Pharmacodynamics
PDX	Patient-derived xenograft
PEG	Polyethylene glycol
pERK	Phosphorylated ERK
PfOS	Powder for oral suspension (term interchangeable with the term Powder for Reconstitution)
PfR	Powder for reconstitution
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PNOC	Pediatric Neuro-Oncology Consortium
PO	Oral(ly)
PR	Partial response
PT	Preferred term
PVC	Premature ventricular contractions
Q2D	Once every 2 days or every other day
Q3D	Once every 3 days
QD	Once a day

Abbreviation	Definition
QW	Once a week
RAF	Rapidly accelerated fibrosarcoma
RANO	Response Assessment in Neuro-Oncology
RAPNO	Response Assessment in Pediatric Neuro-Oncology
RAS	Rat sarcoma virus
SAE	Serious adverse event
SLC	Solute carrier transporter
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System organ class
SPPD	Sum of product of perpendicular diameters
TAE	Time-averaged exposure
TEAE	Treatment emergent adverse event
TGI	Tumor growth inhibition
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization
WT	Wild-type
ΔQTcF	baseline-adjusted QT interval corrected for heart rate using Fridericia's method
ΔQTcP	baseline-adjusted population-corrected QT interval

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Table 1: Information on the product

Product data	
Product name	Ojemda
Active substance	Tovorafenib
INN or common name	Tovorafenib
Applicant	Ipsen Pharma 70 rue Balard, 75015 Paris FRANCE
EMA Product Number	EMEA/H/C/006140
ATC code and Pharmacotherapeutic group	L01EC04 L Antineoplastic and immunomodulating agents L01: antineoplastic agents, L01E: protein kinase inhibitors, L01EC: b-raf serine-threonine kinase (BRAF) inhibitors
Pharmaceutical form(s) and strength (s)	Film-coated tablet and powder for oral suspension. 100 mg and 25 mg/ml
Packaging	Blister (PVC/PCTFE/PVC/alu) and bottle (glass)
Package size(s)	1 bottle + 1 bottle adaptor + 1 oral syringe, 16 tablets, 20 tablets and 24 tablets
Route of administration	Oral use
Device or diagnostic	Before taking tovorafenib, patients must have confirmation of BRAF fusion or rearrangement, or BRAF V600 mutation assessed by a CE-marked in vitro diagnostic (IVD) medical device with the corresponding intended purpose. If the CE-marked IVD is not available, confirmation of BRAF fusion or rearrangement, or BRAF V600 mutation should be assessed by an alternative validated test.
Orphan designation	Orphan Designation for the treatment of glioma granted on 20 May 2021 (EU/3/21/2434)
Orphan indication status confirmed	Yes
PRIME scheme	No
Type of marketing authorisation granted at opinion	Conditional Marketing Authorisation
Legal basis	Article 8.3 of Directive 2001/83/EC Mandatory Scope (Article 3(1) of Regulation (EC) No 726/2004)
Final indication	Ojemda is indicated as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies (for biomarkers-based patient selection, see

Product data	
	section 4.2).
New active substance status	Yes

1.2. Protocol assistance

Table 2: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
25 July 2024.	quality, non-clinical and clinical	EMA/SA/0000177735/ Brigitte Schwarzer-Daum and Silvijus Abramavicius	Adequacy of the approach to drug substance specification; drug product intermediate's manufacturing process controls, specifications and proposed manufacturing hold time; manufacturing process controls proposed for the powder for oral suspension and drug product specifications for the film coated tablets and powder for oral suspension; need for a usability study to support use of the proposed administration device; Sufficiency of the proposed nonclinical program to support marketing authorisation application; Acceptability of the proposed clinical pharmacology plan, the intended dataset and analysis strategy to support the intended dose, the plan to use historical control data for contextualisation of the primary endpoint and the overall adequacy of the safety database.

1.3. Eligibility to the centralised procedure

The applicant Ipsen Pharma submitted on 26 February 2025 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ojemda (tovorafenib), through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2022.

The applicant applied for the following indication:

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

1.4. Legal basis

The legal basis for this application refers to:

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

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

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0442/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0442/2023) was not yet completed as a measure was deferred.

1.6. Information on orphan market exclusivity

Ojemda was designated as an orphan medicinal product (EU/3/21/2434) on 20 May 2021 in the following condition: treatment of glioma.

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure Spexotras (trametinib), Finlee (dabrafenib) and Voranigo (vorasidenib).

1.7. Applicant's request(s) for consideration

1.7.1. Accelerated assessment request

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004. The CHMP did not grant this request, as it considered that, based on the submitted data package, the justification for an accelerated assessment was not sufficiently substantiated. This was based on the available information at the time of the request, in particular on the possible overlap with the approved indication of dabrafenib and trametinib, the uncertainties regarding the biomarker selection, long-term safety and the absence of mature PFS results from a controlled clinical trial and the slow progression of the disease, with pLGGs histologically classified as benign tumours that exhibit a 10-year overall survival comprised between 85% to 96%.

1.7.2. Conditional marketing authorisation (CMA)

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004. Further details are provided in section 9.6.3.1.

1.7.3. New active substance status

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

1.7.3.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that tovorafenib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to the Appendix on new active substance status claim assessment report.

1.8. Steps taken for the assessment of the product

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

Rapporteur:	Alexandre Moreau
Co-Rapporteur:	Martin Mengel

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

PRAC Rapporteur:	Marie Louise Schougaard Christiansen
PRAC Co-Rapporteur:	Tiphaine Vaillant

The appointed CHMP Co-Rapporteur had no such prominent role in Protocol Assistance relevant for the indication subject to the present application.

The application was received by the EMA on	26 February 2025
An application for accelerated assessment was filed by the applicant. Accelerated assessment procedure was not agreed-upon by CHMP on	30 January 2025
The procedure started on	27 March 2025
The CHMP Rapporteur's first Assessment Report was received on	16 June 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	18 June 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	30 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	07 October 2025
A GCP inspection at 3 sites in Denmark, Canada and US between 7-11 July 2025. The outcome of the inspection carried out was issued on	29 October 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 December 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional	26 February 2026

marketing authorisation to Ojemda on	
The CHMP adopted a report on similarity with Spexotras, Finlee and Voranigo (see Appendix on similarity)	26 February 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	26 February 2026

1.9. CHMP outcome

1.9.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5. of this report.

The European Medicines Agency has deferred the obligation to submit the results of FIREFLY-2 study until July 2030 with Ojemda in one or more subsets of the paediatric population in the treatment of paediatric low-grade glioma.

1.9.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6. of this report.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ojemda as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/ojemda.

1.9.2.1. Similarity with authorised orphan medicinal products

The CHMP by consensusis of the opinion that Ojemda is not similar to Finlee, Spexotras and Voranigo within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See the appendix on similarity.

1.9.3. CHMP Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ojemda is favourable in the following indication:

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

The CHMP, therefore, recommends the granting of the conditional marketing authorisation subject to the conditions described in the following sections.

1.9.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.9.5. Other conditions and requirements of the marketing authorisation

1.9.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder shall submit periodic safety update reports every 6 months.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.9.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.9.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.9.7. Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Table 3: Specific obligations

Description	*Due date*
In order to confirm the efficacy and safety of tovorafenib in the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, the MAH shall conduct and submit the final report of the phase III randomised, parallel-group, two-arm study (FIREFLY-2) to evaluate the efficacy and safety of tovorafenib monotherapy versus standard of care (SoC) chemotherapy in patients with paediatric low-grade glioma harbouring an activating rapidly accelerated fibrosarcoma gene (RAF) alteration requiring first-line systemic therapy.	30 April 2032
The MAH shall generate additional PK data in paediatrics patients below 2 years of age and submit an updated population PK model incorporating these data, including an assessment of systemic exposure and, if necessary, revised dosing recommendations for this subgroup of patients.	30 April 2032

1.9.8. Proposed list of recommendations

Table 4: Proposed list of recommendations

Description of Recommendation(s)
The MAH commits to submit the results of the following studies in the frame of the Phase II Environmental

Description of Recommendation(s)
Risk Assessment: Aerobic Transformation in Aquatic Sediment Systems (OECD 308), Fish sexual development test (OECD 234) and Bioaccumulation in fish (OECD 305).
The MAH commits to submit the results of the study DAY101-105 to assess the effects of gemfibrozil (CYP2C8 inhibitor) and carbamazepine (CYP2C8 inducer) on the pharmacokinetics of tovorafenib in healthy participants.
The MAH commits to submit the results of the study DAY101-104 to assess the effects of tovorafenib on the pharmacokinetics of probe substrates caffeine (CYP1A2), repaglinide (CYP2C8), flurbiprofen (CYP2C9), omeprazole (CYP2C19), midazolam (CYP3A4), bupropion (CYP2B6), and rosuvastatin (BCRP) in healthy participants.
Regarding the specifications, the MAH confirms that at release and shelf-life limit for S-enantiomer will be re-evaluated and tightened, if justified, once there is sufficient data on active substance, intermediate and finished products batches.
Regarding film-coated tablets and powder for oral suspension specifications and the wider assay limit proposed for the shelf-life, which is considered acceptable based on observed analytical and batch variability, the MAH commits to review and re-evaluate shelf-life specifications, if justified, once there is more data available.
The MAH commits to provide data on the second batch related to stability study hold time for PfOS bulk product.

2. Introduction

2.1. Therapeutic Context

Low-grade gliomas are the most common brain tumour diagnosed in children (Ostrom 2019). Paediatric low-grade gliomas have a generally favourable prognosis with 10-year overall survival (OS) between 85–96% (Bandopadhayay 2014; Bergthold 2014, Krishnatry 2016) and, in contrast to adult low-grade gliomas, rarely undergo malignant transformation (Broniscer 2007).

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 (McKinney 2004). 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 (Ris 2019; Strother 2002). Symptoms include vision problems even leading to blindness, hearing or speech problems, neurological issues, premature puberty, physical changes, balance problems, fatigue, and nausea. Its chronic nature and treatment effects can impact children's development, cognition, education, and quality of life, and affect parents' and caregivers' mental health. Adult survivors of paediatric low-grade glioma are at increased risk for long-term disability, visual or motor impairment, neurocognitive impairment, and lower socioeconomic status (Ris 2019; Strother 2002[1]), and for those who require or receive radiation therapy, an increased risk of secondary neoplasms (Rodrigues 2021). 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 (Buhl 2019). 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 (NF-1) has been more widely reported (Bandopadhayay 2014; Rozen 2008). Therefore, the possibility that NF-1 was undiagnosed could explain the regression. Of note, in the FIREFLY-1 study, patients with these alterations are excluded from the trial population.

[1] Strother DR, Pollack IF, Fisher PG, et al. Tumors of the central nervous system. In: Pizzo PA, Poplack DG, ed. Principles and Practice of Pediatric Oncology. 4th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2002:751-824.

The recent World Health Organization (WHO) classification of CNS tumours recognized 4 different types of paediatric low-grade gliomas (Louis 2021), including the "Diffuse low-grade glioma, MAPK pathway-altered". The MAPK-pathway altered gliomas have an astrocytic or oligodendroglial morphology and precise classification now requires both molecular characterization and histopathological information.

The majority of pediatric low-grade gliomas are driven by a single genomic event resulting in up-regulation of the MAPK pathway, particularly alterations in the BRAF gene. For BRAF-altered pediatric low-grade gliomas, the most frequently observed alteration is the KIAA1549-BRAF fusion (approximately 65%) and the BRAF V600E mutation (approximately 30%) (Penman 2015; Ryall 2020b; Schreck 2019; Schreck 2023; Zwaig 2022).

The preferred initial management of pediatric low-grade glioma is surgical resection, with complete resection being the most favorable predictor of patient outcome. For approximately one-half of patients, a single surgical approach is curative (Tihan 2012). However, complete resection is not always feasible, especially for highly infiltrative or deep-seated tumours which have a high risk of functional impact. Patients with tumours that cannot be completely resected or are unresectable experience disease progression or recurrence, with a 5-year progression-free survival (PFS) of approximately 50% (Wisoff 2011).

For patients whose disease recurs after surgery or for whom surgery was not an option, chemotherapy is usually given as first-line systemic therapy. There are no approved chemotherapy regimens for paediatric low-grade glioma, but carboplatin and vincristine (CV) is a widely used combination (Ater 2012; Gnekow 2019) as well as single agent vinblastine (Lassaletta 2016).

The combination of dabrafenib, a Type 1 BRAF inhibitor, plus trametinib, a MEK kinase inhibitor, recently received approval in the European Union (EU) in November 2023 for the treatment of paediatric patients 1 year of age and older with low-grade glioma harboring a BRAF V600E mutation who require systemic therapy. Although the indication is line-independent, the study population was limited to first-line treatment in the pivotal study. The combination of dabrafenib plus trametinib is used for patients with LGG harbouring a BRAF V600E mutation but is not indicated for other BRAF alterations.

For patients with relapsed or recurrent paediatric low-grade glioma with BRAF fusions there are no approved agents and there is no established standard-of-care. The combination of dabrafenib plus trametinib may be used for those patients with relapsed or recurring low-grade glioma harboring a BRAF V600E mutation based on data from the dabrafenib plus trametinib arm of study (X2101, NCT2124772), showing an ORR of 25% (95% CI: 12.1, 42.2) as per independent reviewer (RANO 2017 criteria) (Bouffet 2023a). Chemotherapy may be attempted again, or a targeted therapy may be offered in clinical studies.

As opposed to higher grade CNS tumours, patients with paediatric low-grade glioma typically undergo multiple lines of systemic therapy in an effort to achieve disease stabilization and help patients reach the third decade of life, after which time it is expected that their tumour will undergo senescence.

Radiotherapy is typically reserved as a last resort, particularly for older 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 (de Blank 2019).

As described above, combination treatment with dabrafenib plus trametinib is now an option for the small subset of patients with relapsed paediatric low-grade glioma who harbor a BRAF V600E mutation (Bouffet 2023a). However, the majority of patients with paediatric low-grade glioma harboring BRAF fusions or other RAF alterations still have no approved therapy. Patients with BRAF V600 mutant low-

grade gliomas who have disease progression on or after dabrafenib plus trametinib will also need further options.

All patients with BRAF-altered paediatric low-grade glioma are in need of additional efficacious treatment options that do not confer life-long debilitating side effects. Protecting patients while maintaining tumour control for as long as possible will allow the natural course of the disease to arc towards senescence in order to enable long-term survival while preserving quality of life and quality of survivorship.

2.2. Aspects of development

Tovorafenib is being developed by Day One Biopharmaceuticals, Inc. (the Sponsor of Study FIREFLY-1) for the treatment of solid tumours with RAF alterations. Ipsen (the Applicant) has acquired the rights from Day One Biopharmaceuticals, Inc. to register and commercialize tovorafenib in countries other than the United States (US).

A total of 7 industry-sponsored studies of tovorafenib have been initiated. Of these, four Phase 1 studies are complete, while two Phase 2 studies and one Phase 3 study are ongoing.

Study **DAY101-001/PNOC026 (FIREFLY-1)** is the pivotal clinical study supporting this application. The ongoing study is a Phase 2 efficacy, safety, and pharmacokinetic (PK) study in paediatric patients aged 6 months to 25 years with relapsed or progressive low-grade gliomas and advanced solid tumours harboring an activating RAF alteration. Evaluable patients treated in Arm 1 of the study provide the key efficacy data, and all patients treated in Arm 1 and Arm 2 provide key safety data. This application summarizes data from Study FIREFLY-1 with a data cutoff date of 10 May 2024, which is 24 months after the last patient was enrolled to Arm 1.

Four Phase 1 studies, Study **C28001** and **C28002** (conducted in adult patients with cancer) and Study **QSC205140** and **DAY101-103** (conducted in adult healthy participants), provide supportive safety and pharmacokinetic data.

In addition, Study **PNOC014** is a Phase 1/2 investigator-sponsored study, conducted in cancer patients >1 to < 25 years of age, provides supportive data.

Results from the second Phase 2 study and the Phase 3 study, both ongoing, are not summarized in this application:

- Study **DAY101-002 [LOGGIC/FIREFLY-2]** is a Phase 3, randomized, global, multicenter trial of tovorafenib monotherapy versus standard of care chemotherapy in paediatric low-grade glioma harboring an activating RAF alteration requiring first-line systemic therapy. This global study is enrolling patients from Asia, Europe and North America, with an estimated 20% of patients being forecasted to come from the US sites. The first site was activated on 12 December 2022, the consent of the first patient was on 08 February 2023 (study start date) and the first patient was dosed on 03 March 2023. As of 15 January 2025, there are currently 110 active sites and 169 randomized patients.
- Study **DAY101-102** is a Phase 2 clinical trial evaluating tovorafenib in patients 12 years of age and older with solid tumours that have activating RAF fusions or RAF1 amplification (102a, first patient dosed 17 November 2021) or tovorafenib in combination with pimasertib in solid tumours with aberrations of the MAPK pathway (102b, first patient dosed 02 May 2022).

2.3. Description of the product

Tovorafenib, previously known as DAY101, TAK-580, MLN2480, BSK1369 and BIIB024 at various points during development (these names appear in this submission), is an oral, central nervous system (CNS)-penetrant, selective small-molecule, Type II rapidly accelerated fibrosarcoma (RAF) inhibitor. Tovorafenib inhibits mitogen-activated protein kinase (MAPK) signaling and cell growth of BRAF V600 mutant tumour cell lines in vitro and in vivo tovorafenib also inhibits MAPK signaling in tumors harboring BRAF fusions, including the KIAA1549-BRAF fusion.

This application seeks approval for the use of tovorafenib as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma harboring a BRAF fusion or rearrangement, or BRAF V600 mutation who have received one or more prior systemic therapies.

Tovorafenib is available in 2 oral formulations: as immediate release tablets (100 mg) and as an oral suspension (25 mg/mL, supplied as a powder for oral suspension [PfOS]).

Posology

The recommended dose of tovorafenib based on body surface area (BSA) is 380 mg/m^2 once weekly. The maximum recommended dose is 600 mg once weekly (see table below).

Ojemda may be administered as an immediate release tablet (see table below) or as an oral suspension (see tovorafenib 25 mg/ml powder for oral suspension SmPC).

A recommended dose for patients with BSA less than 0.3 m^2 has not been established.

Table 5: Recommended dose based on body surface area

Body surface area	**Recommended dose** (once weekly)
0.30-0.89 m^2	See tovorafenib powder for oral suspension SmPC
0.90-1.12 m^2	400 mg
1.13-1.39 m^2	500 mg
≥ 1.40 m^2	600 mg

Duration of treatment

Treatment with tovorafenib should be continued once weekly until disease progression, loss of clinical benefit, or unacceptable toxicity.

Dose modifications

The management of adverse reactions may require dose reduction, treatment interruption or treatment discontinuation.

The recommended dose reductions for adverse reactions for tovorafenib tablets are provided in the table below.

Table 6: Recommended dose reductions for adverse reactions

Body surface area	**First dose reduction**	**Second dose reduction**
0.30-1.12 m^2	Administer the oral suspension once weekly (see tovorafenib powder for oral suspension SmPC)	Administer the oral suspension once weekly (see tovorafenib powder for oral suspension SmPC)

1.13-1.39 m^2	400 mg once weekly	Administer the oral suspension once weekly (see tovorafenib powder for oral suspension SmPC)
≥ 1.40 m^2	500 mg once weekly	400 mg once weekly

The recommended dose modifications for adverse reactions for tovorafenib are in the table below.

Table 7: Recommended dose modifications for adverse reactions

Severity of ADR[a]	**Dose modification[b]**
Haemorrhage and intratumoural haemorrhage	
• Intolerable Grade 2 • Grade 3	Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider permanent discontinuation.
• First occurrence of any Grade 4	Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider permanent discontinuation.
• Recurrent Grade 4	Permanent discontinuation.
Skin toxicity, including photosensitivity	
• Intolerable Grade 2 • Grade 3 or 4	Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider permanent discontinuation.
Liver related events	
• Grade 3 AST or ALT • Grade 3 bilirubin	Withhold administration. If improved to Grade ≤ 2 or baseline resume as follows: - If laboratory abnormality resolves within 8 days, resume at the same dose. - If laboratory abnormality does not resolve within 8 days, resume at lower dosage.

Severity of ADR[a]	Dose modification[b]
• First occurrence of any Grade 4	Withhold administration. - If improved to Grade 0-1, resume at lower dosage. - If not improved, consider permanent discontinuation.
• Recurrent Grade 4	Permanent discontinuation.
Other adverse reactions	
• Intolerable Grade 2 • Grade 3	Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider permanent discontinuation.
• Grade 4	Withhold administration. - If improved to Grade 0-1, resume at reduced dose. - If not improved, consider discontinuation.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

[b] See Table 2 in the SmPC for recommended dose reductions.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No GMP inspections were deemed necessary within the scope of this MAA evaluation procedure

2.4.2. Good laboratory practice (GLP) inspection(s)

No GLP inspections were deemed necessary within the scope of this MAA evaluation procedure

2.4.3. Good clinical practice (GCP) inspection(s)

A request for GCP inspection was adopted by the CHMP for the following clinical study: DAY101-001. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure. This routine GCP inspection concluded that the trial was overall conducted in accordance with the principles of GCP and internationally accepted ethical standards, and the data are considered reliable to support regulatory evaluation.

3. Quality aspects

3.1. Introduction

The finished product is presented as film coated tablets containing 100 mg of tovorafenib and powder for oral suspension containing 25 mg/ml of tovorafenib.

Other ingredients of the film-coated tablets (tablets) are:

Tablet content: silica colloidal anhydrous, copovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose;

Film-coating: hypromellose, macrogol, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172).

Other ingredients of the powder for oral suspension are:

copovidone, microcrystalline cellulose, mannitol (E421), sodium lauryl sulfate, simethicone, maltodextrin, silica colloidal anhydrous, sucralose, artificial strawberry flavour (containing maltodextrin, triacetin, artificial flavour).

The tablets are available in blisters of PCTFE laminated between polyvinyl chloride (PVC) and aluminium foil backing containing either 4, 5 or 6 film-coated tablets.

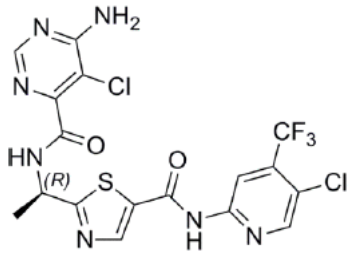
The powder for oral suspension is available 30 ml clear type III glass bottles with induction seal and a white polypropylene cap. Each pack contains one bottle, a 20 ml oral dosing syringe, and a bottle adaptor.

3.2. Active substance

3.2.1. General information

The chemical name of the active substance is 6-amino-5-chloro-N-[(1R)-1-[5-[[[5-chloro-4-(trifluoromethyl)-2-pyridinyl]amino]carbonyl]-2- thiazolyl]ethyl]-4-pyrimidinecarboxamide corresponding to the molecular formula $C_{17}H_{12}Cl_2F_3N_7O_2S$. It has a molecular weight of 506.29 g/mol and the following structure:

Figure 1: active substance structure



The chemical structure of tovorafenib was elucidated by a combination of elemental analysis, ^{1}H NMR, ^{13}C NMR, 2D-NMR, FTIR, mass spectroscopy and UV spectroscopy. The solid-state properties of the active substance were measured by DSC and x-ray crystal structure determination.

The active substance is a non-hygroscopic white to off-white powder. Tovorafenib is practically insoluble in water and across the physiological pH range. The active substance is freely soluble in dimethyl sulfoxide and N,N- dimethylformamide and sparingly soluble in acetonitrile and ethyl acetate.

Tovorafenib active substance has one stereogenic centre of R- absolute configuration. Stereoisomer impurity is the S- enantiomer. Enantiomeric purity is controlled routinely by chiral HPLC in the active substance specifications.

A polymorph screen in various solvent systems identified two potential polymorphic forms. The active substance produced is one of them and is thermodynamically stable. A test is included in the active substance specification for the confirmation of the correct polymorphic form.

3.2.2. Manufacture, characterisation, and process controls

For all sites involved in the manufacture and control of the active substance sufficient evidence of GMP compliance has been provided.

Tovorafenib is synthesised in several main steps using well defined starting materials with acceptable specifications. Sufficient number of chemical transformation steps have been described and are performed under GMP. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials, and reagents have been presented.

No materials of human or animal origin are used in the manufacture of tovorafenib active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Satisfactory overview on the manufacturing process development has been provided. The description of the stages in the evolution of the manufacturing process and relevant changes to the control strategy and description of the material attributes and process parameters identified as impacting active substance critical quality attributes has been covered. The starting materials remain the same over the development. There are changes in the solvents and reagents. Process parameters have been optimised. All changes have been sufficiently described and have been justified. Batch data presented in the dossier show that these changes have no impact on the quality of the active substance. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in bags which comply with Ph. Eur. and Commission Regulation (EU) 10/2011, as amended. The choice of the container closure system is adequate. Satisfactory specifications for the primary packaging material are provided. Batch analyses results and representative IR spectrum have been enclosed.

3.2.3. Specification

The active substance specification includes tests for: appearance (visual), identity (UPLC), assay (UPLC), S-enantiomeric impurity (chiral HPLC), impurities (UPLC), water content (KF), residual solvents (GC), elemental impurities (ICP-MS), residue on ignition (Ph. Eur.) and microbial limits (Ph. Eur.).

The proposed tests and acceptance criteria are based on historical batch data, validation data, stability analysis, as well as non-clinical and clinical evaluation. The tovorafenib active substance specification has been set considering with ICH guidelines Q6A, Q3A, Q3C, and Q3D.

The active substance specifications are based on the active substance critical quality attributes (CQA). The CQA identified are identity, assay, S-enantiomer, impurities, degradation products, water content, residual solvents, and elemental impurities.

Satisfactory information on the impurity control strategy to allow adequate understanding and control of the origin, fate and purge of impurities originating from the tovorafenib route of synthesis has been provided. The provided data demonstrates that the potential impurities are effectively removed by the

current manufacturing process and will not be carried over to the final active substance or are controlled in the subsequent steps demonstrating that the adequate control strategy has been established.

None of the impurities of tovorafenib is found in the active substance above the reporting threshold. No degradation products of the active substance have been observed upon storage as demonstrated in the stability studies. Chiral purity is sufficiently controlled in the final substance. S-enantiomer impurity has been found in the final API at release. Almost no increase can be seen during stability studies.

The UPLC method for related substances in the active substance is specific for relevant isolated intermediates. Therefore, the residues of the isolated intermediates are controlled in the tovorafenib active substance as unspecified impurities. This is acceptable.

The submitted toxicology studies did not raise any concern for S-enantiomer levels. The applicant confirms that the limit for S-enantiomer will be re-evaluated and tightened, if justified, once the manufacturer has data on enough active substance batches at release and up to the re-test date. This is considered acceptable.

Residual solvents are controlled in the final substance or in the starting materials and intermediate products with the limits in line with the ICH Q3C requirements. The control for benzene is in line with ICH Q3C Annex I: Specifications for class 1 and class 2 residual solvents in active substances (CPMP/QWP/450/03, EMEA/CVMP/511/03). A limit test to control benzene has been included in the specification for isopropanol solvent used during manufacture.

ICH M7 guideline is applicable to this source of tovorafenib substance. The Applicant has performed the screening of the impurities of tovorafenib for potential mutagenicity in two complementary in silico software programs. Based on the ICH M7 guideline, the absence of structural alerts from two complementary (Q)SAR methodologies (expert rule-based and statistical) is sufficient to conclude that no impurity is of mutagenic concern, and no further testing is recommended.

No elemental impurity is intentionally added in the active substance route of synthesis. The Applicant has not provided the risk assessment of the elemental impurities. All relevant elements for oral formulation have been included in the active substance specification with ICH Q3D option 1 limit. Batch analyses data show that all the elements are less than 30% of the specification level. The control strategy is satisfactory in the level of active substance.

The applicant has provided a brief summary of the risk assessment on nitrosamine impurities in tovorafenib API. No recovered materials are used in the manufacturing process. The risk from cross-contamination from manufacturing equipment is considered low. Therefore, the risk for presence of nitrosamines in the active substance is considered remote.

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

The suitability of the microbiological purity tests for the active substance was confirmed.

Batch analysis data on eight batches including four commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch. The proposed commercial process generates an active substance that is in line with clinical batches.

3.2.4. Stability

Primary stability data from three batches manufactured at pilot scale of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Supportive stability data on 7 batches were also provided, with some manufactured at commercial scale.

The following parameters were tested*:* appearance, impurities, assay, water content, enantiomeric purity, and microbial limits. The analytical methods used were the same as for release and were stability indicating.

Tovorafenib active substance demonstrates good stability. All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one active substance batch manufactured with the previous Process C. Batches manufactured with the Process C process are representative of commercial batches manufactured with the Process D. The results demonstrate that tovorafenib is not sensitive to light.

Results on stress conditions under acid, base, oxidation, thermal, and photolytic stress conditions as part of the validation of specificity for the UPLC identification, assay, and impurity method were also provided.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months with no special storage conditions in the proposed container.

3.3. Finished medicinal product – Film-coated tablets

3.3.1. Description of the product and pharmaceutical development

Description of the product and pharmaceutical development

Tovorafenib is formulated as an immediate release film coated tablet for oral administration in a 100 mg dosage strength. Tablets are of orange colour, oval, 16 mm in length and 9 mm width with "100" debossed on one side and "D101" on the opposite side.

The critical quality attributes (CQA) have been determined and investigated during the development. DoE studies were used for different steps of the proposed intermediate finished product manufacturing process.

Critical quality attributes (CQA) for film-coated tablets were defined as: appearance, identity, assay, related substances, S-enantiomer content, content uniformity, dissolution, water content, microbial limits and crystallinity.

No design space is proposed, and no alternative control strategies are sought.

The active substance, tovorafenib, is a low-solubility compound. In order to increase the aqueous solubility and bioavailability of the active substance, the active substance is transformed from crystalline state to amorphous during manufacture. Tovorafenib intermediate finished product shows improved solubility versus the crystalline active substance. The intermediate manufacturing process is controlled to deliver intermediate batches with consistent specifications.

The choice, amount and functions of excipients have been discussed and are justified. Compatibility with regard to excipients has been demonstrated as well as justified by stability data.

The functionality-related characteristics of chosen excipients as indicated in the respective Ph. Eur. monographs, in view of a potential impact of these parameters on the finished product manufacturability and performance have been discussed sufficiently.

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

The formulation development has been described in detail. The proposed formulation has been adequately justified.

The development of tovorafenib tablets manufacturing process focused on the optimization of the intermediate finished product manufacturing process, tablet formulation, and tablet manufacturing processes. Formulation and manufacturing process development were conducted using risk assessments to establish the areas of focus for process optimization.

A Failure Mode and Effects Analysis (FMEA) evaluation was performed to establish the main risks for the manufacture of the intermediate product and immediate release tablets.

Upon completion of the development work and establishing control strategy, all investigated risks related to formulation were subsequently identified as low risks.

The manufacturing process development has been well described, both for the tovorafenib intermediate and for the film-coated tablets. The results reported of the intermediate and film-coated tablet manufacturing process development support the manufacturing process and process controls. An adequate control strategy based on the observations form the development studies has been established.

The primary packaging is PCTFE laminated between polyvinyl chloride (PVC) and aluminium foil backing which is common for the proposed pharmaceutical form. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.3.2. Manufacture of the product and process controls

The batch release site is Ipsen Pharma Biotech, Parc d´Activites Du Plateau De Signes, Chemin Departemental 402, Signes 83870, France. For all sites involved in the manufacture, control, and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process consists of two main stages: the first stage is the preparation of an intermediate. The second stage is the manufacturing of the tablets.The provided data are considered sufficient for manufacturing procedures of conventional solid oral dosage formulation.

Critical process parameters have been identified for the extrusion manufacture: screw configuration, feed rate, screw speed and temperature.

As the product has an orphan indication, a batch size smaller than stated in guideline "Guideline on manufacture of the finished dosage form" (EMA/CHMP/QWP/245074/2015) was established and batch formula for this commercial batch size has been presented. No overage is used.

The batch formulae for the intermediate have been provided for tablets and considered acceptable.

It is stated that film-coated tablets will be placed in bags placed into drums and shipped to the packaging contract manufacturer where they are blistered. No holding times have been fixed.

Transportation of bulk tablets between manufacturing sites is proposed, and the impact of excursions outside of the original storage conditions are supported by accelerated stability data.

The intermediate finished product serves as product intermediate to the tablet finished product.

Specifications for the intermediate finished product have been provide including tests for appearance,

identification, assay, S-enantiomer content, water content and particle size.

The methods, method validations, batch analysis of representative batches are presented. Acceptable method validation protocols, along with linearity graphs and representative chromatograms have been presented for intermediate finished product analytical methods.

A brief description of the intermediate container is provided, along with the specifications of PE bags, foil bags and desiccant bag. PE bag compliance with EU Commission Regulation No 10/2011/EC on plastic materials and articles intended to come into contact with food is stated.

The tovorafenib intermediate has been placed on stability storage. Two batches of intermediate have been studied under ambient storage conditions (20°C ±4°C/45% ±15% RH). Results remained within specified limits.

Process validation data on three tovorafenib intermediate finsihed product validation and three production scale batches have been presented, and the process is considered satisfactorily validated. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, UV), assay (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), S-enantiomer content (HPLC), dissolution (Ph. Eur.), water content (KF), crystallinity (XRPD) and microbial contamination. The specification limits are the same for release and during shelf life, except acceptance criteria proposed for assay.

The finished product specifications cover appropriate parameters for this dosage form. The limits are based on batch and stability data and on the relevant guidelines.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed. Initially provided risk assessment was not considered complete and a major objection was raised by CHMP in this regard. As requested, the risk assessment has been complemented considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary. The major objection was resolved.

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

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

3.3.4. Stability of the product

Stability data from seven batches at different scales of the finished product stored for up to 36 months under long-term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal products are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Further supportive stability data was provided on bulk tovorafenib tablets and for tovorafenib tablets made from aged intermediate and packaged into blisters. Packaging for bulk stability studies was in a bag and stored in a drum.

Samples were tested for: appearance, assay, related substances, S-enantiomer content, dissolution, water content, crystallinity, and microbial contamination.

In all studies performed, no significant changes were observed in any of the parameters tested for the registration batches of tovorafenib tablets stored under long-term or accelerated conditions.

Forced degradation studies have previously been performed on the method to determine identity, assay, and impurities by HPLC to verify stability indicating ability. These were conducted using one batch of tablets, and included stress by elevated temperature and humidity, oxidation, and exposure to acid, base, and light.

Sufficient data have been provided to demonstrate the stability-indicating nature of the HPLC method used for identification, assay and related substances has been studied performing the forced degradation studies. Stability indicative nature of HPLC method used for S-enantiomer have been demonstrated. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product is not sensitive to light.

Based on available stability data, the proposed shelf-life of 36 months and no special storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Three months' stability of uncoated tablets have been demonstrated with one batch. It is confirmed that bulk uncoated tablets will not be stored for more than 30 days.

Adventitious agents

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

3.4. Finished medicinal product – Powder for oral suspension

3.4.1. Description of the product and pharmaceutical development

Description of the product and pharmaceutical development

The finished product – powder for oral suspension (PfOS) is a white to off-white powder packaged as a 300 mg strength to be reconstituted with 12 ml water to deliver 25 mg/mL reconstituted product. It is dosed with a 20 ml oral dosing syringe which is included in the pack together with a bottle adaptor. The bottle is overfilled to 430 mg tovorafenib active and reconstituted with 14 mL of water to allow for reproducible dosing delivery of 300 mg tovorafenib (i.e., 12 mL of 25 mg/mL tovorafenib with an oral syringe).

The aim of pharmaceutical development was to develop an age-appropriate dosage form for the treatment of patients 6 months of age and older.

The critical quality attributes (CQA) have been determined and investigated during the development. Intermediate finished product process development included a design of experiments (DoE) study to evaluate the impact of key process parameters (barrel temperature, screw speed and feed rate) on critical quality attributes. The optimized parameters reduced risks related to assay, appearance, S-enantiomer content, impurities and crystalline form. Critical quality attributes (CQA) for the powder for oral suspension were defined as: appearance, identity, assay, related substances, S-enantiomer content, content uniformity, dissolution, water content, reconstitution time, syringeability, microbial limits and crystallinity.

No design space is proposed, and no alternative control strategies are sought.

Active substance, tovorafenib, is a white to off-white crystalline powder with low solubility and high permeability (BCS class II).

The choice, amount and functions of excipients have been discussed and are justified. Compatibility with regard to excipients has been demonstrated as well as justified by stability data.

The functionality-related characteristics of chosen excipients as indicated in the respective Ph. Eur. monographs, in view of a potential impact of these parameters on the finished product manufacturability and performance have been discussed sufficiently.

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

The formulation development has been described in detail. The proposed formulation has been adequately justified. The palatability and dosing accuracy of the PfOS formulation were evaluated. Additionally, administration through a 12 French nasogastric (NG) tube ($\leqslant$109 cm) was tested, demonstrating the formulation is suitable for NG tube administration.

The development of tovorafenib formulations focused on optimising the intermediate finsihed product manufacturing process, the PfOS formulation, and its manufacturing process. Risk assessments guided the formulation and process development to identify key areas for optimization. The work was aligned with the Quality Target Product Profile (QTPP), and product attributes were classified as critical or non-critical based on their impact on quality. For critical quality attributes (CQAs), corresponding control strategies were detailed, and acceptable parameter ranges for consistent product quality were established.

The manufacturing process development has been well described, both for the tovorafenib intermediate and for the powder for oral suspension dosage form. The results reported of the intermediate and PfOS manufacturing process development support the manufacturing process and process controls. An adequate control strategy based on the observations form the development studies has been established.

Dissolution media were selected based on the physicochemical properties of tovorafenib, its intended dose range, and tablet formulation. Conditions were optimised to ensure sink conditions while maintaining the method’s discriminatory ability. Sufficient discriminatory power of the proposed dissolution method has been demonstrated.

To support the dosing of the PfOS finished product several in-use and compatibility studies were conducted including: in-use stability and robustness sample preparation study, in-use stability (compatibility) study of the PfOS after reconstitution prior to oral administration, in-use sample reconstitution robustness study, in-use dosing/stability in nasogastric (NG) tubes, a controlled

extractable/ leachable study with the PfOS dosing components and a study to determine the solubility of tovorafenib in milk products. The compatibility studies results support the proposed administration of the product as described in the SmPC. In-use stability data has been provided the dossier and discussed later in this report.

The primary packaging is Type III, 30mL clear glass bottles and capped with an induction-sealed white polypropylene cap which is common for the proposed pharmaceutical form. Secondary packaging also contains an oral dosing syringe and a 20 mm bottle adaptor, which comply with the relevant medical device legislation. According to the Declaration of Conformity the bottle adapter is manufactured in accordance with the EU Medical Device Regulation 2017/745. EU Quality management system certificate has been presented for manufacturer of oral syringe which confirms compliance with Regulation (EU) 2017/745 on Medical Devices. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

During the development, adequacy of the bottle adaptor and the syringe with the finished product has been demonstrated. No incompatibilities between the finished product and the packaging materials were observed, and the compatibility of the co-packaged devices with the finished product has been confirmed. The suitability of the selected packaging is demonstrated in stability studies.

3.4.2. Manufacture of the product and process controls

For all sites involved in the manufacture and control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process consists of two main stages: the first stage is the preparation of an intermediate and the second stage is the manufacturing of the powder for oral suspension.

The provided data are considered sufficient for manufacturing procedures of powder for suspension oral dosage formulation.

Critical process parameters have been identified for the manufacture: screw configuration, feed rate, screw speed and temperature.

As the product has an orphan indication, a smaller batch size smaller than stated in guideline "Guideline on manufacture of the finished dosage form" (EMA/CHMP/QWP/245074/2015) was established and batch formula for this commercial batch size has been presented. No overage is used.

The intermediate manufacturing process together with in-process controls, specifications, packaging material and storage have been described earlier in this report, relating to (tovorafenib tablets).

Process validation data on three tovorafenib intermediate validation and three production scale batches have been presented, and the process is considered satisfactorily validated. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

3.4.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of the powder and of reconstituted suspension (visual), identification (HPLC, UV), syringeability (in house), reconstitution time (in house), assay (HPLC), content uniformity (Ph. Eur.), S-enantiomer content (HPLC), related substances (HPLC), dissolution (Ph. Eur.), water content (KF), crystallinity (XRPD) and microbial contamination. The specification limits are the same for release and during shelf life, except acceptance criteria proposed for assay based on observed analytical and batch variability, which was considered acceptable. The Applicant commits to review and re-evaluate shelf-

life specifications, if justified, once there is more data available. This point is recommended to the applicant as quality recommendation 2.

The finished product specifications cover appropriate parameters for this dosage form. The limits are based on batch and stability data and on the relevant guidelines.

The proposed limit for dissolution is considered justified based on the provided data.

The limit for S-enantiomer content in finished product specifications is acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been discussed earlier in this report. The risk assessment covers the powder for oral suspension dosage form and is adequate.

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

Batch analysis results are provided on four batches of the finished product representative of the commercial process batch size confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.4.4. Stability of the product

Stability data from three primary pilot scale batches of the finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Further supportive stability data was provided, including on 3 commercial scale validation batches. Total data on 12 batches has been provided.

Samples were tested for: appearance of the powder and of reconstituted suspension, syringeability, reconstitution time, pH (later excluded from final specification which is agreed), assay, S-enantiomer content, related substances, dissolution, water content, crystallinity and microbial contamination.

In all studies performed, no significant changes were observed in any of the parameters tested for the registration batches of tovorafenib tablets stored under long-term or accelerated conditions.

The Applicant has confirmed that the expiry date on the product label will be calculated from the date of manufacture also known as the date when the tovorafenib active substance is added to the first excipient in the finished product intermediate manufacturing process. This is acceptable.

Forced degradation studies have previously been performed on the method to determine identity, assay, and impurities by HPLC to verify stability indicating ability. These were conducted using one batch of tablets, and included stress by elevated temperature and humidity, oxidation, and exposure to acid, base, and light. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product is not sensitive to light.

Based on available stability data, the proposed shelf-life of 36 months and no special storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Stability of reconstituted powder for suspension has been studied to confirm suitability under actual conditions of use. Results show that all tests performed meet the specification acceptance criteria up to 15 minutes after reconstitution. In-use shelf life is reflected in the SmPC.

Adventitious agents

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

3.4.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure a major objection was raised on the comprehensiveness of the risk assessment on the presence of nitrosamine impurities. The applicant complemented the risk assessment, and the risk assessment is considered satisfactory, resolving the major objection. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. CHMP recommends three points that have no effect on benefit risk for consideration for future quality development.

3.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

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

3.5. Recommendations for future quality development

1. Regarding the specifications, the applicant confirms that at release and shelf-life limit for S-enantiomer will be re-evaluated and tightened, if justified, once there is sufficient data on active substance, intermediate and finished product batches.

2. Regarding film-coated tablets and powder for oral suspension specifications and the wider assay limit proposed for the shelf-life, which is considered acceptable based on observed analytical and batch variability. The applicant commits to review and re-evaluate shelf-life specifications, if justified, once there is more data available.

3. The applicant commits to provide data on the second batch related to stability study hold time for PfOS bulk product.

4. Non-clinical aspects

4.1. Introduction

Tovorafenib has been subjected to nonclinical pharmacologic, pharmacokinetic (PK), and toxicologic evaluation, thirteen non-clinical safety GLP studies have been submitted.

4.2. Analytical methods

The applicant has submitted the reports of the analytical assays that were used to characterise *in vitro* studies, the non-clinical pharmacokinetic and toxicokinetic studies, including assay accuracy, precision,

and limits of quantification. Acceptance criteria and validation parameters were determined according to the EMA Guideline on Bioanalytical Method Validation, EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2, July 2011. Statements on GLP compliance indicated that these validation studies were conducted in line with the GLP principles and with no significant deviations from the GLP Regulations.

The qualified assays are clearly segregated from pivotal GLP data, and their limitations are transparently described.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Tovorafenib is a type-II RAF kinase inhibitor that inhibits RAF monomers and dimers. Crystallographic studies showed tovorafenib to be an R-enantiomer that displaces the phenylalanine out of the back-pocket of the active site of BRAF, shifts the orientation of the C-helix, and changes the conformation of the glycine-rich loop. This binding mode is similar to that of sorafenib and differs from that of the Type-I BRAF inhibitor vemurafenib. *In vitro*, tovorafenib inhibited the kinase activity of BRAF V600E, WT BRAF, and WT CRAF kinases, with IC50 values of 7.1, 10.1, and 0.7 nM, respectively. However, activity on ARAF was not presented, but it was reported in the literature that tovorafenib is not potent against ARAF (Tkacik et al., 2023).

In vivo and *in vitro* pharmacology studies established pharmacodynamic activity through pERK inhibition in the MAPK pathway in cell lines and tumour-bearing mice harbouring BRAF mutations and/or fusion, with additional anti-proliferative effect *in vitro* and efficacy *in vivo* which translated into tumour growth inhibition and/or tumour regression.

In vitro, cell lines harbouring either a BRAF V600E/D mutation (melanoma and colon cell lines) were sensitive to tovorafenib activity reflected by inhibition of pERK inhibition and associated anti-proliferative activity *in vitro* (RSCH-2010-009). The EC_{50} values for tovorafenib were below 2 µM in seven cell lines, six of them being colon or melanoma cells with either BRAFV600D or BRAFV600E. Tovorafenib activity in K562 CML cells with WT BRAF can be explained by the activity of the compound on BCR-ABL. Proliferation inhibition pattern correlated well with pERK inhibition, with the exception of the above-mentioned K562 cell line. Sensitivity to tovorafenib for Ras mutations and WT B-RAF was variable.

Overall, *in vivo*, tovorafenib distributed to different tumour types xenografts (WM-266-4 B-Raf mutant melanoma model, Calu-6 B-Raf wild-type lung cancer model, and BxPC-3 B-Raf wild-type pancreatic cancer model) and resulted in TGI or even regression in melanoma xenograft models notably harbouring BRAF mutation (WM-266-4 (BRAF V600D) and A375 (BRAF V600E)) or fusion (ME11971 (AGK-BRAF fusion) and including large tumours. Tovorafenib also had adequate potency against *in vivo* BRAF WT tumours.

Efficacy was dependent of administration and tumours regrew when treatment was stopped. Upon reinitiating treatment, tumours-maintained sensitivity to tovorafenib which is indicative of lower resistance probability. No evidence of paradoxical activation was observed in these studies. *In vivo* studies were performed only on female mice.

Only two BRAF fusion models were presented. In genetically engineered murine models of paediatric low-grade astrocytoma with either KIAA1549:BRAF fusion or the BRAFV600E expression (p53-/- mouse neuroprogenitor cells stably transduced with the indicated constructs) described by Sun et al. (2017), tovorafenib inhibited pERK in a concentration-dependent manner and reduced cell proliferation with an

IC50 of 190 and 248 nM, respectively, which is in range of the clinically attainable plasma concentrations and retarded the growth of both of these tumour types and increased survival of the treated mice at 30 mg/kg BID.

Exposure and efficacy were not always dose-dependent *in vivo* depending on dose and administration schedules. Regarding dose-response, in WM-266-4 xenograft model, at the 25 mg/kg dose, both the QD and Q2D dosing schedules showed similar efficacy. Also, there was no apparent increase in concentrations from the 50 mg/kg dose to the 75 mg/kg dose at D2. In study 705 also on WM-266-4 xenograft model, tovorafenib demonstrated comparable efficacy on a Q2D schedule either at the 25 or 12.5 mg/kg. On the Q2D dosing schedule, no dose-dependency was observed across 25, 50, and 75 mg/kg dose groups. Regarding plasma dosing of tovorafenib in melanoma xenograft study RSCH-2010-011, intragroup variation was high; variation coefficient was up to 70%, which was attributed to variations during the elimination phase. Based on exposure-efficacy *in vivo*, it was concluded the target efficacious exposure of tovorafenib in mice is an AUC0-∞ range of approximately 56.3 to 111 µg•h/mL as observed in mice administered 12.5 to 25 mg/kg tovorafenib. It was also estimated that 1400 ng/g tovorafenib would be required in the tumour for strong pERK inhibition (RSCH-2010-010).

Regarding NF1 models, tovorafenib was inactive in 2 of 3 NF1-LOF mutant tumour cell lines in proliferation assays. Increased pERK levels were observed at lower concentrations of tovorafenib and decreased pERK at higher concentrations of tovorafenib. The trend of the pERK increase at lower concentrations was different between the NF1-LOF tumour cell lines. *In vivo*, in $Nf1^{flox/flox}$, Postn-Cre+ mice, tovorafenib did not inhibit ERK phosphorylation and did not reduce proximal nerve volume. A subset of larger tumours (n=5) was also observed in treatment group with an increase in tumour number in 2/12 mice, although both parameters were not statistically significant. However, this entails that (i) tovorafenib as monotherapy is not sufficient to prevent tumour growth in the NF1-LOF setting and (ii) in the NF1-LOF setting, there is a potential risk of amplified tumour growth in response to tovorafenib treatment, as mentioned by Rastogi et al., 2025 based on presentation of the poster result by the academic lab. Poster also mentions that kinomics and transcriptomic data were being generated.

4.3.1.2. Secondary pharmacodynamics

Tovorafenib was profiled in a non-kinase selectivity screening panel of 169 receptors, transporters, and channels, together with the 5 major CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). Secondary pharmacology CYP450 screening assay did not indicate significant inhibition of major CYP enzymes at 10 µM, while PBPK studies indicate inhibitory potential on CYP2C8 (7.8 µM). Tovorafenib inhibited ligand binding to 3 targets, Adenosine A2A, Adenosine A3 and Glutamate/N-methyl-D-aspartic acid (NMDA)/polyamine, with the IC50 values of 1.11, 5.42 and 5.81 µM, respectively. The free clinical Cmax concentration of 0.28 µM is approximately 4-fold lower than the most potent IC50 (for Adenosine A2A) observed for these non-kinase receptors and is not seen as clinically relevant.

Kinase selectivity profiling was performed on a panel of 257 discrete kinase inhibition assays, 222 of which were unique kinases and 35 of which were kinases from other species or cancer-derived mutants.

Tovorafenib inhibited 14 human relevant kinases at 0.2 µM, which is lower than the Cmax unbound reported for adults (Arg, Abl, DDR2, EphA1, EphA2, EphA8, Fyn, Lck, Lyn, MuSK, PTK5, SAPK2a and SAPK2b as well as transformed cKit(V560G) and PDGFRα(V561D)), IC50 was determined for 10 of these kinases all of which are within therapeutic exposure. Of the inhibited kinases at 0.2 µM tovorafenib, several are ubiquitously expressed and have been shown to be involved in many physiological and bone development such as SAPK2a and SAPK2b, DDR2, ABL/ARG (Rodríguez-Carballo et al., 2014; Wang, 2015; Xu et al., 2018). Inhibition of these kinases is therefore relevant to

observed toxicities of tovorafenib. Tovorafenib also inhibited Adenosine A2A, Adenosine A3 and Glutamate/N-methyl-D-aspartic acid (NMDA)/polyamine at IC50 of 1.11 µM, 5.42 µM and 5.81 µM.

4.3.1.3. Safety pharmacology

Regarding *in vivo* safety pharmacology, there was no apparent effect of tovorafenib administration on CNS on parameters measured such as autonomic nervous system parameters, sensorimotor reactions, neuromuscular function, or body temperature in rats. In respiratory safety pharmacology performed in rats, respiratory parameters were altered differently in male and female rats. Female rats had increased respiratory rates starting 1000 mg/kg, male rats had moderately increased tidal volume (with no dose-dependent pattern) and mild to moderate increase in minute volumes starting 500 mg/kg. Effects were considered non-adverse and no-observed-adverse-effect level (NOAEL) was determined to be 1500 mg/kg. Regarding cardiovascular safety pharmacology, a non-GLP study was performed in telemetered beagle dogs and a GLP study in cynomolgus monkeys. Both evidenced a dose-dependent increase in HR due to tovorafenib treatment, QT shortening and increase in SAP and MAP. Effects were considered non-adverse in monkeys and were not reported in repeated-dose toxicology studies. In monkeys, mild PR prolongation was also observed at 60 mg/kg.

The section 5.3 of the SmPC includes the following information: *In vitro* testing revealed potential for hERG inhibition by tovorafenib with an IC50 of 8.9 µM, resulting in an exposure margin of 32-fold compared to unbound clinical Cmax in adult of 0.280 µM.

4.3.1.4. Pharmacodynamic drug interactions

No studies were conducted.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

The Applicant has submitted a series of repeat-dose toxicokinetic (TK) studies in rats and cynomolgus monkeys using suspension formulations (NaCMC/Tween 80 or PEG400). While these studies are GLP-compliant and provide high systemic exposures (exceeding clinical levels), no repeat-dose TK study was conducted

Systemic exposure in monkeys was dose-proportional up to 20 mg/kg. At higher doses, absorption slowed but continued to increase. No sex-related differences were observed in monkeys. In contrast, in rats, exposure plateaued above 150–300 mg/kg. A consistent 2-fold higher exposure in females was observed associated with greater toxicity.

No or limited accumulation was observed in either species under Q2D dosing. Clearance remained time-independent throughout, with no evidence of auto-induction. These data support the selected QW dosing regimen in humans.

The absence of GLP TK data with the clinical formulation limits the direct characterization of steady-state kinetics and bioavailability.

4.3.2.2. Distribution

Tovorafenib demonstrates a distribution profile consistent with a lipophilic, highly protein-bound kinase inhibitor, featuring predictable and reversible extravascular distribution. Plasma protein binding is strong (human fu ≈ 2.5%) and dominated by albumin, with no evidence of saturation over the tested concentration range and minimal influence from alpha-1-acid glycoprotein.

Distribution into red blood cells is moderate in humans ($K_{RBC/plasma}$> ≈ 4-6), providing some dampening of Cmax without altering elimination kinetics. Liver microsomal binding is low, confirming that the prolonged half-life observed *in vivo* results primarily from tissue distribution rather than hepatic trapping.

The quantitative whole-body autoradiography (QWBA) study performed in male pigmented rats demonstrates rapid and extensive tissue distribution, with peak concentrations in most organs at 1 hour and a return to below quantifiable levels by 72 hours. Notably, brain exposure was measurable (brain/plasma AUC ≈ 0.6), supporting blood-brain barrier penetration adequate for the treatment of paediatric low-grade gliomas.

Tovorafenib also demonstrates a reversible affinity for melanin-rich tissues, including pigmented skin, the uveal tract or substantia nigra.

4.3.2.3. Metabolism

The non-clinical metabolism of tovorafenib has been adequately explored through a series of *in vitro* studies in microsomes and hepatocytes from multiple species, including human. The data support a low metabolic turnover profile, with unchanged parent compound as the predominant species. Enzyme phenotyping confirms the involvement of multiple CYP isoforms (CYP3A4, CYP2C8, CYP2C9, CYP2C19) and aldehyde oxidase, suggesting a metabolically redundant clearance pathway and a limited risk of drug–drug interactions.

Only a small number of oxidative metabolites were identified (M2–M4), with no major or disproportionate human metabolites expected. No glucuronide or phase II conjugates were observed. A rodent-specific hydrolysis product (M1) was detected but is not considered relevant to humans. No reactive intermediates were detected under GSH-trapping conditions, and in vivo bioactivation appears minimal.

However, *in vivo* metabolite profiling was conducted only in rat, whereas one of the pivotal species for toxicology is monkey.

No stereochemical or tautomeric evaluation has been presented.

Overall, the metabolic profile is simple and consistent with the expected behaviour of a low-clearance kinase inhibitor.

4.3.2.4. Excretion

The excretion profile of tovorafenib has been characterised in two complementary non-GLP studies conducted in male rats. Study PD09-29 assessed clearance pathways following IV and PO administration in bile duct–cannulated animals, while study TAK-R3401 performed a mass balance analysis using [^{14}C]-labelled compound in both intact and BDC rats. Together, the data demonstrate that unchanged tovorafenib is minimally excreted in urine or bile, and that elimination occurs primarily via hepatic metabolism.

Overall, the available data support a metabolism-driven clearance mechanism for tovorafenib, with minimal renal or biliary elimination of unchanged drug.

4.3.2.5. Pharmacokinetic drug interactions

Tovorafenib as an object

In vitro phenotyping studies demonstrated that tovorafenib is primarily metabolised by aldehyde oxidase and CYP2C8 *in vitro*. CYP3A, CYP2C9 and CYP2C19 metabolise tovorafenib to a minor extent.

The relative contribution was 64.8%, 21.9%, 1.34%, 4.47%, and 7.47% for AO, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5.

Based on a combination of the *in vitro* phenotyping study data and biotransformation pathway information determined from the human ADME study, the contributions of AO, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 were refined and estimated to correspond to 23.35%, 49.23%, 11.63%, 9.41%, and 6.38% of the metabolism of tovorafenib, respectively.

Following a single oral dose of radiolabelled tovorafenib, 65% of the total radiolabelled dose was recovered in the faeces (8.6% unchanged) and 27% of the dose was recovered in the urine (0.2% unchanged).

Tovorafenib exhibited high permeability *in vitro* and was not a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Tovorafenib was not an in vitro substrate of human OATP1B1 and OATP1B3 transporters at concentrations up to 20 µM.

Tovorafenob as a precipitant

- **Reversible CYP inhibition potential of tovorafenib evaluated *in vitro* sing human liver microsomes (HLM) (P024-11-01)**

The potential for tovorafenib to reversibly inhibit 8 major CYP isoforms was evaluated in HLMs using CYP-isoform specific probe substrates in P024-11-01. The results showed that the IC_{50} values for the inhibition of 5 CYP isoforms (CYP1A2, 2B6, 2D6, 2E1, and 3A4/midazolam) are greater than 100 µM. The IC_{50} values for CYP2C8, 2C9, 2C19, and 3A4/testosterone were 7.79, 46.5, 82.8, and 40.5 µM, respectively.

- **Reversible CYP inhibition potential of tovorafenib as determined *in vitro* using human liver microsomes (PD09-25)**

The potential for tovorafenib to reversibly inhibit CYP3A4, 2C9, 2C19, 2D6, and 1A2 was determined in PD09-25. Nine concentrations of tovorafenib (20 µM to 3.1 nM) were incubated with HLMs (0.5 mg/mL final concentration), 2 mM NADPH, and isoform-specific probe substrates (at or around each substrate's respective Km value) for 15 minutes at 37°C for all CYPs except CYP2C19 which was incubated for 30 minutes. Isoform-specific inhibitors were similarly incubated with the probe substrates as a positive control. The enzymatic reactions were quenched with addition of ACN to the incubation. Each plate was centrifuged to precipitate the microsomal protein, and supernatants were analysed. Metabolite formation was monitored by LC/MS.

Tovorafenib was not an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4 at or below concentrations of 20 µM.

- **CYP450 time-dependent inhibition potential of tovorafenib**

The potential for tovorafenib to inhibit CYP3A4 in HLM by mechanism-based inactivation was evaluated in PD09-26. Tovorafenib at concentrations of 0, 1, 10, and 30 µM was pre-incubated with HLM (2.5 mg/mL) in 0.1 mM potassium phosphate buffer, pH 7.4 in the presence of 2 mM NADPH and 3 mM MgCl 2 CYPA34 activity, as measured by formation of 6β-hydroxyl testosterone, was unchanged by increasing pre-incubation time or increasing tovorafenib concentrations. Therefore, the mechanism-based inhibition potential of tovorafenib for CYP3A4 was considered to be low.

The time-dependent inhibitory potential of tovorafenib on human CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 isozyme activity was evaluated in vitro using pooled HLM and a concentration-response IC_{50} method in DOT1-DMPK-004. Tovorafenib and positive control inhibitors (fluvoxamine, ticlopidine, quercetin, sulfaphenazole, omeprazole, and paroxetine) at concentrations ranging from 0 to 50 µM

were incubated with probe substrates for each enzyme, with final substrate concentrations approximately at the Km, and HLM (0.1 mg/mL final concentration) in 100 mM potassium phosphate buffer, pH 7.4 with and without NADPH. Time-dependent inhibition in this assay was indicated if the IC_{50} value shifted greater than 1.5-fold with pre-incubation. Tovorafenib at the highest concentration tested (50 µM) in pooled HLM (0.1 mg/mL) showed no significant inhibition of CYP1A2, 2B6, 2C19, and 2D6 activity. Inhibition of these CYP isozymes by tovorafenib (0.00545 to 50.0 µM) under all assay conditions was 67.3% (CYP2C19) or less and full dose-response curves were not achieved. Inhibition data could not be curve fit to determine IC_{50} values to assess time-dependent inhibition by tovorafenib.

Inhibition of CYP2C8 and CYP2C9 isozymes by tovorafenib at 50 µM under all assay conditions ranged from 87.3% to 94.3% for CYP2C8 and from 71.7% to 74.8% for CYP2C9. Tovorafenib inhibited CYP isozyme activity with IC50 values ranging from 7.18 to 11.4 µM for CYP2C8 and from 10.2 to 19.1 µM for CYP2C9. Under these assay conditions, tovorafenib did not show a signal for time-dependent inhibition (TDI) of CYP2C8 (IC_{50} shift ranging from 0.744 to 1.19) and of CYP2C9 (IC_{50} shift ranging from 0.775 to 1.45).

The results for positive control inhibitors were within the expected ranges, indicating acceptable performance of the assays.

- ***In vitro* UGTs inhibition**

The potential for tovorafenib to reversibly inhibit the activity of the human UDP-glucuronosyltransferase (UGT) isoenzymes 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15 with model substrates was determined using HLMs in DOT1-DMPK-009.

Tovorafenib showed reversible inhibition of UGT1A1, 1A3, 1A4, 1A6, 1A9, and 2B15. Tovorafenib inhibited UGT1A1, 1A3, 1A4, and 1A9, with IC50 values of 16.3 µM, 41.0 µM, 57.8 µM, and 54.4 µM, respectively. For UGT1A6 and 2B15, inhibition at 50 µM was less than 38%, and IC50 values could not be calculated. Tovorafenib did not show reversible inhibition of UGT2B7 when tested at concentrations up to 50 µM.

- ***In vitro* evaluation of tovorafenib as an inducer of CYP450 expression in human cryopreserved hepatocytes and determination of aqueous solubility (DOT1-DMPK-008)**

Inducible cryopreserved hepatocytes from 3 single donors were incubated with concentrations of tovorafenib ranging from 0.781 to 50 µM to assess induction potential for CYP1A2, 2B6 and 3A4), and with tovorafenib (1, 3, and 10 µM) to assess induction potential for CYP2C8, 2C9, and 2C19. Induction was measured after 48 hours by measuring changes in mRNA expression by RT-PCR. An observed increase in mRNA expression relative to the DMSO control that was ≥ 2-fold or a response relative to the positive control that was ≥ 20% were considered positive induction.

Tovorafenib induced CYP1A2 mRNA expression at concentrations of 1.56, 3.13, 6.25, 12.5, and 25 µM in 3 single donor lots of hepatocytes. There was a concentration dependent increase in mRNA expression with mean increases ranging from 2.64-fold at 1.56 µM tovorafenib to 13.4- fold at 12.5 µM tovorafenib. There was no induction observed at tovorafenib concentrations of 0.781 and 50 µM in any of the hepatocyte lots. The mean half-maximal effective concentration (EC50) for CYP1A2 induction was 12.3 µM tovorafenib. Results of the positive control inducer, omeprazole, were acceptable for each of the lots of hepatocytes.

Tovorafenib induced CYP2B6 mRNA expression at concentrations of 1.56, 3.13, 6.25, 12.5, and 25 µM in 3 single donor lots of hepatocytes. There was a concentration dependent increase in mRNA expression with mean increases ranging from 2.48-fold at 1.56 µM tovorafenib to 12.4- fold at 12.5 µM tovorafenib. There was no induction observed at tovorafenib concentrations of 0.781 and 50 µM in any

of the hepatocyte lots. The mean EC50 for CYP2B6 induction was 5.78 µM of tovorafenib. Results of the positive control inducer, phenobarbital, were acceptable for each of the lots of hepatocytes.

Tovorafenib induced CYP3A4 mRNA expression at concentrations of 1.56, 3.13, 6.25, 12.5, 25, and 50 µM in 3 single donor lots of hepatocytes. There was a concentration dependent increase in mRNA expression with mean increases ranging from 3.55-fold at 1.56 µM tovorafenib to 15.5-fold at 12.5 µM of tovorafenib, the response was < 20% of the positive control response. There was no induction observed at tovorafenib concentrations of 0.781 µM in any of the hepatocyte lots. The mean EC50 for CYP3A4 induction was 6.61 µM tovorafenib. Results of the positive control inducer, rifampicin, were acceptable for each of the lots of hepatocytes.

Tovorafenib induced CYP2C8 at 1, 3, and 10 µM in the 3 single donor lots of hepatocytes. There was a concentration dependent increase in mRNA expression, with mean increases ranging from 1.87-fold at 1 µM tovorafenib to 8.11-fold at 10 µM tovorafenib. The mean fold-induction relative to vehicle was at least 2-fold in at least one lot of hepatocytes across all concentrations.

Tovorafenib did not induce CYP2C9 or 2C19 at 1, 3, and 10 µM in the 3 single donor lots of hepatocytes; the fold increase in mRNA expression was < 2-fold relative to the vehicle control and the response < 20% of the positive control response. Results of the positive control inducer, phenobarbital, were acceptable for each of the lots of hepatocytes.

- **Transporter inhibition**

The potential for tovorafenib to inhibit the efflux transporters P-gp and BCRP expressed in Caco-2 cells was determined in RPT-02116.

Tovorafenib did not inhibit the efflux of the P-gp substrate digoxin in Caco-2 cells, suggesting that tovorafenib is not an inhibitor of P-gp at concentrations up to 30 µM. Tovorafenib increased Papp A-to-B and decreased Papp B-to-A of the BCRP substrate E3S in a concentration-dependent manner. The tovorafenib IC50 for the inhibition of BCRP-mediated efflux of E3S, determined by the changes in the E3S B-to-A flux rate when incubated with different concentrations of tovorafenib from 0.04 to 10 µM was estimated to be 1.42 µM in Caco-2 cells.

The potential for tovorafenib to inhibit human SLC transporters was determined in DOT1- DMPK-001. Uptake experiments were performed using MDCKII or HEK293 cells stably expressing the respective uptake transporters. Initial studies determined in the in vitro interaction potential of tovorafenib with human MATE1, MATE2-K, organic anion transporter (OAT1), OAT3, OCT1, and OCT2 SLC transporters at two concentrations of tovorafenib (2 and 20 µM) and OATP1B1 and OATP1B3 at two concentrations of tovorafenib (2.8 and 28 µM). In follow-up assays, IC50 values were determined at 7 concentrations of tovorafenib ranging from 0.027 to 20 µM for MATE1, OAT1, and OAT3 SLC transporters, and 0.038 to 28 µM for OATP1B1 and OATP1B3 SLC transporters.

Tovorafenib was not an *in vitro* inhibitor of OCT1 but did inhibit transport by other SLC transporters. Tovorafenib inhibited transport of MATE2-K and OCT2 substrates by less than 50% at concentrations up to 20 µM. Tovorafenib was an inhibitor of MATE1 (IC50 5.98 µM), OAT1(IC50 13.99 µM), OAT3 (IC50 4.96 µM), OATP1B1 (IC50 10.07 µM), and OATP1B3 (IC50 11.85 µM).

4.3.2.6. Other pharmacokinetic studies

Two exploratory pharmacokinetic studies focused on combination with other oncology agents. These studies, conducted in immunodeficient mice (non-GLP), investigated tovorafenib both as monotherapy and in combination with clinically relevant agents (MLN8237, MLN0128, trametinib, docetaxel), simulating potential co-administration scenarios.

The PK data suggest a low risk of significant pharmacokinetic interactions in combination therapies, with the exception of a potential interaction with MLN8237.

4.4. Toxicology

The non-clinical toxicology program for tovorafenib includes repeat-dose toxicity, genotoxicity, carcinogenicity, and an environmental risk assessment.

4.4.1. Repeat-dose toxicity

Repeat-dose toxicity studies of up to 3 months in rats and monkeys with QD, Q2D, every 3 days (Q3D), and/or once weekly (QW) PO dosing were performed. Since dose range-finding pilot studies with daily dosing showed intolerability in both species, the Q2D regimen showed improved tolerability. Thus, the pivotal GLP toxicology studies were conducted with a Q2D regimen, which is more frequent than the proposed QW clinical regimen of 600 mg or 420 mg/m^2 of tovorafenib. The oral route was chosen since this is the intended clinical route. Sprague Dawley rats and cynomolgus monkeys were used as relevant species based on comparison of metabolite profiles generated by isolated hepatocytes from mice, rats, dogs, rabbits, cynomolgus monkeys, and humans. Rats were about 8 to 10 weeks of age and monkeys 2.3 to 3.9 years of age corresponding to 12 to 16 years of human age. No additional juvenile toxicity studies have been performed. Repeat-dose toxicity studies were performed according to ICH guidance as part of the non-clinical development programme (see section 4.4.4.).

The Q2D dosing regimen in the pivotal rat studies was well tolerated; no treatment-related deaths occurred. At ≥50 mg/kg administration of tovorafenib changes in the hematopoietic system were apparent, including decreases of red blood cell count, haemoglobin, haematocrit. These changes were transient and generally greater in females than in males; (i.e. HCT (M) -8%, -35% (F) at 500 mg/kg). Microscopic changes were present in the reproductive systems in males and females. Changes included degeneration /atrophy in the seminiferous tubules of the testes, reduced luminal sperm in the epididymis at ≥50 mg/kg and reversed at the end of the recovery period. In females' ovarian cystic follicles, decreased corpora lutea, and interstitial cell hyperplasia were noted at the dose of ≥50 mg/kg and did not recover during the treatment-free period in contrast to the effects on males. The relevance of the ovarian and vaginal findings to humans is unclear (see section reproductive toxicology). Effects on thyroid gland (follicular call atrophy), thymus and mesenteric lymph node (minimal to mild depletion) did not resolve at the end of the recovery period in the 3-month study. Liver enzymes (i.e. AST, ALT) increased but recovered except for increased bilirubin. However, there were no microscopic changes in the liver.

In the 3-month study in monkeys, tovorafenib was administered in a Q2D schedule with doses up to 20 mg/kg/day. This treatment regimen resulted in early deaths of 5 females (3 females at 10 mg/kg on day 61 and 63, and 2 females at 20 mg/kg on day 47 and 63) due to GIT including body weight loss, poor body condition scores, and diarrhea, decreases in red blood cell mass, increased bone marrow myeloid to erythroid ratio. These findings occurred at exposures below the exposures observed clinically following administration of 600 mg QW tovorafenib in adults [equivalent to 10 mg/kg for a 60 kg adult] and 420 mg/m^2 (QW) in paediatric patients (clinical AUC0-24 adults 47,143; clinical AUC0-24 paediatric 81,900)]. The remaining mid- and high-dose male and female animals were necropsied early on D72 and D70, respectively, demonstrating similar adverse effects as the females that were early euthanised. Thus, the 3-month dosing was shortened to a 2-month dosing; only animals with the lowest dose tested were administered tovorafenib for the proposed dosing duration of 3-month. The applicant did not include the early euthanasia animals in the data analysis of hematology findings; however, the results in early death animals were similar to surviving animals.

Exposure in female rats was approximately 1.6 to 2.2-fold higher for Cmax and AUC compared to male rats at every dose level. Exposure in monkeys was similar between males and females. However, exposure multiples compared to the NOAEL of the clinical exposure demonstrated no margins of exposure within the pivotal long-term repeat-dose toxicology studies (rats: 0.39 (M) for adults and 0.22 (M) for paediatric patients; monkeys: 0.41 (M) for adults and 0.23 (M) for paediatric patients).

Findings of hemorrhage in the rat ovaries were observed in the 4-week study (study no. P024-09-05), but were not observed in the 13-week study (study no. 20060186). Findings in bone (femur, tibia, sternum), and ovary, were observed in the 3-month study. Findings of hemorrhage in the monkeys included colon in the 4-week study and esophagus, colon and rectumin the 3-month study. Intra-tumoural hemorrhage related to tovorafenib was also found in patients and is included as ADR.

Clinical chemistry parameters included an increase of ALT and AST in rats and monkeys without corresponding histopathology and recovered during the treatment-free period. There were also no treatment emergent adverse events consistent with drug-related liver dysfunction in patients. Nevertheless, higher tovorafenib exposure was associated with elevated liver enzymes in patients (ALT and AST).

Skin toxicities are a well-known side effect of MAPK inhibitors and tovorafenib was present in melanin-containing tissues (e.g., skin-pigmented and eye uveal tract) in the QWBA study in Long Evans rats and concentrations in pigmented skin were notably higher than concentrations in nonpigmented skin. Skin abnormalities were present in patients.

4.4.2. Genotoxicity

The genotoxicity package for tovorafenib includes standard ICH-compliant *in vitro* and *in vivo* assays. The bacterial reverse mutation test (Ames) was performed in multiple Salmonella strains and E. coli, with and without metabolic activation (S9). Concentrations up to 5000 µg/plate were used, with appropriate controls and no evidence of mutagenicity. The study is adequate and supports a negative outcome.

A chromosomal aberration assay was conducted in human peripheral blood lymphocytes. A statistically significant increase in aberrations was observed only at ≥200 µg/mL in the presence of S9, coinciding with visible precipitation and signs of cytotoxicity.

An *in vivo* micronucleus assay in rats (GLP, oral administration up to 2000 mg/kg) showed no increase in micronucleated PCEs and no myelotoxicity.

4.4.3. Carcinogenicity

The study report of 26-week Tg Ras mouse carcinogenicity study was submitted. In this study Tg Ras mice were dosed at 10, 30, and 100 mg/kg/day by oral gavage for 26 weeks. It was concluded that tovorafenib was well tolerated at all doses with no effects on carcinogenicity, survival rate, or adverse findings. No tovorafenib-related neoplastic or non-neoplastic lesions were noted microscopically. Based on these results, the NOAEL was considered to be 100 mg/kg/day. This dose corresponded to mean AUC0–24hr values of 40300 and 48900 ng*h/mL and mean Cmax values of 3180 and 3640 ng/mL for males and females, respectively, on Day 180 yielding AUC-based safety margins of ~1 for adults and ~0.5 for paediatrics. The 2-year rat carcinogenicity study is ongoing.

The carcinogenicity evaluation is considered adequate considering the ongoing 2-year study. The absence of treatment-related neoplastic or non-neoplastic pathology, in conjunction with GLP-

compliant conduct and sufficient systemic exposure, supports the conclusion that tovorafenib does not pose a carcinogenic risk in the Tg Ras mouse model.

4.4.4. Developmental and reproductive toxicity

A fertility study was conducted with administration of tovorafenib to male and female rats at doses up to 150 mg/kg/day from 28 days and 14 days before mating, respectively, continued through cohabitation with untreated animals up to study day 64 and gestation day (GD) 7, respectively. In males, there was no tovorafenib-related effect on mating and fertility, reproductive organ weights, sperm parameters, and early embryonic development at doses up to 150 mg/kg/day. In addition, the data suggest that there was a treatment-related decrease in testes weight at all dose levels – based on statistically significant decrease of absolute left and right testes in all treated groups compared to controls (9.6-15.4%), with values being outside of the historical control range in high dosed animals for absolute weight and at all doses for testes weight relative to body weights. In females, fertility was affected at all doses corresponding to subclinical exposure levels (≥37.5 mg/kg/day, ≥0.8-fold human exposure based on TK data from the embryo-foetal development study) with decreased corpora lutea, implantations as well as an increase in postimplantation loss and dead embryos leading overall to lower numbers of total and live embryos. There was also a trend towards increased preimplantation loss in treated compared to control animals which may have been masked by an unusual higher value in the control group. Consequently, the NOAEL for general toxicity of tovorafenib in males and females as well as the reproductive NOAEL for male rats was 150 mg/kg/day. For the female reproductive performance no NOAEL could be defined. Treatment-related effects on the male and female reproductive systems were reported in repeat-dose toxicity studies conducted in rats at subclinical exposure levels. In males, the 3-month study highlighted decreased testes and epididymal weights with associated microscopic findings of seminiferous tubules degeneration/atrophy and reduced epididymal luminal sperm at all doses (≥ 50 mg/kg Q2D, 0.3-fold human exposure); lower testes weight persisted after 2 weeks of recovery. Testes weight was also decreased in the 4-week study at 500 mg/kg Q2D (0.6-fold human exposure). In females, 4-week and 3-month repeat-dose toxicity studies in rats showed non-reversible changes in ovaries at all doses and (≥50 mg/kg Q2D, ≥0.4-fold human exposure) and interpreted as suggestive of reproductive senescence.

In the preliminary EFD study administration of tovorafenib caused 100% early resorptions and total litter loss in all treated pregnant rats at doses of 37.5, 75, or 150 mg/kg/day. No litters were available for evaluation from tovorafenib-treated dams.

4.4.5. Toxicokinetics and exposure margins

The interspecies comparison and exposure margin analysis raise several concerns regarding the adequacy of systemic coverage, particularly for chronic use in the paediatric population. While toxicokinetic data were robustly collected in both rats and monkeys, systemic exposures at the established NOAELs are close to or below the expected clinical exposure in children receiving the recommended dose (600 mg/week). When recalculated against the paediatric AUC_{0_24} (72,571 ng·h/mL from FIREFLY-1), the margins fall below 1 in all relevant studies, with no NOAELs established in females of either species.

Mechanistically, the lack of explanation for sex-based differences in exposure and toxicity in rats, as well as the non-linear pharmacokinetics observed at higher doses (with exposure plateauing), complicates interpretation. Moreover, the absence of a bridging toxicokinetic study using the clinical ASD formulation under repeated dosing adds further uncertainty when extrapolating from animal to human data.

Nonetheless, the findings appear consistent across species and are qualitatively in line with the known pharmacology of the compound. The toxicities observed are predictable and mostly reversible.

4.4.6. Local tolerance

No dedicated local tolerance studies were conducted. However, across the repeated-dose oral toxicity studies in rats and cynomolgus monkeys (both GLP and non-GLP), no macroscopic or microscopic findings were reported in the oral cavity, pharynx, oesophagus, or upper gastrointestinal tract that would suggest local irritation or intolerance at the site of administration. Some gastrointestinal findings (e.g. cryptic abscesses, epithelial changes) were observed at high doses, primarily in the intestine and colon, and were interpreted as systemic toxicities rather than local effects. The clinical formulations (suspension, PEG-based vehicle, and ASD) were not associated with any overt signs of local intolerance.

4.4.7. Other toxicity studies

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, patients should be monitored for signs of phototoxicity.

4.4.8. Ecotoxicity/environmental risk assessment

Table 8: Summary of main study results: Phase I

Substance (INN/Invented Name):	tovorafenib		
CAS-number (if available):	1096708-71-2		
PBT/vPvB screening			
Study type	***Test protocol***	***Result***	***Conclusion***
Bioaccumulation potential-log Kow	OECD123	3,53 at pH 7 3,43 at pH 9	Potential PBT: N
PBT/vPvB assessment			
Property	***Parameter***	***Result***	***Conclusion***
Bioaccumulation	log Kow	3,53 at pH 7 3,43 at pH 9	Not B
	BCFKgl	X L/kgww	Not B/B/vB
Persistence	Ready biodegradability	Y/N	potentially P/not P
	DT50,X at 12°C	No DT_{50} provided; not readily biodegradable claimed; however, log DOW < 4.5 and no PBT	Not P

		triggered	
Toxicity	$NOEC_{aquatic}$ C, M, R STOT RE 1 or 2*	No NOEC provided; some concern due to potential endocrine activity in rats	Not T
PBT/vPvB statement:	Tovorafenib is considered to be not PBT, nor vPvB		

Phase I			
Parameter	***Value***	***Unit***	***Conclusion***
PEC_{sw}	3.0 default 0.001368 refined	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)	potential to be an endocrine disrupter.		Y

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacology

The inhibitory potency of tovorafenib towards the wild-type and mutant BRAF was compared to that of its *S*-enantiomer in an enzyme-coupled assay revealing higher potency of tovorafenib (*R*-enantiomer). As pan-RAF target all isoforms (ARAF, BRAF and CRAF), classification of tovorafenib as pan-RAF inhibitor is considered misleading for future use. Tovorafenib is considered a type II inhibitor of mutant BRAF V600E, WT BRAF, and WT CRAF, with a variable activity against WT BRAF, based on available data. The lack of ARAF inhibition is not expected to impact tovorafenib therapy in current indication.

Sensitivity of WT BRAF to tovorafenib is variable *in vitro* and suggests that biochemical inhibition does not translate into cellular efficacy *in vitro* and is not correlated with *in vivo* activity. However, since it is the case for mutated and fusion BRAF according to presented data, the matter is not pursued.

Efficacy was dependent on administration and tumours regrew when treatment was stopped. Upon reinitiating treatment, tumours-maintained sensitivity to tovorafenib which is indicative of lower resistance probability. *In vivo* studies were performed only on female mice.

Data generated in preclinical BRAF fusion models suggest that tovorafenib is capable of inhibiting MAPK pathway signalling without inducing paradoxical activation in BRAF fusion–driven systems. However, the translational relevance of these models is limited, as they do not adequately reflect the genetic and biological characteristics of paediatric low-grade gliomas, particularly with regard to TP53 status. Therefore, while the non-clinical findings may be considered supportive, the confirmation of BRAF fusions as a predictive biomarker for tovorafenib efficacy in pLGG ultimately relies on robust clinical data.

Exposure and efficacy were not always dose-dependent *in vivo* depending on dose and administration schedules. There appears to be a limitation of the exposure and efficacy, which could be due to limited absorption and/or saturation in the tumour. Regarding plasma dosing of tovorafenib in melanoma xenograft study RSCH-2010-011, intragroup variation was high; variation coefficient was up to 70%, which was attributed to variations during the elimination phase.

Tovorafenib inhibited 14 human relevant kinases at 0.2 µM, which is lower than the Cmax unbound (Arg, Abl, DDR2, EphA1, EphA2, EphA8, Fyn, Lck, Lyn, MuSK, PTK5, SAPK2a and SAPK2b as well as transformed cKit(V560G) and PDGFRα(V561D)), and IC50 was determined for 10 of these kinases. The choice to determine IC50 for 10 out of 14 kinases is questionable, but adverse events that could emerge from such off-target effects were discussed and taken into consideration in the warnings. Tovorafenib also inhibited Adenosine A2A, Adenosine A3 and Glutamate/N-methyl-D-aspartic acid (NMDA)/polyamine but it was determined to represent a low risk based on adult unbound Cmax, and discussion in relation to paediatric unbound Cmax indicates low risk of inhibition in paediatric population.

Tovorafenib presents a potential risk for QT prolongation, especially in case of association with other QT-prolonging agents. Section 5.3 of SmPC was updated to reflect the hERG assay results and potential risk of QT prolongation. Regarding *in vivo* safety pharmacology, there was no apparent effect of tovorafenib administration on CNS parameters in rats.

Regarding NF1 models, *in vitro*, increased pERK levels were observed at lower concentrations of tovorafenib and decreased pERK at higher concentrations of tovorafenib. The trend of the pERK increase at lower concentrations was different between the NF1-LOF tumour cell lines. This effect is suggestive of paradoxical activation of the pathway in NF1-LOF tumour cell lines. Indeed, paradoxical activation by tovorafenib at subtherapeutic doses (0.01–0.1 µM) was also described in literature. This could be linked to tovorafenib being ARAF sparing. Therefore, the limited non-clinical data do not support consistent activity of tovorafenib, and paradoxical activation could be an issue in this setting. *In vivo*, in $Nf1^{flox/flox}$, Postn-Cre+ mice, tovorafenib did not inhibit ERK phosphorylation and did not reduce proximal nerve volume. A subset of larger tumours (n=5) was also observed in treatment group with an increase in tumour number in 2/12 mice (approximately 17%), although both parameters were not statistically significant. However, this entails that tovorafenib as monotherapy is not sufficient to prevent tumour growth in the NF1-LOF setting. Based on these non-clinical data and discussions, and literature articles Rastogi et al. (2025)/ Bessler et al. (2024)[2], in the NF1-LOF setting, there is a potential risk of increased tumour growth in response to tovorafenib, and this is reflected in the sections 4.4 and 5.3 of the SmPC. Although tumour induction was not statistically significant, in parallel with increase pERK observed *in vitro*, there is a biologically relevant cause for concern regarding safety of this population. The overall data are robust and consistent with the properties of a lipophilic, highly plasma protein-bound kinase inhibitor with extensive tissue distribution and low metabolic clearance. The species used (rat and cynomolgus monkey) are appropriate for safety assessment.

Pharmacokinetics

The pharmacokinetics of tovorafenib was characterised following intravenous and oral administration in mice, rats, dogs, and monkeys. The intended route of administration in humans is oral. Analytical methods employing liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) to analyse tovorafenib in rat and monkey (pivotal toxicological species) plasma were developed and successfully validated under GLP conditions. Tovorafenib is orally absorbed with good bioavailability in animals and humans. All repeated-dose TK data were generated using aqueous suspensions, which allows higher exposition in animals.

Clearance of tovorafenib was low across species. Following oral administration in male SD rats, male Beagle dogs and male cynomolgus monkeys, exposure was less than dose-proportional and was saturated in rats and dogs at higher doses. In contrast, only minimal increase in exposure with dose

[2] Bessler W, Perino S, Venetsanakos E, Jiang L, Li X, Mang H, et al. Impact of the type II RAF inhibitor tovorafenib on tumor development in a genetically engineered mouse model of plexiform neurofibroma (PN). In: Poster presentation at: 2024 Global NF Conference Brussels; 2024 Jun 22; Belgium, 2024.

was noted in female rats. After multiple oral dosing, the half-life was longer and plasma levels higher in female rats, which was attributed to lower CYP levels. In female mice, exposure was dose-proportional and similar in wild-type and immunodeficient mice. Bioavailability of suspension formulations was lower compared to solution formulations and decreased with dose, which was attributed to limited absorption.

The time-independent clearance and absence of frank accumulation in both species support a predictable kinetic profile consistent with once-weekly dosing in humans. In monkeys, systemic exposure is more predictable and proportional up to 20 mg/kg, with moderate accumulation only under daily dosing. No sex differences were observed in primates. The half-life is markedly longer in monkeys (~20 h) than in rats (~6 h).

Protein binding was high across species and increased slightly with concentration in mouse, rat, dog and monkey plasma. Protein binding was not concentration-dependent in rabbit and human plasma.

In vitro, tovorafenib had high affinity for red blood cells across species. However, in a human study the ratio of total radioactivity in whole blood vs. plasma (as assessed by AUC0-∞ and AUC0-tlast) indicated limited partitioning to red blood cells.

The tissue distribution of [^{14}C]-tovorafenib was investigated following single oral dosing to male Long-Evans rats. The tissues with the highest levels of radioactivity were as follows: small intestine, adrenal gland, liver, oesophagus, kidney cortex, brown fat, stomach, kidney medulla, cecum, pancreas, Harderian gland, eye uveal tract, salivary gland, and heart. Tovorafenib was found in melanin-containing tissues but since tissue concentrations gradually declined over time it was concluded that melanin binding is reversible. Blood:plasma ration of drug-related radioactivity was 1.03 suggesting moderate distribution into RBC, consistent with the *in vitro* experiment in rat whole blood. The brain:plasma AUC ratio of tovorafenib-derived radioactivity was 0.57 (cerebellum), 0.54 (cerebrum) and 0.67 (medulla) indicating the passage of the blood-brain barrier. This result agrees with the data from male CD-1 mice having brain:plasma concentration ratios between 0.154 and 0.178.

Tovorafenib is metabolised by aldehyde oxidase and CYP2C8 with a minor contribution of CYP2C9 , CYP2C19 and CYP3A4. Metabolic profile in rat and monkey hepatocytes was more similar to human hepatocytes than that in dog hepatocytes. No unique human metabolites were identified. No toxicological evaluation of metabolites is warranted as no human metabolites exceeded 10% of total drug-related radioactivity.

Biliary-faecal excretion was the major elimination pathway of [^{14}C]-tovorafenib in rats, with over 76% of the dose recovered in faces and approximately 21% of the dose recovered in urine. In bile duct-cannulated rats, 19% of drug-related radioactivity were eliminated in urine, 26% in bile and 52% in faeces.

PK interactions

The applicant has conducted several in vitro studies to assess the DDI risk of tovorafenib as both object and precipitant.

As on object, the results showed that tovorafenib is primarily metabolised through aldehyde oxidase (AO) and CYP2C8, with minimal contributions from CYP3A4/5, CYP2C9, and CYP2C19). These results suggesting that the DDI risk with CYP2C8 modulators and tovorafenib as an object could not be ruled out.

Based on these simulations with CYP2C8 modulators using PBPK modelling outcomes, a statement advising against co-administration of tovorafenib with moderate or strong CYP2C8 inducers, has been included in section 4.5 of the SmPC. Similarly, co-administration with moderate or strong CYP2C8 inhibitors should be avoided or, if unavoidable, patients should be closely monitored for potential

adverse reactions. This risk minimisation approach may be considered acceptable as a conservative measure.

However, the Applicant's PBPK-approach for the estimation of DDI impact with CYP2C8 inhibitors and CYP2C8 inducers is not regarded acceptable from the regulatory perspective, and it is not in accordance with the EMA PBPK guideline. Of further note, Simcyp platform is not considered qualified for the PBPK predictions in such scenarios where no clinical DDI data for the investigational drug with a strong CYP inhibitor are available/generated.

According to the ICH M12 GL, since tovorafenib is metabolised by CYP2C8 (49.23%), which makes it by far the most important enzyme in the metabolism of this drug, a clinical DDI study with a strong CYP2C8 inhibitor (i.e., gemfibrozil) and with strong or moderate inducer should be conducted (**REC**). This is in order to confirm the actual in vivo contribution of CYP2C8 enzyme, as well as to inform SmPC about potential DDI risks when co-administering tovorafenib with CYP2C8 inhibitors and/or inducers.

In conclusion, all PBPK-based claims in this regard were asked to be removed from the SmPC, and a clinical DDI study with strong CYP2C8 inhibitor is requested. In response, the Applicant stated that a Phase 1 drug-drug interaction study of tovorafenib as a victim is ongoing. This study will assess the effects of gemfibrozil (a strong CYP2C8 inhibitor) and carbamazepine (a moderate CYP2C8 inducer) on the pharmacokinetics of tovorafenib in healthy participants (**REC**). The current recommendations regarding the use of moderate or strong CYP2C8 inhibitors or inducers in the SmPC/PIL may be updated based on the results from this clinical study, once available. All PBPK citation was also removed as asked.

As a precipitant, the potential for DDIs risk with CYP2C8 and CYP2C9 substrates cannot be ruled out, as the observed Ki,u values are below the expected maximum systemic concentration under worst-case conditions ($50*C_{max,\,u}$, i.e. 13.95 µM). Tovorafenib is also considred as both inhibitor and inducer of CYP3A4 *in vitro*.

Tovorafenib is an inducer of CYP1A2, 2B7, 3A4 and 2C8, since the fold increase in mRNA expression was > 2-fold relative to the vehicle control and in a concentration dependent manner.

In addition, tovorafenib showed to be an in vitro inhibitor of BCRP, OATP1B1, OATP1B3 and MATES trasporters, therefore, potential DDIs risk between tovorafenib and substrates of these transporters could not be ruled out.

Regarding the P-gp inhibition potential the highest concentration tested do not encompasses the estimated worst-case intestinal concentration (0.1 × dose/250 mL, i.e., 474 µM). The applicant has justified this matter by the fact that the theoretical worst-case intestinal concentration could not be achieved due to solubility limitations in physiological buffer systems (primarily due to precipitation). This approach is considered acceptable. Based on the study results, the DDI risk of tovorafenib on P-gp substrates could be ruled out.

The inhibition potential risk of tovorafenib on these enzymes and transporters was further evaluated using Simcyp PBPK modeling.

A PBPK model was developed and verified based on the clinical data then was used in predicting the DDI potential of Tovorafenib as a perpetrator on CYP3A4, CYP2B6, CYP1A2, CYP2C8 and CYP2C9, as well as on the transporters BCRP, MATE1, OATP1B1, and OATP1B3, with the probe substrates being midazolam (CYP3A4), bupropion (CYP2B6), caffeine (CYP1A2), repaglinide (CYP2C8), tolbutamide (CYP2C9), rosuvastatin (BCRP), pravastatin (BCRP and OATP1B1/1B3), and metformin (MATE1).

Regarding CYP3A4 modulation, The Applicant's PBPK approach to estimate the clinical net interaction effect of these complex simultaneous interaction mechanisms on CYP3A4 is not considered acceptable. Moreover, as already mentioned above, the Simcyp platform is not qualified for the prediction of CYP

induction. Therefore, these positive CYP3A4 *in vitro* DDI signals should be followed up by a clinical DDI study with tovorafenib and a sensitive CYP3A4 substrate **(REC).**

The same applies to other CYP enzymes. Since the PBPK model is considered insufficiently qualified, the induction effects on CYP2B6 and CYP1A2, as well as the inhibition effects on CYP2C8/9 by tovorafenib, need to be further addressed through appropriate SmPC restrictions/information and/or clinical DDI studies. In response, the Applicant stated that a post-marketing clinical DDI study is underway to investigate the impact of repeated doses of tovorafenib on the PK of sensitive CYP1A2, CYP2B6, CYP2C8 and CYP2C9 substrates. The timetable and status for this study were provided. It was stated that the SmPC/PIL will be updated based on the results from this clinical study, if regarded necessary once the study results are available. The applicant has updated section 4.5 of the SmPC to highlight the potential DDI risk with these CYPs substrates, with a recommendation for appropriate monitoring when they are co-administered with tovorafenib (**REC**).

Similarly, the use of PBPK modelling simulations to predict transporter-mediated DDI risk is currently not considered acceptable to support statement in the SmPC. As a consequence, section 4.5 of the SmPC states that in vitro data indicated that tovorafenib may have the potential to inhibit BCRP, OATP1B1, OATP1B3 and MATE1, the clinical relevance of these findings being unknown. When tovorafenib is co-administered with medicinal products that are substrates of these transporters, appropriate monitoring is recommended. A clinical DDI study (Study DAY101-104) evaluating the effect of tovorafenib on BCRP, OATP1B1 and OATP1B3 probe substrate (rosuvastatin) is ongoing (**REC**).

Other DDI risk consideration

Tovorafenib is highly protein-bound in plasma (98%), primarily to human serum albumin (HSA) and, to a lesser extent, alpha-1 acid glycoprotein (AAG). Despite lower HSA and AAG concentrations in 6-month-old patients compared to adults, which could potentially increase the risk of adverse effects and DDIs. The applicant’s rationale, demonstrating that age-related variations in HSA and AAG levels in 6-month-old patients do not alter tovorafenib exposure. This is supported by the drug's pharmacokinetic profile, including its low-extraction-ratio, stable metabolic pathway predominantly mediated by aldehyde oxidase, and low risk of protein binding displacement interactions. The maximum concentration of tovorafenib is below AAG concentrations and significantly lower than HSA's high binding capacity, making saturation or competitive displacement unlikely, and thus the risk of altered free drug exposure or DDIs due to protein binding displacement is negligible. Overall, the pharmacokinetic and metabolic profile of tovorafenib supports the conclusion that age-related variations in HSA and AAG levels do not increase the risk of adverse effects or DDIs.

No DDI studies have been conducted to evaluate the impact of AO inhibitors or inducers on the PK of tovorafenib. The clinical relevance of AO-mediated interactions remains uncertain and there are no “AO index inhibitor and inducers” categorized in official EMA (or) FDA guidelines. As tovorafenib metabolism involves multiple CYP enzymes in addition to AO, even if one pathway is inhibited or induced by concomitant medications, the presence of alternative routes would ensure that the elimination process would remain largely unaffected. SmPC amendments based on the current knowledge about AO-mediated metabolism of tovorafenib are not warranted.

PK results of drug-drug interaction studies cannot be interpreted based on postulated no-effect boundaries. Therefore, a cautious approach should be taken regarding DDIs and hepatic and renal impairment in the SmPC. As noted in Section 4.5 of the SmPC, concomitant use of strong and moderate CYP2C8 inducers or inhibitors should be avoided.

The applicability of the DDI assessment to paediatric patients is plausible, especially for CYP2C8 and aldehyde oxidase (AO) which are the main enzymes of concern considering the ontogeny. Regarding the maturation of CYP2C8, the classical sigmoidal Hill function shows a rapid increase after birth in

the study by Vijay et al. (2016), reaching near-adult levels within six months. Therefore, no significant impact on CYP2C8 maturation is expected after six months. On AO ontogeny, according to Tayama et al. (2012), young children (aged 13 days to 4 months) exhibited low levels of AO activity in their liver cytosol. However, these oxidase activities increased markedly after 4 months, reaching adult levels by around 2 years of age. Therefore, as with rats, AO activity in humans increases rapidly soon after birth and is regulated at the level of protein expression. More importantly, tovorafenib metabolism involves multiple CYP enzymes as well as AO, suggesting a metabolically redundant clearance pathway and a limited risk of drug–drug interactions.

Toxicology

Repeat dose toxicity studies have been conducted in line with ICH requirements. These studies did not identify safety concerns at the intended clinical exposure. The available data were considered sufficient to characterise the non-clinical safety prodile of tovorafneib for the proposed use.

In the non-clinical repeat-dose toxicity studies, the oral route was chosen since this is the intended clinical route. Sprague Dawley rats and cynomolgus monkeys were used as relevant species based on comparison of metabolite profiles generated by isolated hepatocytes from mice, rats, dogs, rabbits, cynomolgus monkeys, and humans

In rats, although the dosing regimen was generally well tolerated, haematological effects, including decreases in red blood cell parameters, were observed, along with reproductive changes in both males and females. Some of the female reproductive findings persisted throughout the recovery period, whereas male reproductive effects were generally reversible. The translational relevance of these findings to humans, particularly in the paediatric population, remains uncertain.

In monkeys, the studies indicated that gastrointestinal and haematological adverse effects occurred at exposures below those expected clinically. These effects led to early termination of several high-dose groups and shortening of the planned dosing duration, which limits the interpretation of long-term toxicity at clinically relevant exposures. The data suggest that, although the non-clinical findings are indicative of potential toxicities, the exposure margins relative to the proposed clinical doses are limited. Furthermore, no juvenile toxicity studies were conducted. Rats were about 8 to 10 weeks of age and monkeys 2.3 to 3.9 years of age corresponding to 12 to 16 years of human age. While this is in line with ICH S9 guidance for oncology indications, it represents a deviation from ICH M3(R2) and should be considered in the context of the intended paediatric use. Exposure in female rats was approximately 1.6 to 2.2-fold higher for Cmax and AUC compared to male rats at every dose level. Exposure in monkeys was similar between males and females. However, exposure multiples compared to the NOAEL of the clinical exposure demonstrated no margins of exposure within the pivotal long-term repeat-dose toxicology studies (rats: 0.39 (M) for adults and 0.22 (M) for paediatric patients; monkeys: 0.41 (M) for adults and 0.23 (M) for paediatric patients). dFindings of hemorrhage in the rats included thymus, mesenteric and submandibular lymph nodes, and bone (femur) in the 4-week study, and bone (femur, tibia, sternum), ovary, and liver in the 3-month study. Findings of hemorrhage in the monkeys included esophagus and colon in the 4-week study and rectum, thyroid, lymph node, and uterus in the 3-month study. Intra-tumoural hemorrhage related to tovorafenib was also found in patients and is included as ADR. However, it should be mentioned as important identified risk rather than as important potential risk in the RMP (see below). Clinical chemistry parameters included an increase of ALT and AST in rats and monkeys without corresponding histopathology and recovered during the treatment-free period. There were also no treatment emergent adverse events consistent with drug-related liver dysfunction in patients. Nevertheless, higher tovorafenib exposure was associated with elevated liver enzymes in patients (ALT and AST). This is adequately mentioned in the SmPC. Skin toxicities are a well-known side effect of MAPK inhibitors and tovorafenib was present in melanin-containing tissues (e.g., skin-

pigmented and eye uveal tract) in the QWBA study in Long Evans rats and concentrations in pigmented skin were notably higher than concentrations in nonpigmented skin. Skin abnormalities were present in patients. Therefore, patients should be monitored for signs of phototoxicity which is addressed under the appropriate sections of the SmPC.The following information is included in section 5.3 of the SmPC: *In repeat dose toxicology studies in rats of up to 3 months duration, tovorafenib related findings in female rats included 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 doses approximately 0.4 fold the human exposure at the recommended dose based on AUC. 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 doses approximately 0.3 fold the human exposure at the recommended dose based on AUC.*

Genotoxicity and Carcinogenicity

The genotoxicity studies conducted were comprehensive and consistent with ICH S2(R1) standards. Exposure was adequate based on toxicokinetics. The species is relevant, and the model is validated. Despite a transient positive chromosomal aberration result at precipitating concentrations *in vitro*, the overall evidence strongly indicates that tovorafenib lacks clinically relevant genotoxic potential, a conclusion reinforced by negative *in vivo* micronucleus testing. This was considered as not biologically relevant due to the absence of a clear concentration–response and the artefactual nature of the findings at precipitating concentrations. The carcinogenicity evaluation is considered adequate considering the ongoing 2-year study. The absence of treatment-related neoplastic or non-neoplastic pathology, in conjunction with GLP-compliant conduct and sufficient systemic exposure, supports the conclusion that tovorafenib does not pose a carcinogenic risk in the CD-1 mouse model.

The following information is included in the section 5.3 of the SmPC:

Tovorafenib was not carcinogenic in a 26-week (or 6 month) study in transgenic mice at exposures approximately 0.6-fold the human exposure (AUC) at the recommended human dose. Based on in vitro and in vivo studies, tovorafenib is not considered genotoxic at clinically relevant exposures.

Developmental and reproductive toxicity

The rationale supporting the conduct of the fertility study is unclear considering the toxicological data available in rats at subclinical exposure levels suggesting already that human male and female fertility may be impaired during treatment with tovorafenib. In addition to the known low sensitivity of mating trials in male rodents for risk assessment of human male fertility due to higher sperm production in these species, it has to be pointed out that the premating treatment duration of male rats was most likely not long enough to induce a sufficient degree of testicular toxicity in that study. Therefore, it is considered that the results obtained in the male rat fertility study would anyway not mitigate concerns for human male fertility identified from repeat dose toxicity studies in rats. For females, a similar conclusion may have been raised based on non-reversible ovarian changes interpreted as suggestive of reproductive senescence that were reported at all doses and at subclinical exposure levels in repeat-dose toxicity studies. Overall, section 4.6 of the SmPC reflects the potential impact on fertility of tovorafenib based on animal data. The following information is included: *There are no data on the effects of tovorafenib on fertility in humans. Based on findings in animals, tovorafenib may impact fertility in males and females of reproductive potential and may not be reversible*.

In consistency with reproductive toxicity findings in the FEED study, in the preliminary EFD study, administration of tovorafenib caused 100% early resorptions and total litter loss in all treated pregnant rats at doses of 37.5, 75, or 150 mg/kg/day. No litters were available for evaluation from

tovorafenib-treated dams. Based on this outcome, the NOAEL for embryo-foetal development could not be established and the teratogenic-potential of toforafenib on the foetus is unknown. The maternal NOAEL of the highest tested dose of 150 mg/kg/day is agreed, as body weight loss was secondary to the high early resorptions that resulted in total litter loss. Consequently, and in line with ICH S5 (R3), it is agreed that due to the massive embryo lethality observed in this preliminary rat EFD study at exposures roughly similar to that at the projected clinical exposure at the maximum recommended human dose (MRHD), additional EFD studies are not considered reasonable/warranted. This is reflected in section 5.3 and section 4.6 of the SmPC, indicating that *tovorafenib should not be administered to pregnant women unless the potential benefit to the mother outweighs the possible risk to the foetus. Pregnant women should be advised of the potential risk to the foetus. If a patient becomes pregnant while taking tovorafenib, the patient should be informed of the potential hazard to the foetus*. In addition, measures included in sections 4.4 and 4.6 of the SmPC to mitigate potential developmental toxicity in humans are acknowledged: *Before initiating treatment in women of childbearing potential, appropriate advice on effective methods of contraception should be provided. Women of childbearing potential must use effective non-hormonal contraception such as a barrier method during therapy and for 28 days after the last dose of tovorafenib. Male patients with female partners of reproductive potential must use condoms and effective contraception during treatment with tovorafenib and for 2 weeks after the last dose*.

Juvenile animal studies (JAS) were not conducted to support treatment of patients from 6 months of age. Based on the available toxicity studies, findings of concern for paediatric patients are notably those observed in rats on testes and ovaries. Of note, these effects were not seen in the 3-month monkeys study at up to 1.2- to 1.5-fold human exposure in animals aged 2.3-3.9 years of age at initiation of treatment, i.e. either prepubertal or pubertal according to ICH S11 (puberty occurs at ~3-4 years) and with histopathological examination of male reproductive tissues (epididymides, seminal vesicle, prostate, testes) reporting immaturity for all males. Considering the overall toxicological data with identified irreversibility of ovarian findings in rats, it is agreed that a JAS would not provide additional information because sufficient information for the target paediatric population is already available from non-clinical toxicity studies in rats and monkeys as well as from clinical studies. This is in line with PIP (EMEA-002763-PIP01-20) for patients aged 6 months to 18 years of age.

Interspecies exposure comparison

Exposure-based safety margins calculated using clinical adult data from study C28001 appear underestimated when considering clinically relevant paediatric exposure data (FIREFLY-1 study). Recalculated margins are significantly narrower, suggesting potential underestimation of risk in paediatric patients.

Other studies

No dedicated local tolerance studies were conducted. Nonetheless, existing repeat-dose toxicity studies did not indicate local irritancy or intolerance.

Based on its UV absorption profile and tissue distribution to melanin-containing tissues, tovorafenib poses a potential phototoxic risk. Clinical monitoring and sun-protection recommendations are endorsed.

Environmental Risk Assessment

A Phase I ERA concluded a low environmental risk based on predicted concentrations below the action limit (0.01 µg/L) and a negative PBT profile. However, pronounced reproductive effects observed in rats raise significant concerns regarding endocrine disruption potential.

Given reproductive toxicity findings indicative of endocrine disruption, further clarification regarding potential endocrine-disrupting properties is essential. The Applicant commits to perform the following studies as follow-up measures: Aerobic Transformation in Aquatic Sediment Systems (OECD 308), Fish sexual development test (OECD 234) and Bioaccumulation in fish (OECD 305) by October 31, 2027 (**REC**).

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of tovorafenib to the environment.

4.5.2. Conclusions

Tovorafenib demonstrated significant activity *in vitro* through RAF kinase inhibition and *in vivo* through tumour growth inhibition or regression, notably in models harboring BRAF V600E mutation. The toxicology programme identified systemic haematological, hepatic, and reproductive toxicities across species, with sex-specific sensitivity.

The Applicant commits to perform the following studies as follow-up measures: Aerobic Transformation in Aquatic Sediment Systems (OECD 308), Fish sexual development test (OECD 234) and Bioaccumulation in fish (OECD 305) by October 31, 2027.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant (see section 2.4.3.).

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

5.1.2. Tabular overview of clinical trials

Table 9: Tabular overview of main clinical studies

Status Study Number	Study Design	Study Population	Tovorafenib Dosing Regimen	Study objectives and primary endpoint	Number of subjects total randomised (treated)/completed study
Completed					
C28001	Phase 1, first-in-human, open-label, multicenter, with dose escalation and dose expansion phases	**Dose Escalation** Adult patients aged ≥18 years with advanced, solid (nonhematologic) malignancies **Dose Expansion** Adult patients ≥ 18 years old with advanced, solid (nonhematologic) malignancies or locally advanced, metastatic, or unresectable melanoma	**Dose Escalation** Q2D (22-day cycles): 20, 40, 80, 135, 200, 280 mg Q2D (28-day cycles): 200 mg QW (28-day cycles) 400, 600, 800 mg **Dose Expansion** Q2D (28-day cycles): 200 mg QW (28-day cycles) 600 mg	**Primary:** • Safety and tolerability • Determine the MTD • Determine the RP2D **Secondary:** • Preliminary efficacy per RECIST v1.1 • PK • PD markers in paired tumor biopsies	Planned: 198 Treated: 149 • Q2D Dose Escalation; N = 30 • QW Dose Escalation; N = 20 • Q2D Dose Expansion; N = 80 • QW Dose Expansion; N = 19

Status Study Number	Study Design	Study Population	Tovorafenib Dosing Regimen	Study objectives and primary endpoint	Number of subjects total randomised (treated)/completed study
C28002	Phase 1b, open-label, multicenter, with dose escalation and dose expansion phases	Adult patients aged ≥18 years with advanced solid tumors (excluding lymphoma)	**Dose Escalation** Arm 1: 100 mg tovorafenib (Days 1, 3 and 5 of each week) + MLN0128 Arm 2: 100 mg, 160 mg, 200 mg tovorafenib (Days 1, 3 and 5 of each week) + alisertib Arm 3: 100 mg, 160 mg, 200 mg tovorafenib (Days 1, 3 and 5 of each week) or 400 mg, 600 mg tovorafenib (QW) + paclitaxel Arm 4: 400 mg, 600 mg tovorafenib (QW) + cetuximab Arm 5: 300 mg, 400 mg tovorafenib (QW) + irinotecan (All 28-day cycles) **Dose Expansion** 600 mg (QW) + paclitaxel	**Primary:** • Safety • MTD and/or RP2D of each combination regimen **Secondary:** • Plasma PK • Preliminary efficacy per RECIST v1.1	Planned: approx 125 Treated: 81 • Dose Escalation; N = 71 • Dose Expansion; N = 10
DAY101-103	Phase 1, open-label study of the absorption, metabolism and excretion of [14C]-tovorafenib	Healthy adult males, aged ≥18 to ≤55 years	100 mg (200 µCi) single dose [^{14}C]tovorafenib	**Primary:** • Routes, elimination rates, and mass balance of total radioactivity • Characterize PK and total radioactivity **Secondary:** • Metabolite profiles in plasma, urine, and	Planned: 8 Treated: 7

Status Study Number	Study Design	Study Population	Tovorafenib Dosing Regimen	Study objectives and primary endpoint	Number of subjects total randomised (treated)/completed study
	following a single oral dose			feces Safety and tolerability	
DAY 101 QSC205140	Phase 1, single-center, 2-part, open-label, randomized, single-dose, crossover study Part 1: 6-way crossover study to evaluate the taste and palatability of tovorafenib intermediate drug product PfR suspension formulations Part 2: 3-period crossover study to evaluate the relative bioavailability of the PfR suspension formulation compared with the tovorafenib tablet formulation, and the effect of food	Healthy adults, aged ≥18 to ≤55 years	100 mg, 300 mg single dose[a]	**Primary, Part 1:** • Evaluate palatability and overall acceptability of PfR suspension formulations **Primary, Part 2:** • Determine rBA of PfR compared to tablet • Evaluate PK profiles of tablet and PfR • Assess effect of food on the single dose PK profiles for the tablet **Secondary, Part 2:** Safety and tolerability	Planned: 24 Treated: 24 • Part 1; N = 12 • Part 2; N = 12

Status Study Number	Study Design	Study Population	Tovorafenib Dosing Regimen	Study objectives and primary endpoint	Number of subjects total randomised (treated)/completed study
	on tovorafenib tablet exposures				
Ongoing					
FIREFLY-1 (DAY101-001, PNOC026)	Phase 2	Patients 6 months to 25 years of age (inclusive) with RAF-altered, relapsed or refractory pediatric low-grade glioma and advanced solid tumors	420 mg/m^2 (not to exceed 600 mg) QW on a 28-day cycle	Arm 1 Primary: IRC-assessed ORR by RANO criteria Secondary: • Safety and tolerability • PK • QTcF prolongation and ECG • Investigator-assessed ORR by RANO criteriaa • IRC-assessed ORR by RAPNO criteria • PFS, DOR, TTR, and CBR by RANO and RAPNO criteria • Duration of OS • Changes in BCVA • Concordance of local and central BRAF molecular Profiling Arm 2 Primary: Safety and tolerability Secondary: • ORR by RANO criteria • PFS, DOR, TTR, and CBR by RANO criteria • Duration of OS Arm 3 Primary: IRC-assessed ORR by RECIST v1.1 Secondary: • Safety and tolerability	Planned: 141 Treated: 143 • Arm 1; N = 77 • Arm 2; N = 60 • Arm 3; N = 6

Status Study Number	Study Design	Study Population	Tovorafenib Dosing Regimen	Study objectives and primary endpoint	Number of subjects total randomised (treated)/completed study
				• PFS, DOR, TTR, and CBR by RECIST v1.1 or RANO	

Abbreviations: C = cycle; D = day; h = hour;; PfR = powder for reconstitution; Q2D = once every other day; QW = once weekly; PK = pharmacokinetics; RAF = rapidly accelerated fibrosarcoma.

5.2. Clinical pharmacology

5.2.1. Methods

Several bioanalytical methods were used throughout the clinical development program to quantify tovorafenib in plasma and in urine. Of note, the bioanalytical methods employed were achiral in the PK investigation program. Considering that the active substance is the pure R-isomer of tovorafenib, a stereo-selective bioanalysis method was expected for the PK characterisation of the drug.

An additional LC-MS/MS method was developed to quantify both enantiomers of tovorafenib in K_2EDTA human plasma. Samples taken on day 1 and day 21 from 8 subjects from study #CS28001 and dosed with R-enantiomer were pooled into two samples before their analysis. Interconversion was found to be less than 4% in each of the pooled samples.

The sample stability over the long storage period between sample collection and analysis (up to 770 days) is established.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Tovorafenib has been initially developed in adult patients with solid cancers. In the context of this development, a study (dose-escalation) was conducted in small cohorts of patients. No formal studies were conducted in paediatric and young adult patients with glioma. In this target group of patients only sparse samples were collected and analysed according to a PPK approach.

5.2.2.1.1. Bioanalysis methods:

Several bioanalytical methods were used throughout the clinical development program to quantify tovorafenib in plasma and in urine. Generally, the used bioanalytical methods appear to comply with acceptance criteria regarding sensitivity accuracy and precision. Analytical validation reports were provided with satisfactory results for the method used. Short and long-term stability of the analytes in biological matrix were tested and shown to be satisfactory. Of note, the bioanalytical methods employed were achiral in the PK investigation program. Considering that the active substance is the pure R-isomer of tovorafenib, a stereo-selective bioanalysis method was expected for the PK characterisation of the drug.

An additional LC-MS/MS method was developed to quantify both enantiomers of tovorafenib in K_2EDTA human plasma. Samples taken on day 1 and day 21 from 8 subjects from study #CS28001 and dosed with R-enantiomer were pooled into two samples before their analysis. Interconversion was found to be less than 4% in each of the pooled samples.

The sample stability over the long storage period between sample collection and analysis (up to 770 days) is established.

5.2.2.1.2. Population Pharmacokinetics

The primary aim of this PPK analysis is to provide post-hoc estimates of systemic exposure parameters (AUC, Cmin, Cmax) in patients of study FIREFLY- based on the dosing regimen of 380 mg/m^2 (not to exceed 600 mg) QW. Additionally, exposure/efficacy and exposure/safety models were performed.

According to the applicant, tovorafenib concentration-time course was described by a one-compartment model with three-transit compartments absorption model (designated as Ka [Tablet]) for

the tablet formulation and first order absorption model with no transit compartment (designated as Ka [PfR]) for the powder for reconstitution (abbreviated PfR, equivalent to the term powder for oral suspension used in the SmPC).

A two-compartment model was explored and some information regarding this investigation is provided. The 2-CMT model resulted in a lower objective function value (OFV, ΔOFV=-23.853). According to the applicant, the 2-CMT model did not offer meaningful improvements in GOF diagnostics or pcVPCs. Based on these findings, the more parsimonious 1-CMT model was selected for further development and refinement, as it adequately captured the central tendency and variability in the available data without evidence of systematic bias.

PK simulations of systemic exposure in paediatric were performed using both the original 1-CMT model and the updated 2-CMT model. These simulations incorporating physiological scaling and enzyme maturation (CYP C18 and aldehyde oxydase). Simulations using both the original 1-CMT (run15pred) and updated 2-CMT (run48d) models, with and without maturation functions, yielded consistent conclusions regarding paediatric dosing.

5.2.2.1.3. Physiology based pharmacokinetic model

In the DDI risk assessment, the applicant developed a PBPK model to simulate the DDI risks of tovorafenib using both *in vitro* data and clinical pharmacokinetic data after an oral dose of 800 mg tovorafenib QW in cancer patients from Study C28001.

In the model validation, the simulated PK profiles, steady state AUC_{0-tau}, and Cmax for tovorafenib were compared to observed data that were reported from Study C28001, which involved oral doses of repeated 20, 40, 80, 135, 200, and 280 mg Q2D and 400 and 600 mg QW. The simulated outcomes in the validation were within a 1.25-fold range from the observed data for the higher dose (400mg to 600mg QW) and within a 1.5 to 2-fold for lower doses, demonstrating the ability of the model TO predict the observed data at higher doses (dose used to assess the DDI risk).

The PBPK model was then used in predicting the DDI potential of tovorafenib as a perpetrator on CYP3A4, CYP2B6, CYP1A2, CYP2C8 and CYP2C9, as well as on the transporters BCRP, MATE1, OATP1B1, and OATP1B3, with the probe substrates being midazolam (CYP3A4), bupropion (CYP2B6), caffeine (CYP1A2), repaglinide (CYP2C8), tolbutamide (CYP2C9), rosuvastatin (BCRP), pravastatin (BCRP and OATP1B1/1B3), and metformin (MATE1).

The PBPK model was refined by adjusting the CYP2C8 fractional metabolism value to 49.23%, based on available enzyme kinetic and clinical mass balance data. This updated model was subsequently used to evaluate the DDI risk of tovorafenib as an object of CYP2C8 modulation, including co-administration with moderate and strong CYP2C8 inhibitors and inducers.

5.2.2.2. Absorption

In vitro preclinical investigations evaluated for tovorafenib, the bidirectional permeability across Caco2 cells (reports PD09-24 and DOT1-DMPK-012) or its possible interaction with human transporters P-gp and BCRP (report DOT1-DMPK-012 and RPT-02116). The outcome of these investigations suggested that tovorafenib has high absorption permeability and low potential for P-gp mediated efflux.

The net uptake ratios of tovorafenib were less than 2 suggesting again that tovorafenib is not a substrate of BCR. Information on the PK profile of tovorafenib after single (here first dose) and repeated dose administration could be drawn from study C28001 and indicate that tovorafenib appears to be readily absorbed. The Cmax is reached about three hours after oral administration of an immediate release tablet.

No estimation of the absolute bioavailability could be made as no investigation of the IV route was performed. A BCS-class 2 classification (low solubility/high permeability) of the drug substance is proposed, based on *in-vitro* data (bidirectional permeability across Caco2 cells) and clinical investigation (Mass-Balance study).

Effect of food

Based on clinical study in healthy volunteers, no clinically significant differences in tovorafenib Cmax and AUC were observed following administration of tablets with a high fat meal (approximately 859 total calories, 54% fat) compared to fasted conditions, but the Tmax was delayed to 6.5 hours.

5.2.2.3. Bioequivalence

Tovorafenib is supplied as oral immediate release film-coated tablet containing 100 mg tovorafenib (abbreviated *IR tablet*) and 25 mg/ml powder for reconstitution. The tovorafenib 100 mg tablet and PfR 300 mg bottle (for reconstitution with water to 25 mg/mL) were used in the pivotal clinical trial Study *DAY101-001/PNOC026* (*FIREFLY-1*) and Phase 1 study *QSC201540* (relative BE and food effect study). In the initial Phase 1 clinical studies, an earlier formulation called T1 tablets was used. The T1 tablets and commercial tablets (T2 tablets) were comparable as demonstrated by *in vitro* dissolution with the clinical quality control (QC).

No relative BA investigation including the T1 formulation was performed.

5.2.2.4. Distribution

Based on *in vitro* investigations tovorafenib was found to be highly bound to both albumin (95%) and moderately on AAG (around 40%).

The apparent volume of distribution (V/F) was estimated at 118 L (approximately 60 L/m^2) by the PPK model analysis. Based on pop-PK modelling, tovorafenib apparent volume of distribution is 60 L/m^2 (23%).

5.2.2.5. Metabolism

An attempt to elucidate the metabolism pathway is made by the applicant based on *in vitro* investigations on human materiel and metabolite profiling in plasma, urine and faeces, performed in the mass-balance study (Study Day 101-103). Main results are:

- No major metabolite (>10% the exposure to parent drug) was identified in the mass balance study. No key enzyme was involved in the metabolism was identified neither.
- No major circulating metabolites present in human plasma and metabolites M3 and M26 accounted for <10% of total tovorafenib-related exposure in study C28001
- Aldehyde oxidase (AO) and cytochrome P450 (CYP) 2C8 are the major enzymes involved in the metabolism of tovorafenib; all other CYP isoforms (2C9, 2C19, and 3A4) involved in the metabolism of tovorafenib are minor (fraction metabolized < 10%).

5.2.2.6. Elimination

Information regarding the elimination of tovorafenib could be gathered from the mass-balance study (Study Day101-103).

The metabolism appears to be the major elimination pathway of tovorafenib. Following oral administration of 100 mg (200 µCi) of [^{14}C]-tovorafenib, approximately 66% of the radioactive material was recovered in faeces and 29 % in urine.

The geometric mean terminal $t_{1/2}$ of tovorafenib was estimated to be approximately 48 hours (and approximately 56 hours [CV: 33%] based on pop-PK modelling). Apparent oral clearance, calculated using noncompartmental analysis, was estimated to be 1.66 L/h (0.7 L/h/m^2). Renal clearance was minimal (0.00253 L/h).

5.2.2.7. Dose proportionality and time dependency

Based on the available investigations no shift from dose proportionality after single-dose was evidenced.

5.2.2.8. Pharmacokinetics in the target population

No formal investigations were performed in the target population. However, in patients over two years of age, the systemic exposure could be predicted by the refined PPK model. No reliable estimation could be made in patients under two-years of age even with the model incorporating maturation functions.

5.2.2.9. Special populations

The claimed indication implies the use of the in paediatric and young adults aged 6 months to 25 years.

The available data indicate that tovorafenib is eliminated primary by metabolism. No major metabolite is identified in the single dose mass-balance study. Drug related material (metabolites) were excreted mainly in faeces (66%) and secondary by urine (29%).

No formal study was performed in subjects with renal impairment. According to the applicant, renal impairment (RI) was not identified as a covariate of clearance in population PK analysis. In this PPK analysis 21 patients with moderate and 107 patients with mild RI were part of the analysed dataset. No patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) have been enrolled in clinical studies of tovorafenib and thus in the PPK analysis. Based on the drug elimination profile and the findings of the PPK, no dose adjustment is recommended in patients with renal impairment.

Despite liver being the primary route of elimination of tovorafenib, no dedicated study in patients with hepatic impairment (HI) was conducted.

Regarding gender, no comparison based on data from formal studies is provided. However, gender was tested as a covariate in the PPK modelling. Based on this analysis CL /F was associated with sex, where males were estimated to have a 21.5% higher CL/F than females. The systemic exposure estimation made the PPK model, indicates that exposure is slightly higher in female patients.

5.2.2.10. Pharmacokinetic interaction studies

5.2.2.10.1. PK drug-drug interactions

No clinical DDI studies were conducted.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Tovorafenib is an oral, central nervous system (CNS)-penetrant, selective small-molecule, type II rapidly accelerated fibrosarcoma (RAF) inhibitor.

Tovorafenib inhibits mutant v-raf murine sarcoma viral oncogene homolog B (BRAF) V600E, wild-type BRAF, and wild type v-raf murine sarcoma viral oncogene homolog C (CRAF) kinases with *in vitro* concentration required for 50% inhibition (IC50) values of 7.1, 10.1, and 0.7 nM, respectively. Tovorafenib inhibits mitogen-activated protein kinase (MAPK) signaling and cell growth of BRAF V600 mutant tumor cell lines *in vitro* and *in vivo* tovorafenib also inhibits MAPK signaling in tumors harboring BRAF fusions, including the KIAA1549-BRAF fusion.

5.2.3.2. Primary and secondary pharmacology

Study C28001 was the first-in-human Phase 1, multicenter, non-randomised, open-label, dose escalation and expansion study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and antitumor activity of tovorafenib in adult patients with advanced, solid (nonhematologic) malignancies.

The study consisted of a dose escalation phase and a dose expansion phase and tested 2 dosing schedules (Q2D and QW). In the dose escalation phase, which used a 3+3 dose escalation design, tovorafenib was administered orally Q2D in 22-day and 28-day treatment cycles, at doses of 20 mg, 40 mg, 80 mg, 135 mg, 200 mg, and 280 mg. Tovorafenib was also administered QW in 28-day treatment cycles, with a starting dose of 400 mg, then escalated to doses of 600 mg and 800 mg. Once weekly dosing was assessed in this study as an alternate dosing schedule to Q2D dosing because a majority of patients required early dose reductions following Q2D dosing at 200 mg. In addition, QW dosing schedule was expected to achieve higher tovorafenib concentrations, and therefore a higher degree of pathway inhibition within the dosing interval, without compromising overall dose intensity. The maximum tolerated doses (MTDs) were reached at 200 mg Q2D and 600 mg QW. Both 200 mg Q2D and 600 mg QW were further evaluated in the dose expansion phase. Patients fasted (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose of tovorafenib. Serial blood samples for plasma PK analysis were collected before and after dosing on Days 1 and 21 of Cycle 1 for the Q2D cohorts and on Days 1 and 22 for the QW cohorts. Additionally, for the Q2D cohorts, predose or trough samples were collected on Days 9 and 15 to evaluate time to steady-state. The study enrolled 149 patients (50 patients in the dose escalation phase and 99 patients in the dose expansion phase). All enrolled patients received at least 1 dose of tovorafenib, and 50 patients and 75 patients were PK-evaluable in the dose escalation phase and dose expansion phase, respectively.

5.2.3.3. Pharmacodynamic biomarker evaluation

As a RAF inhibition biomarker, the extent of pERK staining was assessed in the melanoma expansion cohorts by a pathologist (semi H-scores) and by quantitated image analysis (quant H-scores), with comparable results.

pERK staining in each of the 5 melanoma Q2D expansion cohorts (by pathologist) was medium-to-high at screening and decreased to low-to-medium levels on Day 21. There were median decreases from baseline in the level of pERK staining on Day 21 of ≥70% in the BRAF mutation-positive treatment-naïve cohort (-94.5% [range: -100% to -89%]), in the BRAF mutation-positive previously treated

cohort (-80.5% [range: -100% to 2207%), and in the NRAS mutation-positive treatment-naïve cohort (-70.0% [range: -100% to 603%]).

The median level of pERK staining in the melanoma QW expansion cohort (by pathologist) was medium at screening and decreased slightly on Day 21. The median percentage change from baseline in the level of pERK staining on Day 21 was small (-12.0% [range: -12% to -12%]) in this cohort.

5.2.3.4. Analysis of Efficacy – Q2D Cohorts

In the Dose Escalation phase, the ORR in the 22 patients assigned to TAK-580 Q2D and included in the response-evaluable population was 0% (Table below). A total of 5 patients (23%; 95% CI: 8, 45) in this group had a best response of stable disease.

In the Dose Expansion phase, the ORR in the 68 patients assigned to TAK-580 Q2D and included in the response-evaluable population was 15% (10 patients; 95% CI: 7, 25). There were 10 patients with a partial response to TAK-580 Q2D (15%; 95% CI: 7, 25) in this group: 8/16 patients (50%; 95% CI: 25, 75) in the BRAF mutation–positive treatment-naïve cohort, 1/6 patients (17%; 95% CI:<1, 64) in the BRAF mutation–positive previously treated cohort, and 1/14 patients (7%; 95% CI: <1, 34) in the NRAS mutation– positive treatment-naïve cohort. The median DOR in the 10 patients was 6.0 months (95% CI: 3.7, not estimable). The DORs ranged from 2 months (censored observation) to 42 months (censored observation) in the 8 patients from the BRAF mutation-positive treatment-naïve cohort with a partial response (median DOR: 6.0 months; 95% CI: 3.7, not estimable). The DOR was censored at 3 months in the patient from the BRAF mutation-positive previously treated cohort with a partial response. The DOR was 1.5 months in the patient from the NRAS mutation-positive treatment-naïve cohort who had a partial response. A total of 21/68 patients (31%; 95% CI: 20, 43) had a best response of stable disease (Table below).

In the PK Expansion cohort, the ORR in the 14 patients assigned to TAK-580 Q2D and included in the response-evaluable population was 0% (Table below). A total of 8 patients (57%; 95% CI: 29, 82) in this group had a best response of stable disease.

5.2.3.5. Analysis of Efficacy – QW Cohorts

In the Dose Escalation phase, the ORR in the 14 patients assigned to TAK-580 QW and included in the response-evaluable population was 14% (2 patients; 95% CI: 2, 43) (Table below). There were 2 patients with a partial response to TAK-580 QW (14%; 95% CI: 2, 43) in this group: 1/8 patients (13%; 95% CI: <1, 53) in the TAK-580 (600 mg) QW cohort and 1/3 patients (33%; 95% CI: <1, 91) in the TAK-580 (800 mg) QW cohort. The patient with a partial response in the TAK-580 (600 mg) QW cohort had Stage IV endometrial cancer at study entry; the patient in the TAK-580 (800 mg) QW cohort had thyroid cancer at study entry. The KRAS, BRAF, and NRAS mutation status of the tumors in the 2 patients was unknown or not reported.

The durations of response were censored at 2 months and 0 months in the patients with a partial response from the 600 mg QW group and 800 mg QW group, respectively. A total of 4/14 patients (29%; 95% CI: 8, 58) had a best response of stable disease (Table below).

In the Dose Expansion phase, the ORR in the 17 patients with NRAS mutation-positive treatment-naïve melanoma) assigned to TAK-580 QW and included in the response-evaluable population was 0% (Table below). A total of 9 patients (53%; 95% CI: 28, 77) in this group had a best response of stable disease.

Table 10: Best Response by RECIST 1.1 criteria based on investigator assessment (Response-evaluable population) - Study C28001

	Dose Escalation Phase			Dose Expansion Phase			
	Q2D Total N=22 Patients n (%) (95% CI)	QW Total N=14 Patients n (%) (95% CI)	Total N=36 Patients n (%) (95% CI)	PK Cohort N=14 Patients n (%) (95% CI)	Q2D Total N=68 Patients n (%) (95% CI)	QW Total N=17 Patients n (%) (95% CI)	Total N=85 n (%) (95% CI)
ORR [a]	0	2 (14) (2, 43)	2 (6) (<1, 19)	0	10 (15) (7, 25)	0	10 (12) (6, 21)
Complete response	0	0	0	0	0	0	0
Partial response	0	2 (14) (2, 43)	2 (6) (<1, 19)	0	10 (15) (7, 25)	0	10 (12) (6, 21)
Stable disease	5 (23) (8, 45)	4 (29) (8, 58)	9 (25) (12, 42)	8 (57) (29, 82)	21 (31) (20, 43)	9 (53) (28, 77)	30 (35) (25, 46)
Progressive disease	17 (77) (55, 92)	8 (57) (29, 82)	25 (69) (52, 84)	6 (43) (18, 71)	37 (54) (42, 67)	8 (47) (23, 72)	45 (53) (42, 64)

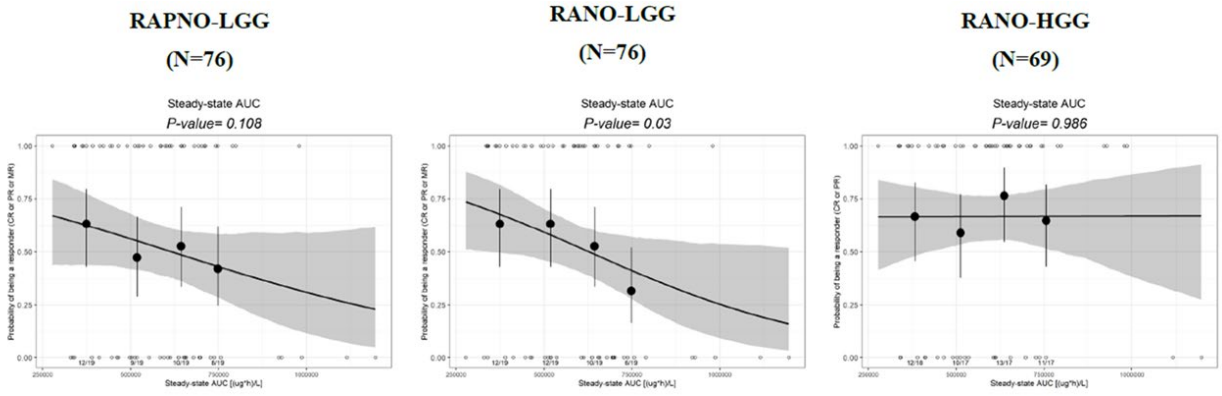
Percentages were based on the total number of patients in the response-evaluable population. 95% confidence intervals were based on exact binomial distribution. Abbreviations: ORR, overall response rate; PK, pharmacokinetic; Q2D, every other week; QW, weekly; RECIST, Response Evaluation Criteria in Solid Tumors. a ORR was defined as the proportion of patients whose best overall response was either complete response or partial response.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Exposure-Efficacy Analyses

Exposure-efficacy analyses consisted of exposure-tumor response (i.e. overall response rate) analysis and exposure-tumor size analysis. All efficacy data used in the exposure-efficacy analyses were from Arm 1 of Study FIREFLY-1.

Figure 2: Probability of Being a Responder versus Tovorafenib Exposure (AUCss) by Response Criteria (Primary Analysis that includes MR as responder for RAPNO and RANO-LGG)



Abbreviations: AUCss = steady-state area under the plasma concentration-time curve; CI = confidence interval; CR = complete response; PR = partial response; MR = minor response; N = number of patients

Notes: Open circles at y = 0 represent non-responders, and open circles at y = 1 represent responders. Patients are stratified into exposure quartiles. Black circles are the observed proportions of responders per exposure quartile, also shown as numerical values above the x-axis. Black vertical lines are the 95% CI of the probability of being a responder. Black curved lines are the linear logistic regression fit, and the gray shaded region represents the

corresponding 95% CI. The numbers above the x-axis represent the number of responders out of the total number of patients within each exposure quartile. The p-value is a likelihood ratio test comparing the logistic regression fit against the null hypothesis that probability of response is independent of exposures.
Data cutoff date: 05 June 2023

Exposure-Safety Analyses

The predicted exposure metrics (AUC, Cmax, Cmin, and TAE) from population PK model and safety data from Studies C28001 and FIREFLY-1 (data cutoff of 22 December 2022) were used in exposure-AE analysis. AEs of interest for exposure-AE analysis were fatigue, skin rash, anemia, myalgia, nausea and/or vomiting, elevated ALT, elevated AST, elevated bilirubin, elevated CPK, ophthalmologic (eye) events, facial edema, skin rash including dermatitis acneiform, TEAE and SAE. The AEs were considered binary endpoints as either Grade ≥2 or Grade ≥3.

Logistic regression analysis identified statistically significant positive correlations between Cmin and reporting of the following AEs: Grade ≥2 elevated ALT, Grade ≥2 or Grade ≥3 elevated AST, Grade ≥2 fatigue, Grade ≥1 or ≥2 facial edema, Grade ≥2 or Grade ≥3 skin rash, and Grade ≥3 TEAE. Positive correlations were also noted between TAE and reporting of the following AEs: Grade ≥2 anemia, Grade ≥2 or Grade ≥3 elevated CPK, Grade ≥2 myalgia, Grade ≥1 ophthalmologic (eye) events (including modified definition), Grade ≥1 facial edema, Grade ≥2 or Grade ≥3 skin rash, Grade ≥1 dermatitis acneiform, and Grade ≥2 TEAE. Higher Cmin or TAE was associated with higher probability of these AEs being reported.

No exposure-safety relationships were observed between tovorafenib exposure (Cmax, Cmin, AUC and TAE) and the following reported AEs: elevated blood bilirubin (Grade ≥2 or Grade ≥3), Grade ≥2 nausea and/or vomiting, Grade ≥3 anemia, Grade ≥3 fatigue, Grade ≥2 ophthalmologic (eye) events (including modified definition), Grade ≥2 dermatitis acneiform, or SAE. There were too few cases of Grade ≥3 nausea and/or vomiting (N=3) and Grade ≥3 elevated ALT (N=4) to enable reliable modeling.

Separate PK/PD models demonstrated a correlation between tovorafenib concentration and hemoglobin, AST, and CPK. Higher tovorafenib concentrations were associated with decreased hemoglobin and increased AST and CPK.

5.2.5. Dose selection and therapeutic window

The claimed dose has been investigated in the pivotal clinical study. No therapeutic window could be drawn from the available data.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Pharmacokinetics

Several (achiral) bioanalytical methods were used throughout the clinical development program to quantify tovorafenib in plasma and in urine. Generally, the used bioanalytical methods appear to comply with acceptance criteria regarding sensitivity accuracy and precision.

An initial population PK (PPK) model was proposed by the applicant. The PPK approach followed by the applicant was questioned regarding many aspects: strategy of the models' development, mis-specification of the model. Most of the issues raised were addressed by the applicant. The initial model development documentation was provided in the response documentation. In order to address the misspecification issue, the applicant tested an alternative model (two-compartment model). The

alternative model seems to be more appropriate. However, the predictions made by both models are very similar.

The reliability of the predictions of the systemic exposure in paediatric patients below 2 years could not be confirmed as very few data are available in this sub-group of patients (three observations). Besides, Individual Random Effects (ETAs) for Apparent Clearance (CL/F) versus Age Group of the Updated 2-CMT Model with and without Maturation Function shows that both models fail to predict the CL/F in this sub-group of patients. Two out of three estimations fall outside the prediction interval. However, it is agreed that the observed bias in ETA for CL in patients under two years of age is probably due to the scarcity of data in this subgroup. As this could not be confirmed and a shift in clearance in very young infants could not be excluded on the basis of the available data, more data should be collected in patients under two years of age in order to gather reliable prediction in this age group and to inform dosing recommandations. Folllowing a request from the CHMP, the applicant agreed to generate additional PK data in paediatric patients below 2 years of age as part of the agreed SOB under the CMA and submit an updated population PK model incorporating these data, including an assessment of systemic exposure and, if necessary, revised dosing recommendations for this subgroup of patients (**SOB with due date 30 April 2032**).

The basic PKs of tovorafenib have mainly been characterised using non-compartmental analysis in the Phase I ADME study (*DAY101-103*) in HVs and in the Phase 1 and 2 studies (*C28001* and *Firefly 1*) after single and/or multiple doses of tovorafenib in patients with cancer. Results for bioanalytical methods validation as well as sample analysis reports (for the analytical runs) have been provided.

The potential effect of extrinsic factors on tovorafenib PK has only been quantitatively assessed in the food effect study (*Day 101 QSC205140*), no DDI studies have been performed. Potential effect of intrinsic factors like hepatic impairment, renal impairment or ethnicity have also not been investigated in dedicated clinical studies.

The results for dose proportionality are based on a very limited sample size per dose group (both Q2D and QW cohort), they are, however, overall consistent and regarded acceptable.

No apparent accumulation was observed with the QW dose regimens (terminal half-life of tovorafenib is approximately 56 hours).

Tovorafenib can therefore be taken with or without food (see section 4.2 and 5.2 of the SmPC).

Distribution

Based on popPK modelling, tovorafenib apparent volume of distribution is 60 L/m2 (23%). Tovorafenib is 97.5% bound to human plasma proteins in vitro. Tovorafenib is highly proteinbound to albumin (≈ 95%) and moderately bound to alpha1 acid glycoprotein (AAG) (≈ 42%) (see section 5.2 of the SmPC).

Elimination

The results of mass balance study DAY101-103 indicate that faecal excretion is the major route of elimination, while urinary excretion is the minor elimination pathway: The arithmetic mean (SD) cumulative recovery over the initial collection period (0-480 h) was 94.8% (5.75), with 28.7% (3.11) being excreted in urine and 66.1% (5.70) in faeces. In combined excreta, the majority (91%) of the radioactive dose was recovered through 288 h postdose. The geometric mean value for AUC0-8 for tovorafenib in plasma was approximately 84.2% of that for total radioactivity in plasma, indicating that a majority of total radioactivity is accounted for by parent drug. Of the radioactivity excreted, unchanged parent tovorafenib was a minor component in faeces and accounted for a mean of 8.64% of dose, and for a mean of 0.147% regarding urinary excretion.

The elimination pathways were investigated. Liver is identified as the main route of elimination.

Metabolism

Results from *in vitro* studies suggest that the primary enzymes responsible for tovorafenib metabolism in humans are AO, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 (refer to Non-Clinical Part of the dossier).

In clinical ADME study DAY101-103, except for the unchanged parent tovorafenib in plasma which accounted for 78.7% of total plasma radioactivity exposure, no single, radioactive component accounted for more than 10% of the circulating radioactivity (plasma) or the total administered dose (urine). There was one metabolite quantified, oxy-DAY101 (M26), representing a major faecal metabolite that accounted for a mean of 47.5% of dose.

Overall, tovorafenib underwent extensive metabolism in human subjects after an oral dose of [^{14}C]-tovorafenib to yield five characterised and identified metabolites; an additional six trace unidentified metabolites were also quantified. Metabolism of tovorafenib was mediated primarily by oxidation and, to a lesser extent, by amide hydrolysis.

Special populations

Hepatic impairment

Tovorafenib is extensively metabolized by the liver. Consequently, use in patients with hepatic impairment should be considered to have potential effects on the PK of tovorafenib, and caution should be exercised during use in these patients particular since tovorafenib will also be applied to older patients (up to 25 years). Information has been reflected in section 4.2 of the SmPC informing that no dose adjustments are recommended for patients with mild hepatic impairment. Tovorafenib has not been studied in patients with moderate or severe hepatic impairment. Patients with moderate or severe hepatic impairment should be monitored carefully when treated with tovorafenib. Also, information has been added to section 5.2 to reflect that based on pop-PK modelling, no clinically significant differences of tovorafenib were observed in patients with mild hepatic impairment. Tovorafenib has not been studied in patients with moderate or severe hepatic impairment.

Potential effect of intrinsic factors like hepatic impairment, renal impairment or ethnic factor have not been investigated in dedicated clinical studies. As tovorafenib is mainly metabolized by the liver, it should be used with caution in patients with moderately abnormal liver function tests (defined as bilirubin > 1.5x to 3x ULN and any AST) or severely abnormal liver function tests (defined as bilirubin > 3x ULN and any AST) as reflected in the section 4.2 of the SmPC. Patients with moderately or severely abnormal liver function tests should be monitored carefully when treated with tovorafenib. No dose adjustment is recommended for patients with mildly abnormal liver function tests (defined as bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or bilirubin > 1x to 1.5x ULN and any AST).

Moderate and mild hepatic impairment was not identified as a significant covariate of clearance in population PK analysis by the applicant.

Renal impairment

As 0.147% of the administered dose was recovered as unchanged tovorafenib in urine, renal impairment is not expected to impact Tovorafenib PK. Thus, it is agreed that no dose adjustment is recommended in patients with renal impairment. However, of note no dedicated study has been conducted in this regard. Information has been added in 4.2 to inform that no dose adjustments are recommended for patients with mild-to-moderate renal impairment and that tovorafenib has not been studied in patients with severe renal impairment. Information has also been added to section 5.2 of

the SmPC to reflect that based on pop-PK modelling, no clinically significant differences of tovorafenib were observed in patients with mild-to-moderate renal impairment.

Based on the fact that renal clearance was minimal, the current information in the SmPC are acceptable (section 4.2 states "*No dose adjustment is recommended for patients with mild-to-moderate (eGFR ⩾ 30 ml/min/1.73 m^2 calculated by Schwartz equation or MDRD equation) renal impairment. Tovorafenib has not been studied in patients with severe (eGFR <30 ml/min/1.73 m^2) renal impairment (see section 5.2)*.").

PK interactions

See discussion in section 4.5.1.

Pharmacodynamics

Primary pharmacology

In FIH study C28001 samples were obtained from few melanoma patients (n=5) with BRAF/NRAS mutation for exploratory PD biomarker investigation. This comprised pERK as representative biomarker for inhibition of ERK phosphorylation by RAF, and cPARP as apoptotic biomarker.

Overall, the average AUC and Cmin were comparable to those in mice where antitumour activity was observed to corroborate the adequacy of the QW dose regimen with 380mg/m².

No PD biomarker investigation was performed in the phase II paediatric glioma study FIREFLY-1. While this is understandable for a brain tumour indication that several biopsies cannot be obtained for ethical reasons, it is not understood for the solid tumour arm 3 for which no further information could be located.

Due to absence of biopsies from the pLGG population, there are no data available on clinically investigated resistance mechanisms. However, in absence of other data, it is considered reassuring from a clinical PD point of view that in preclinical melanoma models the re-exposure after tumour regrowth in a treatment pause led to new growth suppression, so that this can be seen as supportive of no immediate resistance mechanism to tovorafenib treatment.

In this regard it is noted that pLGG patients both in the pivotal study FIREFLY-1 and the recruiting phase III study FIREFLY-2 have the possibility of treatment continuation after progression per study protocol. In addition, patients may opt for a drug holiday after 2 years of treatment that could be followed by re-initiation of tovorafenib following clinical or radiographic evidence of disease progression. These data will provide relevant new information to the question of secondary resistance to tovorafenib.

Exposure-response analyses following treatment with tovorafenib

Exposure response relationships were evaluated for efficacy and safety. While there seemed no conclusive relationship for the evaluated exposure metrics and tumour response, for all of the evaluated TEAEs positive exposure-relations were found, except for eye events and acneiform dermatitis ≥grade 2 and SAEs.

5.2.6.2. Conclusions on clinical pharmacology

Pharmacokinetic properties of tovorafenib have been overall adequately described. However, uncertainty remains regarding the pharmacokinetics and appropriate dosing in paediatric patients below 2 years of age due to the limited available data in this subgroup. Under the agree SOB, the MAH shall generate additional PK data in paediatrics patients below 2 years of age and submit an updated population PK model incorporating these data, including an assessment of systemic exposure

and, if necessary, revised dosing recommendations for this subgroup of patients.

Overall, clinical pharmacodynamics for tovorafenib are considered sufficiently described in the context of the disease, considering that in an orphan disease like paediatric glioma the limited feasibility of repeated tumour biopsies in pLGG is recognised. However, clinical PD biomarker data are scarce and currently PD mostly relies on pre-clinical models and few solid tumour data like melanoma, which were thus used as an alternative non-wt BRAF condition. Residual uncertainty therefore remains regarding the full characterisation of clinical PD in the intended population.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

In Study FIREFLY-1, a protocol-defined 420 mg/m^2 dosing regimen, not to exceed 600 mg (adult MTD) was selected based on safety data from Studies C28001 and PNOC014.

The applicant proposes that the recommended dose of tovorabenib is 380 mg/m^2 QW (not to exceed 600 mg) for the treatment of patients 6 months of age and older with paediatric LGG harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies. The evidence supporting the 380 mg/m^2 dose is derived from modelling and simulation only.

PNOC014

Study PNOC014 is an ongoing investigator-sponsored, Phase 1, dose-escalation study in patients 1 to < 25 years of age, with radiographically confirmed recurrent or progressive nonhematologic malignancies (solid tumors or primary central nervous system disease) with a genomic alteration resulting in the activation of the RAS/RAF/MEK/ERK pathway.

Part A of Study PNOC014 was opened for enrollment on 27 February 2018. Part A of the study was designed as a dose-escalation component that used a 3 + 3 design with a starting tovorafenib dose of 280 mg/m^2 and then escalating to 350 mg/m^2 and 420 mg/m^2. In Part B, the first patient was dosed on 11 June 2020 and the last patient was dosed on 14 October 2021. In Part B, tovorafenib was further evaluated higher doses of tovorafenib (350, 420, 530, and 660 mg/m^2).

As of the data cutoff, 13 October 2022, 44 patients with paediatric low-grade glioma or other MAPK pathway activated tumors, including five high-grade tumors, and one non-CNS tumors, received tovorafenib across four dose levels (280, 350, 420, and 530 mg/m^2).

All patients demonstrated evidence of a genomic alteration resulting in the activation of the MAPK pathway. Twenty-nine of these patients harbored a RAF fusion (24 patients with the canonical KIAA1549:BRAF). One patient had an optic pathway glioma in the setting of an NF1 loss-of-function mutation without a documented RAF alteration.

Patients with brain tumors had measurable disease and were evaluable for response assessment using RANO criteria for CNS tumors.

Forty-one patients underwent post-baseline imaging: 3 had a best overall response of CR, 12 had PR, 17 had stable disease, and 9 had PD. Five of the 9 patients with PD were patients with high-grade tumors (four glioma and one soft tissue sarcoma).

Of 31 patients who had paediatric low-grade glioma and post-baseline imaging, 3 had a best overall response of CR, 10 had PR, 16 had stable disease (10 remained on treatment for over 1 year), and 2 had PD.

According to the Wright at al (2022) there were 6 dose-limiting toxicities (DLTs), reported all at 530 mg/m^2/dose.

5.3.2. Main study(ies)

5.3.2.1. FIREFLY-1

5.3.2.1.1. Study title

FIREFLY-1: A phase 2, open-label, multicenter study to evaluate the safety and efficacy of the oral pan-RAF inhibitor DAY101 in pediatric patients with RAF-altered, recurrent or progressive low-grade glioma and advanced solid tumors.

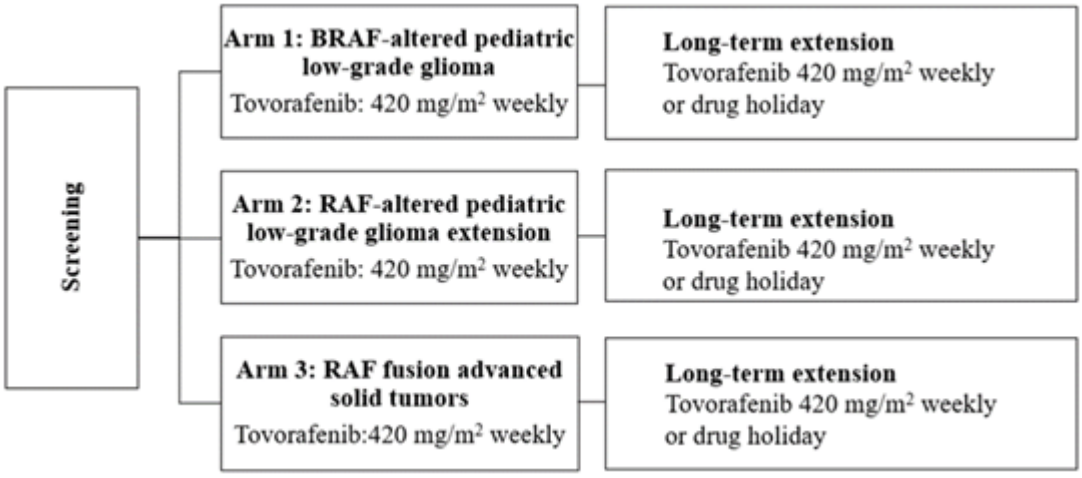
5.3.2.1.2. Study design

FIREFLY-1 is an ongoing phase 2, multicenter, multi-arm, uncontrolled, open-label study evaluating tovorafenib in patients with paediatric low-grade gliomas and advanced solid tumors. The study consists of the following treatment arms:

- Arm 1 (pivotal, low-grade glioma): Patients aged 6 months to 25 years, inclusive, with relapsed or progressive low-grade glioma harboring an activating BRAF alteration, including BRAF V600 mutations and BRAF fusions.
- Arm 2 (expansion cohort, low-grade glioma): Patients aged 6 months to 25 years, inclusive, with relapsed or progressive low-grade glioma harboring an activating or expected to be activating RAF alteration (eg, BRAF or CRAF/RAF1 fusion or BRAF V600 mutations).
- Arm 3 (advanced solid tumor): Patients aged 6 months to 25 years, inclusive, with relapsed or progressive advanced solid tumors harboring an activating or expected to be activating RAF fusion (eg, BRAF or CRAF/RAF1 fusion).

The study includes a 2-year treatment period during which all patients are treated with tovorafenib and a 3-year follow-up period (long-term extension) during which patients may continue treatment with tovorafenib or opt to enter a drug holiday. Patients on long-term follow-up after permanently discontinuing tovorafenib will continue applicable assessments and be followed for survival throughout the long-term extension. The study design schema is shown in the figure below:

Figure 3: Study schema



Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homolog B; RAF, rapidly accelerated fibrosarcoma.
The 36-month long-term extension is considered the long-term follow-up for the study.

Treatment

Tovorafenib was administered at the recommended Phase 2 dose (RP2D) of 420 mg/m^2 (not to exceed 600 mg) by mouth (PO), once weekly (QW) (Days 1, 8, 15, and 22 of a 28-day cycle). For all arms, treatment cycles were to be repeated every 28 days until radiographic evidence of disease progression as determined by the treating investigator (by RANO-HGG criteria), unacceptable toxicity, decision to enter a drug holiday period, patient withdrawal of consent, or death.

Patients who had radiographic evidence of disease progression while taking tovorafenib were allowed to continue tovorafenib treatment if, in the opinion of the investigator and approved by the Sponsor, the patient was deriving clinical benefit from continuing study treatment. Patients who were treated with tovorafenib beyond disease progression were reconsented prior to continuation of therapy. Disease assessments for patients treated beyond disease progression were to continue as per the regular assessment schedule.

Patients in Arm 1 entered the 36-month follow-up/long-term extension phase after the last patient enrolled in Arm 1 completed 26 cycles of treatment.

During the follow-up/long-term extension phase, patients either continued on tovorafenib or opted to enter a drug holiday treatment discontinuation period after completion of at least 26 cycles of treatment. Patients continued 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.

Patient population

Key inclusion criteria for treatment Arm 1 and Arm 2 are listed below:

- Patients 6 months to 25 years of age, inclusive, with
    - Arm 1 (pivotal, low-grade glioma): a relapsed or progressive low-grade glioma with a documented known activating BRAF alteration, as identified through molecular assays as routinely performed at CLIA-certified or other similarly certified laboratories (more detailed presented below);
    - Arm 2 (expansion cohort, low-grade glioma): a relapsed or progressive low-grade glioma with a documented known or expected to be activating BRAF mutation or RAF fusion, as identified through molecular assays as routinely performed at CLIA-certified or other similarly certified laboratories.
- Patients must have had histopathologic verification of malignancy at either original diagnosis or relapse;
- Patients must have had
    - Arm 1 (pivotal, low-grade glioma): at least one measurable lesion as defined by RANO-HGG criteria (T1-weighted lesion that can be reproducibly measured in at least two dimensions of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0 mm skip);
    - Arm 2 (expansion cohort, low-grade glioma): evaluable (either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm) and/or measurable disease as defined by RANO-HGG criteria.

- Patients must have had received at least one line of prior systemic therapy and have documented evidence of radiographic progression and must have fully recovered from any acute toxic effects of all prior anticancer chemotherapy with the washout periods specified in the study protocol.
- Radiation therapy to the measurable lesion(s) must have been completed at least 6 months prior to administration of tovorafenib. Patients with documented radiographic progression less than 6 months from radiotherapy in one or more measurable lesions were eligible;
- Patients must also have had adequate hematologic, hepatic, renal, thyroid, and cardiac functions as defined in the study protocol, and Karnofsky (those 16 years and older) or Lansky (those younger than 16 years) performance score of at least 50;
- Patients must have fully recovered from any prior surgery;
- An archival tumor tissue sample must have been available. If an archival tumour tissue sample was not available, a fresh biopsy should have been performed at baseline.

For patients enrolling to Arm 2 (expansion cohort, low-grade glioma) who do not have archival tumour tissue, enrollment may be considered on a case-by-case basis following a discussion between the investigator and the Day One medical monitor.

Key exclusion criteria include the following:

- Additional previously known or expected to be activating molecular alteration(s), eg, histone mutation, IDH1/2 mutations, FGFR mutations or fusions, MYBL alterations, NF1 somatic or germline mutations
- Known or suspected diagnosis of neurofibromatosis type 1 via genetic testing or current diagnostic criteria
- History or current evidence of central serous retinopathy, retinal vein occlusion, or ophthalmopathy present at baseline that would be considered a risk factor for central serous retinopathy or retinal vein occlusion
- Clinically significant history of or active cardiovascular disease
- Active systemic bacterial, viral, or fungal infection
- Patient was pregnant or lactating

5.3.2.1.3. Objectives and estimands

Primary objective

Primary objectives

For Arm 1: to evaluate the efficacy of tovorafenib as measured by the overall response rate (ORR) (determined by an independent radiology review committee IRC)

For Arm 2: to evaluate the safety and tolerability of tovorafenib

Primary endpoints

For Arm 1: ORR, as defined by the proportion of patients with best overall confirmed response of complete response (CR) or partial response (PR), and determined by an IRC using the RANO-HGG criteria

For Arm 2: type, frequency and severity of adverse events (AEs) and laboratory abnormalities

Estimands for the primary objective

No formal estimand table in accordance with ICH E9(R1) was included in the SAP, protocol nor CSR.

Statistical methods for estimation and sensitivity analysis on primary estimand

The primary efficacy endpoint ORR for Arm 1 was calculated by the number of patients with best overall confirmed response of CR or PR as determined by an IRC, using the RANO-HGG criteria on the full analysis set (FAS) of Arm 1. A response was considered as confirmed response when a response assessment of CR or PR was confirmed by a second scan ≥28 days after the initial response. If a CR with confirmation scan showed PR, or if a PR with confirmation scan showed CR, PR was assigned. An exact binomial test was used to compare the observed response rate to the hypothesised null ORR of 21%, and a 95% CI was calculated using the Clopper-Pearson method.

No formal estimand table was pre-specified in the SAP.

Secondary objectives

Secondary Objectives	***Endpoints***
To assess the safety and tolerability of tovorafenib	Type, frequency, and severity of adverse events (AEs) and laboratory abnormalities
To determine the relationship between pharmacokinetics (PK) and drug effects, including efficacy and safety	Pharmacokinetic profile of tovorafenib (e.g., area under the concentration-time curve [AUC], C_{min}, etc.)
To evaluate the effect of tovorafenib on the QT interval corrected for heart rate by Fridericia's formula (QTcF) prolongation and to explore the effects of tovorafenib on electrocardiogram (ECG) parameters	Change from baseline QT interval corrected for HR by Fridericia's formula (ΔQTcF) Change from baseline PR interval (ΔPR) Change from baseline QRS interval (ΔQRS) Change from baseline heart rate (ΔHR) ECG waveform morphology
To determine the ORR based on the treating investigator's response assessment using RANO-HGG criteria	Measured by the proportion of patients with best overall confirmed response of CR or PR by RANO-HGG
To determine the ORR based on Response Assessment in Paediatric Neuro-Oncology –low-grade glioma (RAPNO-LGG) criteria as determined by an IRC	Measured by the proportion of patients with best overall confirmed response of CR or PR or Minor Response (MR) by RAPNO-LGG criteria
To evaluate the duration of progression-free survival (PFS) based on RANO-HGG and RAPNO-LGG criteria following initiation of tovorafenib as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the time following initiation of tovorafenib to progression or death in patients treated with tovorafenib
To evaluate the duration of response (DOR) in patients with best overall response (BOR) of CR or PR or MR (RAPNO-LGG only) based on RANO-HGG and RAPNO-LGG criteria as determined by	Measured by the length of response in patients with best overall confirmed response of CR or PR

1) an IRC and 2) the treating investigator (RANO-HGG only)	or MR (RAPNO-LGG only) by RANO-HGG and RAPNO-LGG criteria, as applicable
To evaluate time to response (TTR) (CR or PR or MR (RAPNO-LGG only) based on RANO-HGG and RAPNO-LGG criteria) following initiation of tovorafenib as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the time to first response following initiation of tovorafenib in patients with best overall confirmed response of CR or PR by RANO-HGG and confirmed response CR or PR or MR by RAPNO-LGG criteria
To evaluate the clinical benefit rate (CBR) based on the proportion of patients with BOR of CR, PR, MR (RAPNO-LGG only) or stable disease (SD), based on RANO-HGG and RAPNO-LGG criteria, lasting 12 months or more following initiation of tovorafenib, as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the proportion of patients with BOR of CR, PR, MR (RAPNO-LGG only) or SD lasting 12 months or more following initiation of tovorafenib
To evaluate the duration of overall survival following initiation of tovorafenib	Measured by the time following initiation of tovorafenib to death of any cause in patients treated with tovorafenib
To evaluate changes in best corrected visual acuity (BCVA) outcomes	Measured by change from baseline in BCVA (converted as logMAR) for each eye
To evaluate the concordance of prior local laboratory BRAF molecular profiling with a central BRAF alteration assay being evaluated by the Sponsor	Molecular analysis of cells obtained from archival tissue

Estimand for the secondary objectives

No formal estimand table in accordance with ICH E9(R1) was included in the SAP, protocol nor CSR.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Secondary efficacy endpoints include ORR, BOR, PFS, DOR, TTR, and CBR based on different criteria, as well as OS. If data were sparse for any of the secondary efficacy endpoints, statistical analysis were not performed. Only descriptive summary statistics of available data or listings was produced as appropriate.

BOR was defined as the best response (CR, PR, minor response MR, stable disease SD, progressive disease PD, not evaluable NE, and unknown) recorded from the start of the treatment until disease progression, recurrence or death. First disease assessment occurred at approximately 12 weeks post-treatment.

The DOR was evaluated in FAS patients with BOR of CR or PR as determined by an IRC based for RANO-HGG & CR, PR and MR for RAPNO-LGG criteria; and the treating investigator based on RANO-HGG only.

The duration of PFS was evaluated in FAS patients as the time following initiation of treatment to progression or death and was determined by an IRC using RANO and RAPNO criteria, and the treating investigator using RANO-HGG.

The TTR was evaluated in FAS patients as the time to the first response following initiation of treatment with a BOR of CR or PR as determined by an IRC based for RANO-HGG and CR, PR and MR for RAPNO-LGG criteria; and the treating investigation using RANO-HGG.

The CBR was evaluated based on the proportion of FAS patients with a BOR of CR, PR, MR or SD lasting 12 months or more following initiation of treatment.

Exploratory objectives

Exploratory Objectives	***Endpoints***
To compare the response and time to progression following initiation of DAY101 to that of the prior line of systemic therapy	Measured by the proportion of patients with best overall confirmed response of CR or PR and TTR by RANO criteria based on the prior line of therapy
To characterize changes in total tumor volume following treatment with DAY101 by magnetic resonance imaging (MRI) volumetric image analysis	Measured by determining tumor volume and volume changes based on MRI scan data
To characterize changes in apparent diffusion coefficients following treatment with DAY101 using diffusion-weighted imaging analysis	Measured by diffusion-weighted imaging based on MRI scan data
To evaluate changes in quality-of-life and health utilities measures using the Paediatrics Quality of Life™—Core Module (PedsQL-Core), Paediatrics Quality of Life™—Cancer (PedsQL-Cancer), and Patient-Reported Outcomes Measurement Information System (PROMIS®) assessment	Measured by changes from baseline in quality-of-life and health utilities measures using the PedsQL-Core, PedsQL-Cancer, and PROMIS® assessment
To describe the improvement in motor function	Measured by changes from baseline in the Vineland 3 Adaptive Behavior Scales
To determine the durability of response following discontinuation of tovorafenib for patients with a radiographic response to tovorafenib (CR or PR as based on RANO and RAPNO criteria) as determined by 1) an IRC and 2) the treating investigator (RANO only)	Measured by the proportion of patients with best overall confirmed response of CR or PR who enter a drug holiday period and time to progression as determined by RANO, RAPNO, or clinical criteria
To evaluate time to initiation of next treatment following discontinuation of tovorafenib	Measured by the proportion of patients who discontinue tovorafenib therapy and time to next therapy initiation
To determine the ORR based on Response Assessment in Neuro-Oncology – low-grade glioma (RANO-LGG) as determined by an IRC	Measured by the proportion of patients with best overall confirmed response of CR or PR or MR by RANO-LGG criteria
To evaluate the duration of PFS based on RANO-LGG criteria following initiation of tovorafenib as determined by an IRC	Measured by the time following initiation of tovorafenib to progression or death in patients treated with tovorafenib
To evaluate the DOR in patients with BOR of CR or PR or MR based on RANO-LGG criteria as determined by an IRC	Measured by the length of response in patients with best overall confirmed response of CR or PR or MR by RANO-LGG criteria
To evaluate TTR (CR or PR or MR based on RANO-LGG criteria) following initiation of tovorafenib as determined by an IRC	Measured by the time to first response following initiation of tovorafenib in patients with best overall confirmed response of CR or PR or MR by RANO-LGG criteria
To evaluate the CBR based on the proportion of patients with BOR of CR, PR, MR, or SD lasting 12 months or more following initiation of tovorafenib	Measured by the proportion of patients with BOR of CR, PR, MR, or SD lasting 12 months or more following initiation of tovorafenib

based on RANO-LGG criteria, as determined by an IRC	

5.3.2.1.4. Results

Participant flow and numbers analysed

The data cutoff is 10 May 2024, which is 24 months after the last patient was enrolled to Arm 1. The end of the primary treatment period for Arm 1 also occurred in May 2024.

The end of this study is defined as the date when the last visit occurs for the last patient enrolled in Arm 1. The end of the study is expected to occur 61 months after the last patient is enrolled into Arm 1 (approximately May 2027).

This multicenter study is conducted at 32 study sites that enrolled patients in 11 countries. The countries with the highest percentage of enrolled patients were the United States (36.5%) and Australia (19.0%).

Table 11: Analysis Sets (Arms 1 and 2) Arm

	Arm 1 (LGG)	Arm 2 (LGG)	Arm 1 + Arm 2 (LGG)
Patients in Safety Analysis Set	77	60	137
Patients in PK Analysis Set[a]	77	60	137
Patients in Full Analysis Set	69	0	69
Reason not eligible for Full Analysis Set			
Did not have measurable disease per RANO-HGG criteria as determined by the IRC at baseline[b]	8	0	8
No IRC data available	0	60	60
Patients in the RAPNO Evaluable Analysis Set[c]	76	0	76
Patients in the RANO-LGG Evaluable Analysis Set[c]	76	0	76
Patients in Per-protocol Analysis Set	69	0	69
Patients in Off-treatment/Drug Holiday Population	67[d]	19	86
Patients in Off-treatment (due to Non-PD Reasons)/Drug Holiday Population	57	14	71
Patients in Drug Holiday Population	33[e]	0	33

Abbreviations: IRC = Independent Radiology Review Committee; LGG = low-grade glioma; PD = progressive disease; PK = pharmacokinetics; RANO-HGG = Response Assessment in Neuro-Oncology for High-Grade Glioma; RANO-LGG = Response Assessment in Neuro-Oncology for Low-Grade Glioma; RAPNO = Response Assessment in Pediatric Neuro-Oncology (for low-grade glioma).

[a] There are 5 patients in the PK Analysis Set for Arm 3.

[b] These include 2 patients with no T1 post contrast series provided, 5 patients with enhancing disease that did not meet minimum target lesion size criteria, and 1 patient with no enhancing disease present.

[c] One patient had disease that did not meet the minimum target lesion size requirements at baseline.

[d] Includes 66 patients with disposition as discontinued primary treatment plus 1 patient with disposition listed as ongoing study treatment who was on dose hold $\geqslant$ 3 cycles.

[e] Of the 33 patients with a drug holiday, 3 received tovorafenib re-treatment.

Data Cutoff Date: 10 May 2024.

Table 12: Patient disposition

	Safety Analysis Set			Full Analysis Set
	Arm 1 (LGG)	Arm 2 (LGG)	Arm 1 + Arm 2 (LGG) N=137	Arm 1 (LGG)
Patients received study treatment, n (%)	77 (100)	60 (100)	137 (100)	69 (100)
Patients ongoing primary study treatment,[a]	11 (14.3)	43 (71.7)	54 (39.4)	10 (14.5)
Patients with drug holiday, n (%)	33 (42.9)	0	33 (24.1)	29 (42.0)
Patients with tovorafenib re-treatment, n	3 (3.9)	0	3 (2.2)	2 (2.9)
Patients who discontinued primary study treatment, n (%)	66 (85.7)	17 (28.3)	83 (60.6)	59 (85.5)
Primary reason for primary treatment discontinuation				
Other[b]	35 (45.5)	2 (3.3)	37 (27.0)	31 (44.9)
Progressive disease	10 (13.0)	5 (8.3)	15 (10.9)	8 (11.6)
Adverse event[c]	8 (10.4)	7 (11.7)	15 (10.9)	8 (11.6)
Withdrawal by parent or guardian	7 (9.1)	1 (1.7)	8 (5.8)	6 (8.7)
Death	2 (2.6)	1[d] (1.7)	3 (2.2)	2 (2.9)
Withdrawal by patient	2 (2.6)	1 (1.7)	3 (2.2)	2 (2.9)
Physician decision	2 (2.6)	0	2 (1.5)	2 (2.9)
Patients remaining on study, n (%)	67 (87.0)	57 (95.0)	124 (90.5)	61 (88.4)
Patients who discontinued study early, n	10 (13.0)	3 (5.0)	13 (9.5)	8 (11.6)
Primary reason for early study				
Death	4[e] (5.2)	1[f] (1.7)	5 (3.6)	3 (4.3)
Withdrawal by patient	3 (3.9)	1 (1.7)	4 (2.9)	3 (4.3)
Withdrawal by parent or guardian	3 (3.9)	0	3 (2.2)	2 (2.9)
Adverse event	0	1[d] (1.7)	1 (0.7)	0
Death	4 (5.2)	2 (3.3)	6 (4.4)	3 (4.3)
Death within 30 days after the end of	2 (2.6)	2 (3.3)	4 (2.9)	2 (2.9)
Death ≥ 30 days after the end of	2 (2.6)	0	2 (1.5)	1 (1.4)
Study duration (months)				
Mean (StD)	27.45	20.69	24.49	27.49 (6.399)
Median	28.10	21.10	24.40	27.80
Min, max	1.1, 36.5	2.4, 24.4	1.1, 36.5	1.1, 36.2

Abbreviations: LGG = low-grade glioma; max = maximum; min = minimum; StD = standard deviation.

a Includes 1 patient in Arm 1 (Safety Analysis Set and Full Analysis Set) who was on dose hold ⩾ 3 cycles at the time of data cutoff.

b Includes drug holiday (Arm 1, 33 patients), patient progressed and required different treatment (Arm 1, 1 patient), and clinical progression (Arm 1, 1 patient; Arm 2, 2 patients).

c Includes adverse events that occurred > 30 days post last dose of study treatment.

d One patient discontinued study treatment due to death and discontinued the study due to Grade 5 pneumonia considered not related to tovorafenib.

e One patient had Grade 5 brain death considered not related to tovorafenib. One patient had Grade 5 hydrocephalus > 30 days post last dose of study treatment, considered not related to tovorafenib. One patient died

due to progressive disease > 2 years after discontinuing primary tovorafenib treatment. One patient died due to unexplained death considered not

ted to tovorafenib.

f One patient had Grade 5 tumor hemorrhage considered not related to tovorafenib.

Note: Study duration is defined as (end of study date – first dose date +1)/30.4375. For ongoing patients, data cutoff date is used for end of study date.

Data Cutoff Date: 10 May 2024.

Table 13: Duration of Exposure (Safety Analysis Set; Arms 1 and 2)

	Arm 1 (LGG	**Arm 2 (LGG**	**Arm 1 + Arm 2 (LGG)**
Duration of maximum exposure[a] (days)			
Mean (StD)	581.0 (259.31)	530.7	559.0 (235.25)
Median	722.0	616.0	638.0
Min, max	22, 975	36, 744	22, 975
Duration of primary treatment,[b] n (%)			
≥ 6 months	66 (85.7)	53 (88.3)	119 (86.9)
≥ 12 months	59 (76.6)	49 (81.7)	108 (78.8)
≥ 18 months	50 (64.9)	41 (68.3)	91 (66.4)
≥ 24 months	25 (32.5)	2 (3.3)	27 (19.7)
Duration of drug holiday[c] (days)			
n[d]	32	0	32
Mean (StD)	137.0 (100.73)	-	137.0 (100.73)
Median	104.5	-	104.5
Min, max	9, 323	-	9, 323
Total expected dose (mg)			
Mean (StD)	36711.2 (18975.85)	32590.0 (15921.85)	34906.3 (17759.80)
Median	37400.0	31475.0	33600.0
Min, max	1300, 75600	3300, 63600	1300, 75600
Total actual dose received (mg)			
Mean (StD)	36689.1 (18981.79)	32536.3 (15913.14)	34870.3 (17761.79)
Median	37400.0	31475.0	33500.0
Min, max	1300, 75600	3300, 63600	1300, 75600
Number of cycles treated[e]			
Mean (StD)	20.9 (9.16)	19.3 (7.06)	20.2 (8.32)
Median	26.0	23.0	23.0
Min, max	1, 35	2, 27	1, 35
Number of patients with ≥ 26 cycles,[e] n (%)	44 (57.1)	5 (8.3)	49 (35.8)
Treatment compliance[f] (%)			
Mean (StD)	99.92 (0.320)	99.81 (0.563)	99.87 (0.445)

Median	100.00	100.00	100.00
Min, max	97.7, 100.4	97.0, 100.3	97.0, 100.4
Patients with dose interruptions due to AE,[g] n	44 (57.1)	35 (58.3)	79 (57.7)
Duration of interruptions[h] (days)			
Mean (StD)	42.0 (54.10)	40.0 (58.85)	41.1 (55.89)
Median	17.5	21.0	21.0
Min, max	7, 210	7, 259	7, 259
Patients with dose reductions due to AE, n (%)	25 (32.5)	19 (31.7)	44 (32.1)

Abbreviations: AE = adverse event; LGG = low-grade glioma; max = maximum; min = minimum; StD = standard deviation.

a Duration of maximum exposure = date of last dose of study treatment excluding tovorafenib re-treatment after drug holiday – date of first dose of study treatment + 1.

b Duration of treatment (months) = (date of last dose of primary study treatment – date of first dose of study treatment + 1)/30.4375.

c Duration of drug holiday = 1 day prior to the date of first dose of tovorafenib re-treatment or subsequent anticancer therapy – (date of last dose of study treatment prior to drug holiday + 30 days). For patients without tovorafenib re-treatment or subsequent anticancer therapy, the end of drug holiday was entered as the clinical cutoff date or study discontinuation date.

d Only patients with drug holiday duration > 0 days were included. If the date of primary treatment discontinuation is within 30 days of the last dose, duration of off-treatment/drug holiday is not available. As a result, there is 1 additional patient that started their drug holiday on the data cutoff date and was not included in the calculation of duration of drug holiday (Listing 16.2.1, Listing 16.2.5.1, Listing 16.2.5.2).

e A cycle is counted if the patient received at least one dose of tovorafenib in a cycle.

f Treatment compliance (%) = total actual dose (mg) / total expected dose (mg) × 100.

g Patients with dose interruption due to AE based on primary action taken.

h Duration of interruptions (days) = number of times dose not administered due to AE × 7.

Data Cutoff Date: 10 May 2024.

Deviations from study plan

The initial protocol has been amended several times, primarily to add two new arms to the study, and to add the powder for reconstitution formulation of tovorafenib.

Several major protocol deviations have been identified and reported. 30 patients (22.1%) had major protocol deviations, most involving informed consent (most commonly failure to reconsent to revised versions of the informed consent form). The patients within this category of deviations were enrolled at different study sites. These major protocol deviations did not impact patient safety or data quality and none of the patients with major protocol deviations were excluded from Per-protocol Analysis Set.

A protocol deviation for a single time point missed bicarbonate analyte at Cycle 1 Day 1 was incorrectly categorised as major, as it does not significantly affect the completeness, accuracy, and/or reliability of the study data nor does it affect the patient's rights, safety or well-being.

Baseline data

Table 14: Demographic Characteristics (Safety Analysis Set; Arms 1 and 2)

	Arm 1 (LGG)	**Arm 2 (LGG)**	**Arm 1 + Arm 2 (LGG) N=137**
Age at baseline (years)			
Mean (StD)	9.169 (3.9947)	9.328 (5.3108)	9.238 (4.6000)
Median	8.000	9.500	9.000

Min, max	2.00, 21.00	1.00, 24.00	1.00, 24.00
Age group, n (%)			
6 months to < 2 years	0	3 (5.0)	3 (2.2)
2 years to < 6 years	14 (18.2)	13 (21.7)	27 (19.7)
6 years to < 12 years	42 (54.5)	24 (40.0)	66 (48.2)
12 years to < 16 years	15 (19.5)	11 (18.3)	26 (19.0)
16 years to ≤ 25 years	6 (7.8)	9 (15.0)	15 (10.9)
Sex, n (%)			
Male	40 (51.9)	33 (55.0)	73 (53.3)
Female	37 (48.1)	27 (45.0)	64 (46.7)
Race, n (%)			
Black or African American	2 (2.6)	1 (1.7)	3 (2.2)
Asian	5 (6.5)	5 (8.3)	10 (7.3)
White	47 (61.0)	40 (66.7)	87 (63.5)
Multiple	3 (3.9)	0	3 (2.2)
Other	6 (7.8)	2 (3.3)	8 (5.8)
Not reported	14 (18.2)	12 (20.0)	26 (19.0)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.9)	1 (1.7)	4 (2.9)
Not Hispanic or Latino	58 (75.3)	48 (80.0)	106 (77.4)
Not stated	13 (16.9)	11 (18.3)	24 (17.5)
Missing	3 (3.9)	0	3 (2.2)

Height percentile at baseline[a] (%)			
N	76	58	134
Mean (StD)	46.568	47.416 (31.8899)	46.935
Median	41.840	47.730	43.075
Min, max	0.04, 99.84	0.00, 99.99	0.00, 99.99
Weight percentile at baseline[a] (%)			
N	76	58	134
Mean (StD)	59.913	58.862 (33.3762)	59.458
Median	65.650	66.315	66.315
Min, max	0.23, 99.75	0.03, 99.99	0.03, 99.99
BSA at baseline (m^2)			
N	77	60	137
Mean (StD)	1.154 (0.3376)	1.183 (0.4471)	1.166 (0.3881)
Median	1.070	1.165	1.110
Min, max	0.63, 2.07	0.44, 2.19	0.44, 2.19

Abbreviations: BSA = body surface area; LGG = low-grade glioma; max = maximum; min = minimum; StD = Standard deviation.

[a] Only patients with height and weight percentile available per Centers for Disease Control and Prevention standard growth chart are included in the summary.

Note: Baseline is defined as the last available assessments prior to the start of tovorafenib on Cycle 1 Day 1. Data Cutoff Date: 10 May 2024.

Table 15: Patient Disease Characteristics (Safety Analysis Set; Arms 1 and 2)

	Arm 1 (LGG	Arm 2 (LGG	Arm 1 + Arm 2 (LGG) N=137
Primary tumor location, n (%)			
Cerebellum	5 (6.5)	1 (1.7)	6 (4.4)
Cerebral hemisphere	5 (6.5)	5 (8.3)	10 (7.3)
Deep midline structures	9 (11.7)	11 (18.3)	20 (14.6)
Optic pathway	39 (50.6)	29 (48.3)	68 (49.6)
Brain stem	6 (7.8)	2 (3.3)	8 (5.8)
Other	13 (16.9)	12 (20.0)	25 (18.2)
Histology, n (%)			
Astrocytic	72 (93.5)	55 (91.7)	127 (92.7)
Oligodendroglial	0	1 (1.7)	1 (0.7)
Mixed glial-neuronal	4 (5.2)	4 (6.7)	8 (5.8)
Other[a]	1 (1.3)	0	1 (0.7)
Number of patients who received any prior tumor directed surgery for treatment of	60 (77.9)	41 (68.3)	101 (73.7)
Pre-operative staging, n (%)			
Localized disease	60 (77.9)	42 (70.0)	102 (74.5)
Disseminated/metastatic disease	9 (11.7)	11 (18.3)	20 (14.6)
Leptomeningeal spread	8 (10.4)	7 (11.7)	15 (10.9)
Post-operative staging[b], n (%)			
Gross total resection	1 (1.3)	0	1 (0.7)
Sub-total resection	36 (46.8)	28 (46.7)	64 (46.7)
Biopsy only, not attempted	40 (51.9)	32 (53.3)	72 (52.6)
Baseline IRC SPPD (mm^2) by RANO-HGG			
n	69	0	69
Mean (StD)	1221.25	-	1221.25
Median	729.60	-	729.60
Min, max	104.0, 6358.0	-	104.0, 6358.0
BRAF alteration, n (%)			
BRAF V600E mutation	13 (16.9)	9 (15.0)	22 (16.1)
NGS	7 (9.1)	4 (6.7)	11 (8.0)
IHC	4 (5.2)	4 (6.7)	8 (5.8)
Other[c]	2 (2.6)	1 (1.7)	3 (2.2)
KIAA1549:BRAF fusion	56 (72.7)	45 (75.0)	101 (73.7)

RT-PCR	17 (22.1)	6 (10.0)	23 (16.8)
FISH/ISH	8 (10.4)	8 (13.3)	16 (11.7)
NGS	24 (31.2)	26 (43.3)	50 (36.5)
Microarray	5 (6.5)	4 (6.7)	9 (6.6)
Other[d]	2 (2.6)	1 (1.7)	3 (2.2)
Other[e]	8 (10.4)	6 (10.0)	14 (10.2)
FISH/ISH	8 (10.4)	4 (6.7)	12 (8.8)
NGS	0	2 (3.3)	2 (1.5)
Baseline Karnofsky performance score,[f] n			
50-70	2/6 (33.3)	0	2/15 (13.3)
80-100	4/6 (66.7)	9/9 (100)	13/15 (86.7)
Baseline Lansky performance score,[f] n (%)			
50-70	3/71 (4.2)	9/51 (17.6)	12/122 (9.8)
80-100	68/71 (95.8)	42/51 (82.4)	110/122 (90.2)

Abbreviations: FISH/ISH = fluorescence in situ hybridization/in situ hybridization; IHC = immunohistochemistry; IRC = Independent Radiology Review Committee; LGG = low-grade glioma; NGS = next-generation sequencing; RANO-HGG = Response Assessment in Neuro-Oncology for High-Grade Glioma; RT-PCR = reverse transcription-polymerase chain reaction; SPPD = sum of the products of the perpendicular diameters; StD = One patient had ganglioglioma histology (Listing 16.2.4.2.3).

[b] At the time of the initial diagnosis.

[c] Includes Sanger DNA sequencing (Arm 1), pyrosequencing (Arm 1), and in vitro diagnostic strip assay (Arm 2).

[d] Includes digital droplet polymerase chain reaction (Arm 1) and NanoString RNA analysis (Arm 1 and Arm 2).

[e] Includes 9 patients with BRAF duplication (Arm 1: 6; Arm 2: 3), 3 patients with BRAF rearrangement (Arm 1: 2; Arm 2: 1), 1 patient with RNF130-BRAF (Arm 2), and 1 patient with PID1-BRAF fusion (Arm 2).

[f] Denominators for Karnofsky performance score and Lansky performance score summaries are the number of patients whose ages at study enrollment were ⩾ 16 years and < 16 years, respectively.

Note: Baseline is defined as the last available assessments prior to the start of tovorafenib on Cycle 1 Day 1. Data Cutoff Date: 10 May 2024.

The most common medical history events in Arm 1 and Arm 2 by SOC were Nervous System Disorders (83.2%), driven primarily by PTs nystagmus (21.9%), headache (21.2%), and hydrocephalus (21.2%); and Eye Disorders (67.2%), driven primarily by PTs optic atrophy (18.2%), visual impairment (16.1%), and strabismus (13.9%). Skin and Subcutaneous Tissue Disorders were also common at baseline (43.8%), driven by PTs dry skin (11.7%) and eczema (10.9%); as well as Endocrine Disorders (39.4%) driven by PT precocious puberty (19.7%) and Gastrointestinal Disorders (35.8%) driven by PT constipation (20.4%).

Table 16: Prior Anticancer Therapy (Safety Analysis Set; Arms 1 and 2)

	Arm 1 (LGG)	**Arm 2 (LGG)**	**Arm 1 + Arm 2 (LGG) N=137**
Number of patients who received any prior anticancer therapy, n (%)	77 (100)	60 (100)	137 (100)
Any prior radiotherapy	8 (10.4)	6 (10.0)	14 (10.2)
Any prior systemic anticancer therapy	77 (100)	60 (100)	137 (100)
Prior MEK inhibitor,[a] n (%)			
Yes	43 (55.8)	34 (56.7)	77 (56.2)

No	34 (44.2)	26 (43.3)	60 (43.8)
Prior BRAF inhibitor, n (%)			
Yes	8 (10.4)	7 (11.7)	15 (10.9)
No	69 (89.6)	53 (88.3)	122 (89.1)
Prior MEK and BRAF inhibitors, n (%)			
Yes	5 (6.5)	4 (6.7)	9 (6.6)
No	72 (93.5)	56 (93.3)	128 (93.4)
Prior MEK and/or BRAF inhibitors, n (%)			
Yes	46 (59.7)	37 (61.7)	83 (60.6)
No	31 (40.3)	23 (38.3)	54 (39.4)
Number of prior systemic lines of therapy, n (%)			
1	17 (22.1)	14 (23.3)	31 (22.6)
2	21 (27.3)	13 (21.7)	34 (24.8)
3	16 (20.8)	17 (28.3)	33 (24.1)
> 3	23 (29.9)	16 (26.7)	39 (28.5)
Line of prior systemic therapies			
Median	3.0	3.0	3.0
Min, max	1, 9	1, 10	1, 10
Duration of last prior systemic line of therapy (months)[b]			
n[c]	66	54	120
Mean (StD)	12.66	15.39	13.89
Median	10.20	12.25	11.05
Min, max	1.1, 63.5	1.0, 45.5	1.0, 63.5
Best response to prior MEK and/or BRAF inhibitors[d]			
Complete response (CR)	0	0	0
Partial response (PR)	19/46 (41.3)	8/37 (21.6)	27/83 (32.5)
Stable disease	20/46 (43.5)	19/37 (51.4)	39/83 (47.0)
Progressive disease (PD)	6/46 (13.0)	10/37 (27.0)	16/83 (19.3)
Best response to prior MEK and BRAF inhibitors[d]			
Complete response (CR)	0	0	0
Partial response (PR)	2/5 (40.0)	2/4 (50.0)	4/9 (44.4)
Stable disease	3/5 (60.0)	1/4 (25.0)	4/9 (44.4)
Progressive disease (PD)	0	1/4 (25.0)	1/9 (11.1)
Best response to prior MEK inhibitors[d]			
Complete response (CR)	0	0	0
Partial response (PR)	16/43 (37.2)	8/34 (23.5)	24/77 (31.2)
Stable disease	20/43 (46.5)	16/34 (47.1)	36/77 (46.8)
Progressive disease (PD)	6/43 (14.0)	10/34 (29.4)	16/77 (20.8)

Best response to prior BRAF inhibitors[d]			
Complete response (CR)	0	0	0
Partial response (PR)	5/8 (62.5)	2/7 (28.6)	7/15 (46.7)
Stable disease	3/8 (37.5)	4/7 (57.1)	7/15 (46.7)
Progressive disease (PD)	0	1/7 (14.3)	1/15 (6.7)

Abbreviations: LGG = low-grade glioma; max = maximum; min = minimum; StD = standard deviation.

[a] Patients were included if they previously received a prior MEK inhibitor either as monotherapy or as part of a combination.

[b] (Treatment end date - Treatment start date + 1)/30.4375.

[c] Only includes patients for whom actual dates were provided.

[d] Percentages are based on number of patients who received any prior MEK and/or BRAF inhibitors. Best response for one patient was unknown.

Data Cutoff Date: 10 May 2024

Outcomes and estimation

Efficacy analyses are presented only for Arm 1 of FIREFLY-1.

Primary Endpoint – IRC-assessed ORR Based on RANO-HGG Criteria

Table 17: IRC-assessed Overall Response Rate and Clinical Benefit Rate Based on RANO-HGG Criteria (Full Analysis Set; Arm 1)

	Arm 1 (Low-grade Glioma) N=69
Best overall response, n (%)	
Complete response (CR)	16 (23.2)
Partial response (PR)	33 (47.8)
Stable disease	15 (21.7)
Stable disease ≥ 12 months	4 (5.8)
Stable disease < 12 months[a]	11 (15.9)
Progressive disease (PD)	4 (5.8)
Not evaluable	1 (1.4)
Number of patients with confirmed response	49
ORR (95% CI)[b]	71.0 (58.8, 81.3)
Number of patients with confirmed response or stable disease ≥ 12 months	53
Clinical benefit rate (95% CI)[b]	76.8 (65.1, 86.1)

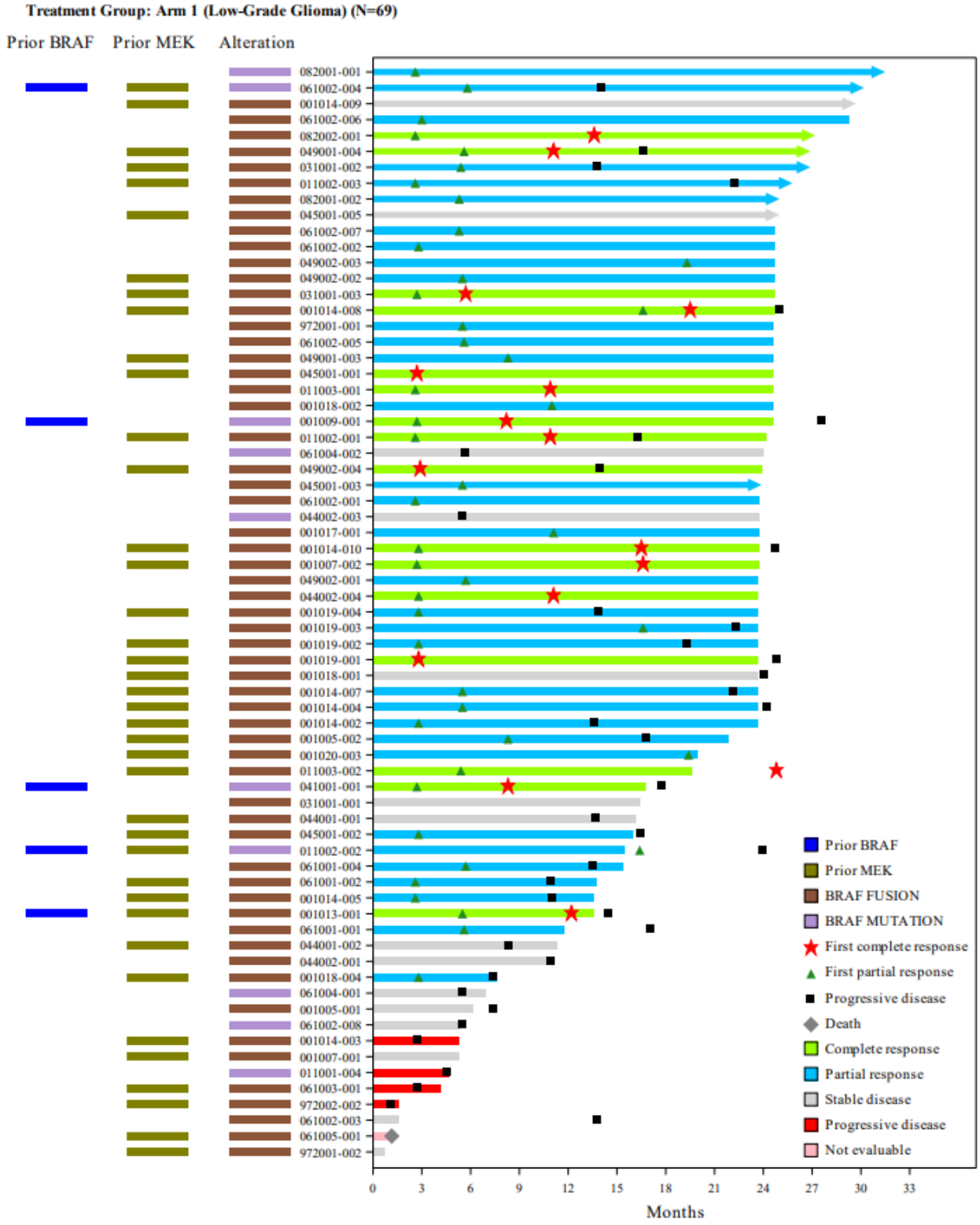
Abbreviations: CI = confidence interval; IRC = Independent Radiology Review Committee; ORR = overall response rate; RANO-HGG = Response Assessment in Neuro-Oncology for High-Grade Glioma.

a Among 11 patients with stable disease < 12 months, none were continuing on treatment as of the 10 May 2024 data cutoff date.

b The exact 95% CIs are calculated using Clopper-Pearson method.

Data Cutoff Date: 10 May 2024.

Figure 4: Swimmer Plot for IRC-assessed Overall Response Based on RANO-HGG Criteria (Full Analysis Set; Arm 1)



Abbreviations: BRAF = v-raf murine sarcoma viral oncogene homolog B; IRC = Independent Radiology Review Committee; MEK = mitogen-activated protein kinase; RANO-HGG = Response Assessment in Neuro-Oncology for High-Grade Glioma.

Bar color represents best overall response. Bar length represents duration of treatment. Arrow at the end of the bar represents ongoing study treatment.

Data Cutoff Date: 10 May 2024.

Sensitivity Analysis of IRC-assessed ORR Based on Per-protocol Analysis Set

All patients in the Full Analysis Set were included in the Per-protocol Analysis Set. Therefore, the results of the sensitivity analysis were the same as for the Full Analysis Set.

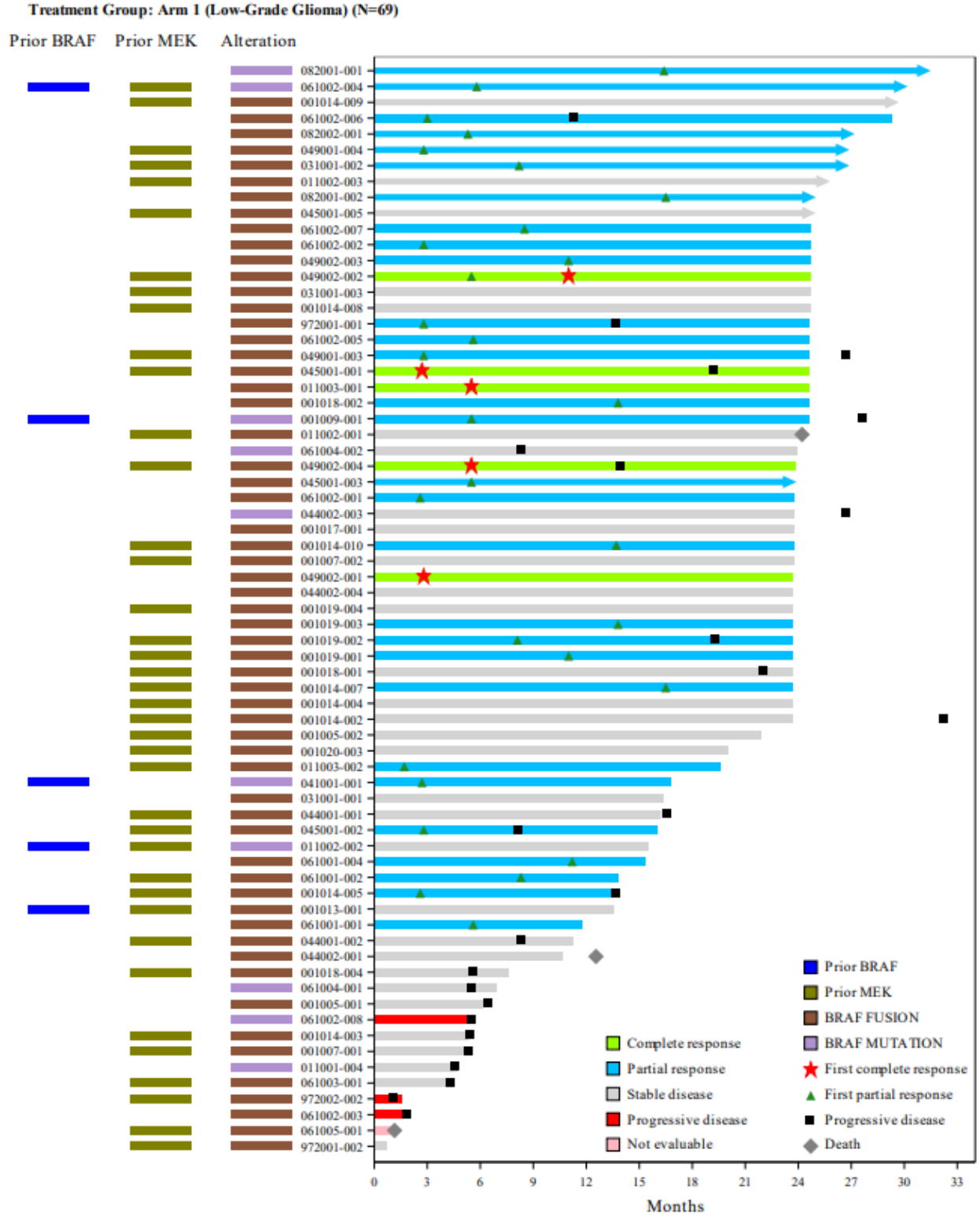
Secondary endpoint - Investigator-assessed ORR based on RANO-HGG

Table 18: Investigator-assessed Overall Response Rate Based on RANO-HGG Criteria (Full Analysis Set; Arm 1)

	Arm 1 (Low-grade Glioma) N=69
Best overall response, n (%)	
Complete response (CR)	5 (7.2)
Partial response (PR)	29 (42.0)
Stable disease	31 (44.9)
Stable disease ≥ 12 months	20 (29.0)
Stable disease < 12 months	11 (15.9)
Progressive disease (PD)	3 (4.3)
Not evaluable	1 (1.4)
Number of patients with confirmed response	34
Overall response rate (95% CI)[a]	49.3 (37.0, 61.6)
Number of patients with confirmed response or stable disease ≥ 12	54
Clinical benefit rate (95% CI)[a]	78.3 (66.7, 87.3)

Abbreviations: CI = confidence interval; RANO-HGG = Response Assessment in Neuro-Oncology for High-Grade Glioma. a The exact 95% CIs are calculated using Clopper-Pearson method. Data Cutoff Date: 10 May 2024.

Figure 5: Swimmer Plot for Investigator-assessed Overall Response Based on RANO-HGG Criteria (Full Analysis Set; Arm 1)



Abbreviations: BRAF = v-raf murine sarcoma viral oncogene homolog B; MEK = mitogen-activated protein kinase; RANO-HGG = Response Assessment in Neuro-Oncology for High-Grade Glioma.

Bar color represents best overall response. Bar length represents duration of treatment. Arrow at the end of the bar represents ongoing study treatment.

Data Cutoff Date: 10 May 2024.

Secondary endpoint – IRC-assessed ORR Based on RAPNO Criteria

Table 19: IRC-assessed Overall Response Rate and Clinical Benefit Rate Based on RAPNO Criteria (RAPNO Evaluable Analysis Set; Arm 1)

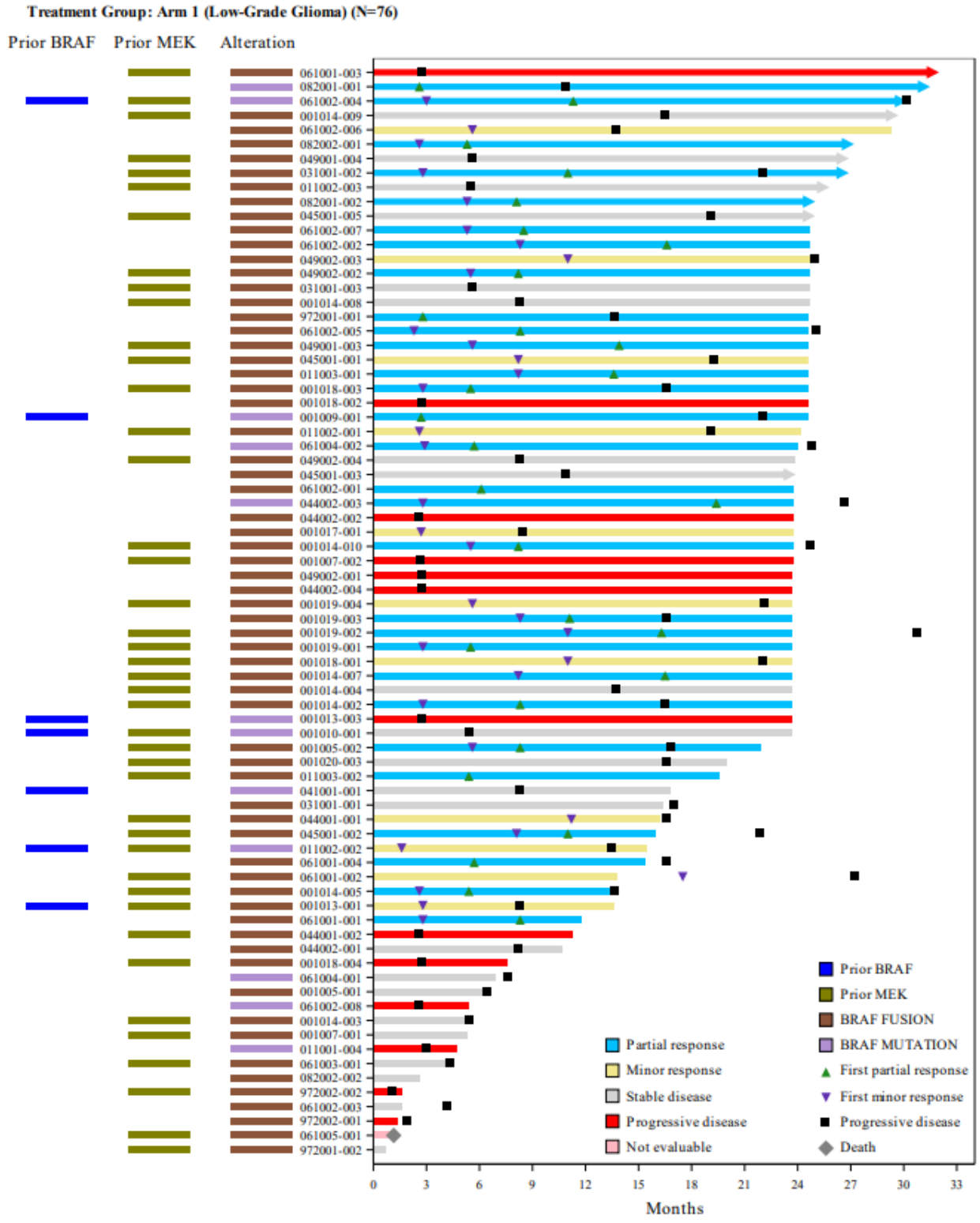
	Arm 1 (Low-grade Glioma) N=76
Best overall response, n (%)	
Complete response	0
Partial response	29 (38.2)
Minor response	11 (14.5)
Stable disease	22 (28.9)
Stable disease ≥ 12 months	4 (5.3)
Stable disease < 12 months	18 (23.7)
Progressive disease	13 (17.1)
Not evaluable	1 (1.3)
Number of patients with confirmed response	40
ORR (95% CI)[a]	52.6 (40.8, 64.2)
Number of patients with confirmed response or stable disease ≥ 12	44
Clinical benefit rate (95% CI)[a]	57.9 (46.0, 69.1)

Abbreviations:. CI = confidence interval; IRC = Independent Radiology Review Committee; N = number of patients in RAPNO Evaluable Analysis Set; n = number of patients with data; RAPNO = Response Assessment in Pediatric Neuro-Oncology.

a The exact 95% CIs are calculated using Clopper-Pearson method.

Data Cutoff Date: 10 May 2024.

Figure 6: Swimmer Plot for IRC-assessed Overall Response Based on RAPNO Criteria (RAPNO Evaluable Analysis Set; Arm 1)



Abbreviations: BRAF = v-raf murine sarcoma viral oncogene homolog B; IRC = Independent Radiology Review Committee;

MEK = mitogen-activated protein kinase mitogen-activated protein kinase; N = number of patients in RAPNO Evaluable Analysis Set; RAPNO = Response Assessment in Pediatric Neuro-Oncology

Bar color represents best overall response. Bar length represents duration of treatment. Arrow at the end of the bar represents ongoing study treatment.

Data Cutoff Date: 10 May 2024

Secondary endpoint - IRC-assessed Duration of Response

Table 20: IRC-assessed Duration of Response (Arm 1)

	Arm 1 (Low-grade glioma)	
	RANO-HGG (N=69)	**RAPNO (N=76)**
Number of patients with response	49	40
Number of patients with the event[a] n (%)	26 (53.1)	28 (70.0)
Progressive disease (PD)	26 (53.1)	28 (70.0)
Death	0	0
Number of patients censored[a] n (%)	23 (46.9)	12 (30.0)
No PD or death at time of analysis	23 (46.9)	12 (30.0)
Estimated time to PD or death after response (months)		
Median (95% CI)	19.7 (13.7, -)	18.0 (12.0, 22.8)
Probability of continued response[b] (95% CI)		
3 months	100 (100, 100)	100 (100, 100)
6 months	95.8 (84.2, 98.9)	92.5 (78.5, 97.5)
9 months	78.8 (64.1, 88.0)	85.0 (69.6, 93.0)
12 months	66.0 (50.6, 77.6)	65.0 (48.2, 77.6)
18 months	54.9 (39.6, 67.8)	50.0 (33.8, 64.2)
24 months	43.4 (28.1, 57.8)	25.6 (11.4, 42.6)

Abbreviations: CI = confidence interval, IRC = Independent Radiology Review Committee, PD = progressive disease, RANO-HGG = Response Assessment in Neuro-Oncology for High-Grade Glioma, RAPNO = Response Assessment in Pediatric Neuro-Oncology.oa Percentages are based on number of patients with response. Estimated using Kaplan-Meier method. Data cutoff date: 10 May 2024.

Secondary endpoint - Investigator-assessed DOR

Table 21: Investigator-assessed Duration of Response Based on RANO-HGG Criteria (Full Analysis Set; Arm 1)

	Arm 1 (Low-grade Glioma) N=69
Number of patients with response	34
Number of patients with the event,[a] n (%)	9 (26.5)
Progressive disease (PD)	9 (26.5)
Death	0
Number of patients censored,[a] n (%)	25 (73.5)
No PD or death at time of analysis	25 (73.5)
Estimated time to PD or death after response[b] (months)	
Median (95% CI)	- (22.177, -)
Probability of continued response[b] (95% CI)	
3 months	100 (100, 100)
6 months	97.059 (80.901, 99.580)
9 months	90.993 (74.608, 97.004)

12 months	81.459 (63.256, 91.226)
18 months	77.386 (58.024, 88.626)
24 months	61.557 (34.945, 79.938)

Abbreviations: CI = confidence interval; RANO-HGG = Response Assessment in Neuro-Oncology for High-Grade Glioma.a Percentages are based on number of patients with response. b Estimated using Kaplan-Meier method. Data Cutoff Date: 10 May 2024.

Other secondary endpoints

Visual Acuity Outcomes

Only patients with optic pathway gliomas, or those with underlying visual deficits related to the primary CNS tumor, were required to undergo on-treatment visual acuity assessments.

Of the 51 patients in Arm 1 with both baseline and ≥ 1 post-baseline best corrected visual acuity (BCVA) measurement, 5 (10%), 13 (26%), 14 (28%), and 13 (26%) patients reported a decrease of ≥ 0.2 logMAR from baseline (ie, improved) at Cycles 3, 6, 9, and 12, respectively.

Four (8%), 7 (14%), 4 (8%), and 5 (10%) patients reported an increase of ≥ 0.2 logMAR from baseline (ie, worsened) at Cycles 3, 6, 9, and 12, respectively.

While changes of ≥ 0.2 logMAR occurred, with decreases from baseline more commonly reported than increases, overall visual acuity remained assessed by investigators as stable for the majority of patients.

Quality-of-life assessments and motor function

Not presented in the 2-Year CSR of FIREFLY-1.

Pre-defined and post-hoc subgroup analyses

Adhoc subgroup analyses

Table 22: Subgroup Analyses of Overall Response Rate as Assessed by the IRC Based on RANO-HGG Criteria (Full Analysis Set; Arm 1)

	ORR by BRAF-Alteration		ORR by Prior MAPK Therapy	
	BRAF Fusion[a] (N=59)	BRAF Mutation (N=10)	Prior MAPK Inhibitor (N=41)	No Prior MAPK Inhibitor (N=28)
Best overall response, n (%)				
Complete response	14 (23.7)	2 (20.0)	13 (31.7)	3 (10.7)
Partial response	30 (50.8)	3 (30.0)	17 (41.5)	16 (57.1)
Stable disease	11 (18.6)	4 (40.0)	7 (17.1)	8 (28.6)
Stable disease ≥ 12 months	4 (6.8)	0	3 (7.3)	1 (3.6)
Stable disease < 12 months	7 (11.9)	4 (40.0)	4 (9.8)	7 (25.0)
Progressive disease	3 (5.1)	1 (10.0)	3 (7.3)	1 (3.6)
Not evaluable	1 (1.7)	0	1 (2.4)	0
Number of patients with confirmed	44	5	30	19
O R	74.6 (61.6, 85.0)	50.0 (18.7, 81.3)	73.2 (57.1, 85.8)	67.9 (47.6, 84.1)

Number of patients with confirmed response or stable	48	5	33	20
Clinical benefit rate (95% CI)[b]	81.4 (69.1, 90.3)	50.0 (18.7, 81.3)	80.5 (65.1, 91.2)	71.4 (51.3, 86.8)

Abbreviations: BRAF = v-raf murine sarcoma viral oncogene homolog B; CI = Confidence Interval; IRC = Independent Radiology Review Committee, N = number of patients in subgroup; n = number of patients with data. MAPK = mitogenactivated protein kinase; ORR = overall response rate; RANO-HGG = Response Assessment in Neuro-Oncology high-grade glioma; SD = stable disease
a BRAF fusion includes BRAF duplication or rearrangement.
b The exact 95% CIs are calculated using Clopper-Pearson method.
Data Cutoff Date: 10 May 2024

Table 23: IRC-assessed Overall Response Rate and Clinical Benefit Rate by BRAF Alteration Based on RAPNO Criteria (RAPNO Evaluable Analysis Set; Arm 1)

	Arm 1 (Low-grade Glioma)	
	BRAF Fusion[a]	BRAF Mutation
Best overall response, n (%)		
Complete response	0	0
Partial response	24 (37.5)	5 (41.7)
Minor response	10 (15.6)	1 (8.3)
Stable disease	19 (29.7)	3 (25.0)
Stable disease ≥ 12 months	4 (6.3)	0
Stable disease < 12 months	15 (23.4)	3 (25.0)
Progressive disease	10 (15.6)	3 (25.0)
Not evaluable	1 (1.6)	0
Number (%) of patients with confirmed response	34	6
Overall response rate (95% CI)[b]	53.1 (40.2, 65.7)	50.0 (21.1,
Number (%) of patients with confirmed response or stable disease	38	6
Clinical benefit rate (95% CI)[b]	59.4 (46.4, 71.5)	50.0 (21.1,

Abbreviations: BRAF = v-raf murine sarcoma viral oncogene homolog B; CI = confidence interval; IRC = Independent Radiology Review Committee; N = number of patients in subgroup; n = number of patients with data; RAPNO = Response Assessment in Pediatric Neuro-Oncology.
[a] BRAF fusion includes patients with KIAA1549:BRAF fusion and others (BRAF duplication or BRAF rearrangement).
[b] The exact 95% CIs are calculated using Clopper-Pearson method.
Data Cutoff Date: 10 May 2024.

Table 24: IRC-assessed Overall Response Rate and Clinical Benefit Rate by Prior MAPK Inhibitor Therapy Based on RAPNO Criteria (RAPNO Evaluable Analysis Set; Arm 1)

	Arm 1 (Low-grade Glioma)	
	Prior MAPK Therapy N=45	No Prior MAPK Therapy N=31
Best overall response, n (%)		
Complete response	0	0
Partial response	15 (33.3)	14 (45.2)
Minor response	8 (17.8)	3 (9.7)

Stable disease	15 (33.3)	7 (22.6)
Stable disease ≥ 12 months	3 (6.7)	1 (3.2)
Stable disease < 12 months	12 (26.7)	6 (19.4)
Progressive disease	6 (13.3)	7 (22.6)
Not evaluable	1 (2.2)	0
Number of patients with confirmed response	23	17
Overall response rate (95% CI)[a]	51.1 (35.8, 66.3)	54.8 (36.0, 72.7)
Number of patients with confirmed response or stable disease ≥ 12 months	26	18
Clinical benefit rate (95% CI)[a]	57.8 (42.1, 72.3)	58.1 (39.1, 75.4)

Abbreviations: CI = confidence interval; IRC = Independent Radiology Review Committee; MAPK = mitogen-activated protein kinase; N = number of patients in subgroup; n = number of patients with data; RAPNO = Response Assessment in Pediatric Neuro-Oncology.
[a] The exact 95% CIs are calculated using Clopper-Pearson method.
Data Cutoff Date: 10 May 2024.

Table 25: Radiographic Responses with Tovorafenib by Actual Starting Dose in Arm 1 (FIREFLY-1)

	Arm 1 (Low-Grade Glioma)			
Parameter	**≤ 350**	**> 350 - 420**	**> 420**	**Overall**
RANO-HGG per IRC Assessment	(N=5)	(N=33)	(N=31)	(N=69)
ORR (CR + PR), n (%)	2 (40.0)	26 (78.8)	21 (67.7)	49 (71.0)
(95% CI) [a]	(5.3, 85.3)	(61.1, 91.0)	(48.6, 83.3)	(58.8, 81.3)
CBR (CR + PR + SD ≥ 12 months),	2 (40.0)	27 (81.8)	24 (77.4)	53 (76.8)
(95% CI) [a]	(5.3, 85.3)	(64.5, 93.0)	(58.9, 90.4)	(65.1, 86.1)
Median (95% CI) DOR (months)	- (18.8, -)	24.9 (16.8, -	13.7 (10.9, -)	19.7 (13.7, -)
RAPNO per IRC Assessment	(N=5)	(N=37)	(N=34)	(N=76)
ORR (CR + PR + MR), n (%)	1 (20.0)	22 (59.5)	17 (50.0)	40 (52.6)
(95% CI) [a]	(0.5, 71.6)	(42.1, 75.2)	(32.4, 67.6)	(40.8, 64.2)
CBR (CR + PR + MR + SD ≥ 12	1 (20.0)	24 (64.9)	19 (55.9)	44 (57.9)
(95% CI) [a]	(0.5, 71.6)	(47.5, 79.8)	(37.9, 72.8)	(46.0, 69.1)
Median (95% CI) DOR (months)	8.2 (-, -)	20.7 (11.1,	14.0 (11.0,	18.0 (12.0, 22.8)

CBR=clinical benefit rate; CI=confidence interval; CR=complete response; DOR=duration of response; IRC=Independent Radiology Review Committee; MR=minor response; ORR= overall response rate; PR=partial

response; RANO-HGG=Response Assessment in Neuro-Oncology High-grade Glioma; RAPNO=Response Assessment in Pediatric Neuro-Oncology; SD=stable disease

N is the number of patients in Full Analysis Set for RANO-HGG criteria and RAPNO Evaluable Analysis Set for RAPNO-LGG criteria. Percentage is based on N in each

riterion.

a The exact 95% CIs are calculated using Clopper-Pearson method.

b Estimated using Kaplan-Meier method.

Data cutoff date: 10 May 2024

5.3.3. Clinical studies in special populations

Table 26: Clinical studies in special populations in Patients with Paediatric Low-grade Glioma

	Controlled Trials	Non-controlled trials FIREFLY-1 (N=137)
Renal impairment* patients (Subjects number /total number)	0	0
Hepatic impairment patients (Subjects number /total number)**	0	0
Paediatric patients <18 years (Subjects number /total number)	0	131
Adult patients 18 to <65 years	0	6
Age 65-74 (Subjects number /total number)	0	0
Age 75-84 (Subjects number /total number)	0	0
Age 85+ (Subjects number /total number)	0	0
Other (Subjects number /total number)	0	0

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)

** Hepatic impairment is defined as having Child-Pugh score B or C

5.3.4. In vitro biomarker test for patient selection for efficacy

Patients with BRAF alterations were identified through molecular assays as routinely performed as part of standard of care diagnostic testing at Clinical Laboratory Improvement Amendments (CLIA) of 1988 certified or other similarly certified laboratories. The classification of BRAF fusion includes BRAF tandem duplication, BRAF rearrangement, or other non-KIAA1549- BRAF fusions. These were grouped together along with KIAA1549: BRAF fusions under the classification of BRAF fusion in the analyses. Patients were considered for enrollment based on the following modalities:

- Reverse transcription-polymerase chain reaction (RT-PCR) identifying a KIAA1549: BRAF fusion
- Fluorescence in situ hybridisation (FISH) utilizing dual-probe break-apart FISH identifying a BRAF rearrangement or tandem duplication or a single-probe break apart FISH identifying a tandem duplication in the BRAF gene
- Immunohistochemistry (IHC) identifying a BRAF V600 mutation
- Microarray identifying a KIAA1549: BRAF fusion

- Next-generation sequencing (NGS) (RNA or DNA based panel) identifying a BRAF fusion with a named upstream partner, or BRAF v600 mutation
- Other assays (eg, in vitro diagnostic [IVD] strip assay)

For the purpose of enrollment and this analysis, patients identified by single-probe FISH were inferred to harbor a KIAA1549:BRAF fusion based on the high prevalence of this fusion in patients with paediatric low-grade glioma.

A companion diagnostic was not used to screen participants at entry.

However, for the purpose of assessing patient eligibility in post approval setting, Day One and Foundation Medicine, Inc. (FMI) entered, in July 2022, into a contractual diagnostic development agreement to develop and commercialise a Companion Diagnostic (CDx). Retrospective Clinical Validation was performed to qualify FMI's F1CDx (NGS molecular sequencing) to select tovorafenib-eligible patients based on samples collected during the FIREFLY-1 study.

- Analytical validation
  - Data on the analytical validation, supporting the performance of F1CDx in the detection of BRAF V600 mutations and BRAF fusions in paediatric low-grade glioma patients, is provided in the Summary of Safety and Effectiveness Data (SSED) provided by FMI.
  - This document describes the specific analytical studies conducted to support the indication for BRAF V600 mutations and BRAF fusions in glioma, including assessments of analytical concordance with an orthogonal method, site-to-site precision, and analytical sensitivity with assessment of limit of blank (LoB) and limit of detection (LoD).
- Clinical Validation

A concordance analysis between CTAs and F1CDx was performed with the 75 (excluding the one F1CDx-enrolled patient) RAPNO-LGG evaluable patients with valid F1CDx testing results and 120 CTA-samples.

Table 27: Contingency table comparing BRAF V600 mutation or BRAF Fusion between the CTA and F1CDx based on RAPNO-LGG evaluable population

	CTA		
	CTA+	CTA-	Total
F1CDx+	41	2	43
F1CDx-	12	117	129
F1CDx-unevaluable	22	1	23
Total	75	120	195

A clinical validation study was conducted to assess the clinical effectiveness of F1CDx in identifying BRAF V600 mutations and BRAF fusions in paediatric low-grade glioma patients for treatment with tovorafenib and to assess the concordance in detecting BRAF V600 mutations and BRAF fusions between the CTAs and F1CDx. F1CDx testing was performed retrospectively on the available patient samples from the FIREFLY-1 clinical study. This clinical validation study used clinical efficacy data from the clinical cut-off of June-2023 to support the review and approval in the US. For the future submission of the CDx claim in Europe, FMI intends to update this clinical validation study with the clinical cut-off of May 2024, in line with the clinical efficacy data package of tovorafenib submitted to the EMA.

Table 28: Efficacy (ORR as determined by IRC using the RAPNO-LGG criteria) based on all NDA patients

Sub-population	No. of Patients	No. of Responders	ORR (%)	95% Two-sided Wilson Score CI (%) *
CTA+	75	39	52.00	[40.87, 62.93]
F1CDx+|CTA+	41	21	51.22	[36.48, 65.75]
F1CDx-|CTA+	12	5	41.67	[19.33, 68.05]
F1CDx-evaluable|CTA+	53	26	49.06	[36.12, 62.12]
F1CDx-unevaluable|CTA+	22	13	59.09	[38.73, 76.74]
F1CDx-enrolled	1	0	0.00	N/A

*CIs are only reported if the sample size > 10.

- Effectiveness Conclusions drawn from Analytical and Clinical validations

The data from the analytical validation and clinical bridging studies support the reasonable assurance of safety and effectiveness of the F1CDx assay when used in accordance with the indications for use. Data from the FIREFLY-1 trial show that patients with BRAF V600 mutations and BRAF fusions derived benefit from treatment with tovorafenib, thereby supporting the addition of the CDx indication to F1CDx. The bridging study demonstrated the ability of F1CDx to detect BRAF V600 mutation and BRAF fusion positive patients that benefit from Ojemda (tovorafenib) therapy.

- Definition of biomarker positivity:

A patient whose tumor harboured any of the following genetic aberrations listed in table below was defined as biomarker positive by the F1CDx assay. A discussion on the rationale (based on mechanisms of action and preclinical data) for selecting BRAF V600E mutations and BRAF fusions as predictive biomarkers for tovorafenib in paediatric low-grade glioma was provided.

Table 29: BRAF V600X and BRAF fusion alteration biomarker rules for patients with paediatric low-grade glioma

Genes (Transcript)	Variant Type	Biomarker rules
BRAF (NM_004333)	Short Variant	Any missense alteration resulting in V600X [a]
	Copy Number	N/A
	Rearrangement	Any fusion event that involves BRAF and another protein-coding gene and meets all the following criteria: • *BRAF* and the partner gene must be in the same 5'-3' orientation • *BRAF* must be on the 3' end of the detected fusion • The *BRAF* breakpoint must occur after the autoinhibitory domain and before the kinase domain

a X refers to any single amino acid change resulting from a missense alteration

- Cut point

Detection and reporting of variants by the FMI analysis pipeline are not determined by a singular threshold, but rather, a number of thresholds and quality metrics that are set by the variant class (i.e.

short variants, rearrangements, copy number amplifications and losses).

For short variants, de novo assembly is performed by the analysis pipeline using a proprietary algorithm for each target region of interest.

For rearrangements, including fusions, the same de novo assembler is used which analyzes clusters of chimeric read pairs and detects precise breakpoints. Clusters containing ≥5 chimeric pairs (≥3 for known fusions) are identified as genomic rearrangement candidates.

Beyond the complex algorithm of factors used in the analysis pipeline, no other cut-points/thresholds are used in the process that would directly impact detection and reporting of alterations.

5.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.6. Overall discussion and conclusions on clinical efficacy

5.3.6.1. Discussion

The application is based on an ongoing single, uncontrolled, open-label, multi-centre, phase 2 study FIREFLY 1 evaluating tovorafenib monotherapy in patients 6 months to 25 years of age with low-grade gliomas (Arm 1 and 2) and advanced solid tumours (Arm 3). Patients were enrolled in one of three treatment arms. Efficacy data supporting this CMA come from patients enrolled in Arm 1.

Design and conduct of clinical studies

No dedicated dose response study is submitted with this current application. Per protocol version 4, FIREFLY-1 evaluated tovorafenib administered orally at 420 mg/m^2 (not to exceed 600 mg) once a week. The rationale for the chosen dose is based on Study C28001 and Part A of investigator- sponsor trial Study PNOC014. The Study PNOC014 was only mentioned by the applicant in Summary of clinical efficacy with sparse information. Although initially included in the paediatric investigation plan (PIP), the PNOC014 study was removed as a key measure of the PIP, justified by the applicant with arguments that the data, particularly related to dose and PK will be generated with FIREFLY-1 study. The CSR for study PNOC014 has not been provided in the current application. Nevertheless, it is considered that the data from PNOC014 could have contributed to the assessment of efficacy/dose finding for tovorafenib in the proposed indication.

The recommended dose of tovorabenib in this procedure is now 380 mg/m^2 once per week (not to exceed 600 mg) for the treatment of patients 6 months of age and older with paediatric LGG harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies. The evidence supporting the 380 mg/m^2 dose is derived from post-hoc analysis of the FIREFLY-1 study and the modelling, taking into account the totality of clinical and preclinical data.

In 2024, the pLGG community emphasised (Fangusaro et al. 2024) that the appropriate duration of treatment is unknown, although many pLGG trials have arbitrarily treated children for 2 years without strong rationale, and also highlighted that intermittent dosing and "drug holidays" are utilised by some practitioners to minimize acute toxicity and development of resistance with a goal of maintaining good response rates. Fangusaro et al. 2024 also mentioned that there are some data in adult melanoma, although distinct from pLGG, suggesting treatment with BRAF inhibitors plus/minus MEK inhibitor inhibitors (in BRAFV600E-mutant melanoma) which can be effectively stopped when a patient has a prolonged CR to therapy. As pLGG is now commonly accepted as a chronic disease,

treatment interruption will perhaps be done in clinical practice when the disease is stable in order to preserve the long-term balance between the benefit and the risk. In the FIREFLY-1, patients were to be treated with tovorafenib for a period of 26 cycles (approximately 24 months), after which they could continue tovorafenib or, at any point, opt to enter a "drug holiday" discontinuation period. The wording in Section 4.2 of the SmPC, which recommends treatment continuation until disease progression or unacceptable toxicity occurs, accurately captures the current evidence base and validates clinical flexibility, and is thus considered acceptable. The 2-year duration and the option for a drug holiday or to continue treatment after 2 years were added in the description of the study section 5.1 of the SmPC.

In general, the inclusion / exclusion criteria of the FIREFLY-1 study are considered acceptable.

The study population represents a heavily pre-treated population in a setting with an unmet medical need.

Patients eligible for enrolment in Arm1 included patients (6 months to 25 years) with relapsed or progressive low-grade glioma with a documented known activating BRAF alteration, as identified through molecular assays as routinely performed at CLIA-certified or other similarly certified laboratories. Furthermore, according to the inclusion criteria 3, patients must have received at least 1 line of prior systemic therapy and have documented evidence of radiographic progression (Arm 1 and Arm 2). The SmPC has been updated to reflect this inclusion criterion, changing the wording from referring to patients who 'have received' prior systemic therapies to those who 'have progressed after' prior systemic therapies.

The upper age limit for patient inclusion was increased from 18 years to 25 years at the time of first global amendment Protocol V2.0 (23 October 2020). Although the median age of diagnosis of paediatric low-grade glioma is 7-9 years, older patients in their early twenties may also be affected. This update to the inclusion criteria was beneficial to the generation of efficacy data in older patients although only few patients were ≥ 16 years old. Thus, the current indication has no specified upper age limit.

Since RANO-HGG rely primarily on contrast-enhanced T1-weighted images to determine objective response, patients enrolled in FIREFLY-1 were required to have at least one measurable lesion as defined by RANO-HGG criteria at baseline to enrol in the study. This is acknowledged and reflected in section 5.1 of the SmPC.

Enrolled patients had adequate hematologic, hepatic and renal function, and did not have severe cardiac comorbidity.

Patients with additional previously known or expected to be activating molecular alteration(s) (i.e. histone mutation, IDH1/2 mutations, FGFR mutations or fusions, MYBL alterations, neurofibromatosis type 1 (NF-1) somatic or germline mutations) were not included in the study and this is reflected in section 5.1 of the SmPC. This is especially important as in the association with NF-1, a spontaneous regression has been more widely reported than the spontaneous regression of LGG in paediatric patients without neurofibromatosis. Notably, the planned phase 3 confirmatory study FIREFLY-2 also excluded these diagnosis/mutations.Tumours were assessed by radiographic tumour measurements using MRI of the brain and spine (as indicated). Due to the heterogeneity of paediatric low-grade gliomas and differences between the paediatric and adult manifestations of the disease, to define the optimal imaging characteristics is challenging. Radiographic images were therefore analysed using 3 different assessment criteria: Response Assessment in Neuro-oncology (RANO) criteria (Wen 2010, RANO-HGG), Assessment in Neuro-oncology Low-grade Glioma (RANO-LGG), and Response Assessment in Paediatric Neuro-oncology (RAPNO) criteria (Fangusaro 2020). Although the applicant provided arguments as to why RANO-HGG criteria were originally selected for the primary endpoint

(eg, they have been clinically validated; they are sufficiently similar to the MacDonald criteria used in the study by Bouffet et al (2012) that served as a benchmark in the design of the FIREFLY-1 study), these criteria are actually designed for adult high-grade gliomas, particularly glioblastoma, and are therefore not suitable for LGG and in particular pLGG, where contrast enhancement is variable or minimal. Even RANO-LGG criteria do not fully address the unique behaviour of pLGG. On the other hand, RAPNO-LGG is developed specifically for pLGG, recognizing the biological and radiological differences from adult gliomas. RAPNO-LGG has in the meantime undergone international consensus development and validation efforts and is increasingly used in paediatric LGG clinical trials including the confirmatory FIREFLY 2 study.

The pre-specified primary objective of Arm 1 of the FIREFLY 1 study was to evaluate the overall response rate (ORR) as determined by an independent radiology review committee (IRC) and measured by the proportion of patients with best overall confirmed response of complete response (CR) or partial response (PR) as determined by the Response Assessment in Neuro-Oncology – high-grade glioma (RANO-HGG) criteria. However, considering that the RANO-HGG criteria are not suitable for assessing LGG, and in particular pLGG, benefit assessment in this application is primarily focused on the analysis of ORR using the RAPNO-LGG criteria, despite being a secondary endpoint according to the protocol. Analysis of the response using RANO-LGG was also added as exploratory study endpoint.

Although imaging response measures are suitable endpoints in a single arm trial as these can isolate a treatment effect, it is more difficult to assess in terms of clinical benefit. Regulatory experience in the present setting is limited.

EMA Reflection paper on establishing efficacy based on single-arm trials (SAT) (EMA/CHMP/458061/2024) outlines perspectives on SATs that are submitted as pivotal evidence for establishing efficacy in marketing authorisation applications. Although ORR based on BOR in the current study is acceptable considering the condition and target population, interpretation of the results in single arm setting is challenging and requires careful consideration on the magnitude of the benefit, clinical relevance of the observed responses, and impact of patient selection and concomitant treatments.

The definition of ORR includes minor responses (>25% but <50% decrease in area) in addition to complete and partial responses. The inclusion of MR in the FIREFLY-1 study aligns with updated RAPNO-LGG and RANO-LGG guidelines, which recognize MR as a meaningful indicator of therapeutic benefit in paediatric low-grade glioma. The plan to analyze the RAPNO endpoint using CR+PR+MR was already implemented in the initial Statistical Analysis Plan (version 1, dated March 2022) for FIREFLY-1 and this was carried through all subsequent versions of the SAP although the inclusion of MR responses was included with late protocol amendments. Furthermore, the Investigator-assessed response was only performed for RANO-HGG criteria. For RAPNO and RANO-LGG response, evaluation was assessed by IRC only and was not routinely available to the Sponsor during the study. The Applicant stated that the inclusion of MR in the FIREFLY-1 is not data-driven but is rather based on the evolution of the field, on further FDA discussions and on the updated international guidelines for RAPNO criteria.

The secondary endpoints included analysis of response using RAPNO criteria, DoR, PFS, OS, TTR, change from baseline in best corrected visual acuity (BCVA).

The clinical and symptomatic endpoints may in principle be relevant for benefit-risk assessment, however the interpretation of these endpoints in a SAT is not possible, only controlled (and blinded) design would enable interpretation of such endpoints. Therefore, although quality-of-life and health utilities measures using the PedsQL-Core, PedsQL-Cancer, and PROMIS® assessment, and improvement in motor function measured by changes from baseline in the Vineland 3 Adaptive

Behavior Scales were collected as exploratory endpoints in the FIREFLY-1 study, they are not presented nor discussed in the current application.

As of the data cutoff date (10 May 2024), 77 patients were enrolled and treated in Arm 1 of study FIREFLY-1 (ITT population). However, the efficacy analysis is based on 76 patients with measurable disease at baseline per RAPNO-LGG criteria. Of note, Full Analysis Set included 69 patients in the Arm 1, since overall, 8 patients did not have measurable disease per RANO-HGG criteria as determined by the IRC at baseline, as the initial assessment relied on the investigator's clinical assessment without central confirmation. The IRC later identified these cases as without a measurable disease during retrospective review, leading to their exclusion from the primary efficacy analysis (ORR for RANO-HGG). They were included in the safety analysis and most alternative efficacy analyses (RAPNO/RANO-LGG). While this exclusion departs from the ITT principle, this deviation should have almost no effects on the results based on RAPNO or RANO-LGG (as the difference between the 2 analysis sets is only 1 participant), and minor effects on the results based on RANO-HGG. The rationale provided for this approach is clear and does not compromise the validity of the study's conclusions.

Overall, the changes that were made during the conduct of the study presented and described accordingly. Of note, with the latest global protocol amendment dated 31 October 2023 the objectives and endpoints have been substantially changed. Among other, new exploratory objectives according to RANO-LGG have been included.

Thirty-five (45.5%) patients had major protocol deviations, and most included informed consent (twenty-two [28.6%]) and missing laboratory analytes (seventeen [22.1%]). None of the patients with major protocol deviations were excluded from the Per-protocol Analysis Set.

The most common reason for primary treatment discontinuation in Arm 1 was drug holiday (33 patients (42.9%)). Ten patients (13.0%) discontinued study early, either due to death (5.2%) or withdrawal by patient (3.9%) or parent/guardian (3.9%). The median duration of follow-up across different analysis sets are consistent and in the range of 27.8 to 28.1 months.

The median duration of exposure to tovorafenib was 722.0 days (or 23.7 months) (range: 22 to 975 days). The duration of primary treatment was $\geqslant$ 24 months for 25 (32.5%) patients with a median duration of primary treatment of 24.74 months.

With regards to the baseline patient characteristics in the Arm 1 of the FIREFLY-1 study, patients 2 to 21 years of age were enrolled with a median age of 8.0 years. No patient was in the 6 months to < 2 years of age group. However, the claimed indication includes patients from 6 months of age. Considering the scarcity of efficacy/safety data, further evidence on the systemic exposure in this sub-group of patients are needed. The MAH shall generate additional PK data in paediatrics patients below 2 years of age and submit an updated population PK model incorporating these data, including an assessment of systemic exposure and, if necessary, revised dosing recommendations for this subgroup of patients.

Most patients were white and approximately half of patients were male. Distribution by a geographic region was not reported. However, no epidemiologic differences are expected in pLGG by geographic location.

Most patients (93.5%) had tumours with astrocytic histology, which is expected considering pilocytic astrocytoma is the most common subtype of pLGG. For half of the patients, the primary tumour location was optic pathway, which is not the most usual location of pLGG. Anatomically most pLGGs occur in the cerebellum, with some pathognomonic locations according to mutation, i.e. higher rates of fusion positive LGG occur in the cerebellum and mutation-driven disease in the supratentorium (Behling F 2019). Therefore, the study population was enriched with optic pathway tumours, but this

is understandable as these are not easily removed surgically and therefore require systemic treatment. Pre-operative staging for most patients was localised disease (77.9%). Only one patient in Arm 1 had gross total resection, and either sub-total resection (46.8%) or biopsy only (51.9%) as post-operative staging.

Most (73.7%) patients in Arms 1 and 2 had a KIAA1549:BRAF fusion, while 16.1% of patients had a BRAF V600E mutation and 10.2% had BRAF duplication (Arm 1: 6; Arm 2: 3), 3 patients with BRAF rearrangement (Arm 1: 2; Arm 2: 1), 1 patient with RNF130-BRAF (Arm 2), and 1 patient with PID1-BRAF fusion (Arm 2). While the most frequent molecular alteration in pLGG (KIAA1549-BRAF fusion) is currently suspected to have a favourable impact on OS and PFS, pLGG harbouring the most common mutation in BRAF (BRAF V600E) is presumably associated with unfavourable PFS (Roka K 2024).

Efficacy data and additional analyses

Evidence of the tumour response with tovorafenib can be observed across all three different neuro-oncology response assessment criteria. The results using RANO-LGG and RAPNO are overall consistent (ORR [95%CI] 53.9% [42.1,65.4] and 52.6% [40.8,64.2], respectively), however ORR as determined by RANO-HGG criteria demonstrated approximately 20% larger magnitude of improvement (71.0% [58.8, 81.3]) when compared with both RANO-LGG and RAPNO criteria analysed.

Considering that the RANO-HGG criteria are not suitable for assessing LGG and in particular pLGG, the assessment of efficacy in this application is focused on the analysis of the tumour response using RAPNO criteria in the FIREFLY-1 study.

Of note, time-to-event endpoints such as PFS and OS were also reported but are considered exploratory and not to be robustly interpretable in a single arm study.

RAPNO criteria

The RAPNO evaluable analysis set consisted of 76 patients in Arm 1 with measurable disease at baseline determined by the IRC based on RAPNO criteria. IRC-assessed ORR (CR, PR, or MR) was 52.6% (95% CI: 40.8, 64.2). No patients had a CR, 29 (38.2%) patients had a PR, 11 (14.5%) patients had an MR, and 22 (28.9%) patients had stable disease.

Median IRC-assessed DOR was 18.0 months (95% CI: 12.0, 22.8). The Kaplan-Meier estimate of the probability of continued response was 65.0% (95% CI: 48.2, 77.6) at 12 months, 50.0% (95% CI: 33.8, 64.2) at 18 months, and 25.6% (95% CI: 11.4, 42.6) at 24 months.

Median IRC-assessed TTR was 5.4 months (range: 1.6 to 17.5 months). There was a numerical trend for shorter median TTR for patients with 1 prior line of therapy than for patients with $\geqslant$ 2 prior lines of therapy. There was no observable trend in TTR with regard to BRAF alteration or prior MAPK-targeted therapy.

Thirteen (17.1%) patients had a best overall response of PD based on RAPNO criteria as assessed by an IRC. Eleven of these 13 patients were continued on treatment for 1 month or longer as continuation was based on RANO-HGG criteria and they did not have progression by these criteria. RAPNO central reads were evaluated at a later date. However, an analysis of these patients revealed that 6 patients went on to have subsequent reductions in tumour size below baseline following the initial progression. Of those, 4 patients experienced subsequent tumour reduction of $\geqslant$ 50%, and 2 patients had subsequent tumour maximal reduction of $\geqslant$ 25% to < 50%. In addition, 4 patients had post PD scans that showed less than 25% increase in tumour size compared to the baseline scan.

With a data cutoff date of 10 May 2024, the results overall remained consistent with the primary and

updated analyses. Of note, for the Primary CSR, analyses based on RAPNO criteria were evaluated using the Full Analysis Set. In subsequent reports, analyses based on RAPNO criteria were evaluated using the RAPNO Evaluable Analysis Set.

RANO-LGG criteria

IRC-assessed ORR (CR, PR, or MR) was 53.9% (95% CI: 42.1, 65.5). No patients had a CR, 23 (30.3%) patients had a PR, 18 (23.7%) patients had an MR, and 22 (28.9%) patients had stable disease.

Median IRC-assessed DOR was 16.8 months (95% CI: 12.0, 19.4). The Kaplan-Meier estimate of the probability of continued response was 65.5% (95% CI: 48.8, 77.9) at 12 months, 49.3% (95% CI: 32.9, 63.8) at 18 months, and 18.2% (95% CI: 6.7, 34.1) at 24 months.

RANO-HGG criteria

Although considered exploratory, outcomes of ORR based on RANO-HGG criteria are very discordant between the assessment made by the IRC (71.0% (95% CI: 58.8, 81.3)) and the investigators (49.3% (95% CI: 37.0, 61.6)). The discordance between investigator and IRC assessments, with differences in ORR, reflects the inherent variability in tumor response evaluation. The IRC's standardized, blinded process provides a distinct benchmark compared to investigator assessments, which may be influenced by clinical context or local practices.

Changes in BCVA outcomes

Overall, visual acuity appeared to remain stable for the majority of patients enrolled with optic pathway gliomas or baseline visual deficits related to their CNS tumour as assessed by the investigator. While changes of ≥ 0.2 logMAR occurred, with decreases from baseline more commonly reported than increases, the clinical relevance of visual acuity assessments cannot robustly be interpreted in a single-arm study.

Subgroup analysis

Subgroup analysis of IRC-assessed ORR based on RAPNO criteria was performed by BRAF alteration, prior MEK inhibitor therapy, prior BRAF inhibitor therapy, prior MAPK inhibitor therapy, number of prior systemic lines of therapy, sex, age group, and race. Responses were observed among all subgroups, however, the small number of patients in some subgroup's limits interpretation of the data. The trend in ORR (when only CR and PR were included) could be observed in the analysis of Prior vs No Prior MAPK Therapy (33.3% vs 45.2%, respectively). This trend is however not seen when MR is calculated in ORR (51.1% vs 54.8%, respectively).

The alterations were summarized into two groups: BRAF fusion (includes KIAA1549:BRAF fusion and other alterations) and BRAF mutation (included only BRAF V600E mutation). Similar responses were observed in both these subgroups, 53.1% (95%CI 40.231, 65.720) and 50.0% (95% CI21.094, 78.906), respectively. Overall, there are no significant differences with regard to the subgroup analyses of ORR per RAPNO Criteria by sex, race, prior lines of therapy and BRAF alterations (BRAF fusion vs BRAF mutation vs other). Of note, there is a difference in the ORR with regard to age. However, it is only a subgroup analysis and due to limited sample sizes, it is not possible to draw formal conclusions.

In FIREFLY-1, only 3 patients harboring the mutation BRAF V600E were pre-treated by the combination of dabrafenib and trametinib. Among these 3 patients, 2 patients achieved radiological response, one PR and one MR (ORR: 66.7% 95% CI: 9.43, 99.2), and one demonstrated stable disease based on RAPNO according to IRC assessment. Although, there is currently no evidence to exclude these

patients from benefiting from this treatment as overall response to tovorafenib was observed regardless of the type of BRAF alteration (BRAF fusions vs BRAF mutations), and regardless of prior MAPK therapy, uncertainties remain due to the limited clinical data available in this setting.

Moreover, the large majority of patients included in FIREFLY-1 was patients with KIAA1549:BRAF fusions (74%). At this stage, efficacy data are lacking regarding other types of fusion.

Retreatment

The proposed possibility of a drug holiday of tovorafenib in FIREFLY-1 after 2 years of treatment is considered unusual. Retreatment with tovorafenib is potentially required in these patients. However, in FIREFLY-1, mainly due to the slow progression of the disease, only 3 patients have been retreated with tovorafenib. At this stage, clear and evidence-based criteria regarding the proposed possibility of a drug holiday and the potential necessity of subsequent retreatment remains limited, and no recommendation can be given in the SmPC.

Biomarker

No central confirmation test was performed within the main study (FIREFLY-1). For assessing patient eligibility in post approval setting, Day One and Foundation Medicine, Inc. (FMI) entered into a contractual diagnostic development agreement to develop and commercialize a Companion Diagnostic (CDx). Retrospective analytical and clinical validation was performed to assess in how far F1CDx is suitable to select tovorafenib eligible patients based on samples collected during the FIREFLY-1 study. It might be acceptable to use F1CDx as a (retrospective) central confirmation test as part of the application for authorisation of tovorafenib. However, the positive percentage agreement (PPA) of F1CDx with clinical trials assays (CTAs) of only 77%, and responses being observed in patients that were F1CDx negative suggest that patients not identified by F1CDx could benefit from treatment. The Applicant assumes that higher sample quality, more recent sample collection and minimum tumor content input requirements are sufficient to mitigate the risk of false negative F1CDx results in clinical practice, however, uncertainty remains as there are no data to support this assumption. Furthermore, it remains unclear whether the samples from different sources that were the basis for evaluation of negative percentage agreement (NPA) of F1CDx with CTAs are indeed representative for patients screened negative by the CTAs. Uncertainties regarding how far F1CDx is predictive for response to tovorafenib also remain because of the lack of efficacy data in patients without BRAF V600 mutation or BRAF fusion and the not fully convincing clinical rationale. No single thereshold was applied as cut-point for the assay but a complex algorithm aiming at reliably determining the presence of BRAF alterations or rearrangemens but apparently no clinical thresholding was performed.

5.3.6.2. Conclusions on the clinical efficacy

The available efficacy data from the pivotal study FIREFLY-1 are considered to demonstrate antitumour activity of tovorafenib in the agreed indication.

In the absence of a comparator arm, assessment of clinical benefit relies primarily on ORR. Tumour response was evaluated according to the RAPNO-LGG criteria, which are considered appropriate for the assessment of pLGG. While the initial ORR definition included CR and PR, it was subsequently expanded to also MR, in line with evolving clinical practice and updated guidance in pLGG.

The ORR (including CR, PR and MR) based on RAPNO-LGG criteria was 52.6% (95% CI: 40.8, 64.2), based on 76 evaluable patients, and the median duration of response (DoR) was 18 months (95% CI: 12.0 – 22.8). The antitumour activity of tovorafenib has therefore been demonstrated.

However, due to the limitations in the pivotal study design, including the absence of a randomised comparator arm as well as the limited sample size, the available data are not considered comprehensive within the meaning of the CMA legislation (see section 9.6.3.1.2.). Data from the ongoing study FIREFLY-2 will be submitted as part of the agreed SOB under the CMA (due date 30 April 2032) and are expected to further support the characterisation of the efficacy of tovorafenib, providing comparative data and helping contextualise and address the uncertainty regarding the observed treatment effect.

5.4. Clinical safety

5.4.1. Safety data collection

The safety assessment in the intended population was primarily based on the pivotal phase 2 study FIREFLY-1, which included 137 paediatric patients with LGG. Additional supportive safety data were derived mainly from Study C28001, a completed Phase 1 first-in-human trial that evaluated the safety, efficacy, and pharmacokinetics of tovorafenib monotherapy in adult patients with advanced solid tumors.

Table 30: Description of Clinical Studies in the Summary of Clinical Safety

Study ID/ Status	Data Cutoff Date	Study Title/ Design and Population	Treatment Groups and Number of Patients Included in the Safety Analysis	Treatment Duration	Actual Age Enrolled
DAY101-001/ PNOC026 (FIREFLY-1)/ Ongoing	10 May 2024	A Phase 2, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of the Oral Pan-RAF Inhibitor DAY101 in Pediatric Patients with RAF-Altered, Recurrent or Progressive Low-Grade Glioma and Advanced Solid Tumors Patients 6 months to 25 years of age (inclusive) Arm 1; BRAF-altered, relapsed or progressive pLGG Arm 2; RAF-altered, relapsed or progressive pLGG extension arm	Oral tovorafenib 420 mg/m^2 QW (not to exceed 600 mg QW) on a 28-day cycle Total N = 143 • Arm 1; N = 77 • Arm 2; N = 60 • Arm 3; N = 6	Number of treated cycles, median (min, max): Arm 1; 26 (1, 35) Arm 2; 23 (2, 27) Arm 3; 2.5 (1, 10)	Median (min, max) years: Arm 1; 8 years (2, 21) Arm 2; 9.5 years (1, 24) Arm 3; 13 years (11, 15)

Study ID/ Status	Data Cutoff Date	Study Title/ Design and Population	Treatment Groups and Number of Patients Included in the Safety Analysis	Treatment Duration	Actual Age Enrolled
		Arm 3; advanced solid tumors harboring an activating RAF fusion			
C28001/ Completed	NA	An Open-Label, Phase 1, Dose Escalation Study of MLN2480 in Patients With Relapsed or Refractory Solid Tumors Followed by a Dose Expansion Phase in Patients With Metastatic Melanoma Patients ≥ 18 years of age	Oral tovorafenib • Q2D Dose Escalation: 20, 40, 80, 135, 200, and 280 mg Q2D on a 22-day cycle; and 200 mg Q2D on a 28-day cycle • Q2D Dose Expansion: 200 mg Q2D on a 28-day cycle • QW Dose Escalation: 400, 600, and 800 mg QW on a 28-day cycle • QW Dose Expansion: 600 mg QW on a 28-day cycle Total N = 149 • Q2D Dose Escalation (N = 30) • Q2D Dose Expansion (N = 80)[a] • QW Dose Escalation (N = 20) • QW Dose Expansion (N = 19)	Number of treated cycles, median (min, max): Q2D Dose Escalation; 2.0 (1, 38) Q2D Dose Expansion; 2.0 (1, 49) QW Dose Escalation; 1.0 (1, 10) QW Dose Expansion; 2.0 (1, 8)	Median (min, max): Q2D Dose Escalation; 65.5 years (37, 83) Q2D Dose Expansion; 65.0 years (31, 94) QW Dose Escalation; 60.5 years (39, 74) QW Dose Expansion; 70.0 years (41, 83)

5.4.2. Patient exposure

Table 31: Patient exposure (cut-off 10 May 2024)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
DAY101-001/ PNOC026 (FIREFLY-1)/ phase 2, open-label study, Ongoing	Patients 6 months to 25 years of age, with pediatric LGG (Arm 1 and Arm 2 [extension of Arm 1]) and advanced solid tumors (Arm 3).	N=137 in both Arms (77 in Arm 1 and 60 in Arm 2)	N=137	78.8% of patients had ≥ 12 months of treatment, 66.4% of patients had ≥ 18 months of treatment

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
C28001/ Open-Label, Phase 1, Dose Escalation Study, Completed	adult patients with advanced solid tumors N=149 (Escalation: 50 patients and Expansion: 99 patients)	149 patients (for QW dosing: 400 mg/ 600 mg N = 35 and 800 mg N = 4 and for Q2D dosing 20 mg to 280 mg N = 110)	400 mg/ 600 mg QW dosing N = 35	
Post marketing		Not available		

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

5.4.3. Adverse events

Table 32: Summary of adverse events (full analysis set)

	Arm 1 (LGG) N=77 n (%)	Arm 2 (LGG) N=60 n (%)	Arm 1 + Arm 2 N=137 n (%)
All TEAEs	77 (100)	60 (100)	137 (100)
Grade ≥ 3 TEAEs	64 (83.1)	48 (80.0)	112 (81.8)
Serious TEAEs	41 (53.2)	35 (58.3)	76 (55.5)
Treatment-related serious TEAEs	18 (23.4)	11 (18.3)	29 (21.2)
Fatal (Grade 5) TEAEs[a]	2 (2.6)	2 (3.3)	4 (2.9)
TEAEs leading to dose modification	56 (72.7)	41 (68.3)	97 (70.8)
TEAEs leading to dose reduction	25 (32.5)	19 (31.7)	44 (32.1)
TEAEs leading to dose interruption	51 (66.2)	39 (65.0)	90 (65.7)
TEAEs leading to study treatment discontinuation	8 (10.4)	7 (11.7)	15 (10.9)
Treatment-related TEAEs leading to study treatment discontinuation	6 (7.8)	7 (11.7)	13 (9.5)

Abbreviations: LGG = low-grade glioma; TEAE = treatment-emergent adverse event.
[a] One patient in Arm 1 had Grade 5 brain death considered attributable to the patient's underlying disease, not related to tovorafenib. The other patient in Arm 1 had a TEAE of unexplained death, not related to tovorafenib. One patient in Arm 2 had Grade 5 tumour haemorrhage, considered not related to tovorafenib. The other patient in Arm 2 had Grade 5 pneumonia, considered not related to tovorafenib.

Table 33: Overall Summary of TEAEs by Actual Starting Dose (FIREFLY-1 Safety Analysis Set)

	Arm 1 + Arm 2			
Number of Patients, n (%)	**≤ 350 mg/m² (N=15)**	**> 350 - 420 mg/m² (N=63)**	**> 420 mg/m² (N=59)**	**Overall (N=137)**
All Treatment Emergent Adverse Events (TEAEs)	15 (100.0)	63 (100.0)	59 (100.0)	137 (100.0)
TEAEs with Severity Grade 3 or Higher	11 (73.3)	47 (74.6)	54 (91.5)	112 (81.8)
Serious TEAEs	9 (60.0)	31 (49.2)	36 (61.0)	76 (55.5)
TEAEs Leading to Dose Reduction	5 (33.3)	21 (33.3)	18 (30.5)	44 (32.1)
TEAEs Leading to Study Drug Interruption	9 (60.0)	38 (60.3)	43 (72.9)	90 (65.7)
TEAEs Leading to Study Drug Discontinuation	3 (20.0)	4 (6.3)	8 (13.6)	15 (10.9)
TEAEs Leading to Death	0	2 (3.2)	2 (3.4)	4 (2.9)
TEAEs Related to Study Drug	15 (100.0)	62 (98.4)	59 (100.0)	136 (99.3)
TEAEs Related to Study Drug with Severity Grade 3 or Higher	10 (66.7)	35 (55.6)	44 (74.6)	89 (65.0)
Serious TEAEs Related to Study Drug	5 (33.3)	15 (23.8)	9 (15.3)	29 (21.2)
TEAEs Related to Study Drug Leading to Death	0	0	0	0

Abbreviations: AE = adverse event; MedDra = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Table 34: Treatment-emergent Adverse Events of All Grades (Excluding Laboratory Abnormalities) Reported in ⩾ 10% of All Patients (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

MedDRA Preferred Term	**Arm 1 (LGG) N=77**		**Arm 2 (LGG) N=60**		**Arm 1 + Arm 2 N=137**	
Number of Patients, n (%)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TEAE	77 (100)	64 (83.1)	60 (100)	48 (80.0)	137 (100)	112 (81.8)
Hair colour changes	64 (83.1)	0	42 (70.0)	0	106 (77.4)	0
Fatigue	47 (61.0)	3 (3.9)	36 (60.0)	3 (5.0)	83 (60.6)	6 (4.4)
Vomiting	42 (54.5)	6 (7.8)	35 (58.3)	3 (5.0)	77 (56.2)	9 (6.6)
Headache	42 (54.5)	3 (3.9)	30 (50.0)	0	72 (52.6)	3 (2.2)
Rash maculo-papular	40 (51.9)	8 (10.4)	29 (48.3)	3 (5.0)	69 (50.4)	11 (8.0)
Pyrexia	35 (45.5)	5 (6.5)	29 (48.3)	4 (6.7)	64 (46.7)	9 (6.6)
Growth retardation	32 (41.6)	22 (28.6)	27 (45.0)	22 (36.7)	59 (43.1)	44 (32.1)
Dry skin	30 (39.0)	0	26 (43.3)	0	56 (40.9)	0
Nausea	30 (39.0)	0	21 (35.0)	0	51 (37.2)	0
Constipation	24 (31.2)	0	26 (43.3)	1 (1.7)	50 (36.5)	1 (0.7)
Upper respiratory tract infection	24 (31.2)	0	25 (41.7)	2 (3.3)	49 (35.8)	2 (1.5)
Dermatitis acneiform	23 (29.9)	1 (1.3)	24 (40.0)	0	47 (34.3)	1 (0.7)
Epistaxis	30 (39.0)	0	14 (23.3)	1 (1.7)	44 (32.1)	1 (0.7)
Decreased appetite	27 (35.1)	3 (3.9)	14 (23.3)	2 (3.3)	41 (29.9)	5 (3.6)
Paronychia	25 (32.5)	1 (1.3)	16 (26.7)	1 (1.7)	41 (29.9)	2 (1.5)
Pruritus	25 (32.5)	2 (2.6)	13 (21.7)	0	38 (27.7)	2 (1.5)
COVID-19	24 (31.2)	0	13 (21.7)	0	37 (27.0)	0
Cough	17 (22.1)	1 (1.3)	19 (31.7)	0	36 (26.3)	1 (0.7)
Diarrhoea	18 (23.4)	1 (1.3)	17 (28.3)	1 (1.7)	35 (25.5)	2 (1.5)

MedDRA Preferred Term Number of Patients, n (%)	Arm 1 (LGG) N=77		Arm 2 (LGG) N=60		Arm 1 + Arm 2 N=137	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Weight decreased	20 (26.0)	2 (2.6)	15 (25.0)	0	35 (25.5)	2 (1.5)
Eczema	18 (23.4)	2 (2.6)	15 (25.0)	1 (1.7)	33 (24.1)	3 (2.2)
Abdominal pain	18 (23.4)	0	10 (16.7)	1 (1.7)	28 (20.4)	1 (0.7)
Alopecia	18 (23.4)	0	10 (16.7)	0	28 (20.4)	0
Pain in extremity	21 (27.3)	1 (1.3)	7 (11.7)	0	28 (20.4)	1 (0.7)
Face oedema	14 (18.2)	0	12 (20.0)	0	26 (19.0)	0
Nasopharyngitis	12 (15.6)	0	11 (18.3)	0	23 (16.8)	0
Rash	15 (19.5)	0	8 (13.3)	0	23 (16.8)	0
Myalgia	16 (20.8)	0	6 (10.0)	0	22 (16.1)	0
Erythema	13 (16.9)	0	8 (13.3)	2 (3.3)	21 (15.3)	2 (1.5)
Photosensitivity reaction	8 (10.4)	0	12 (20.0)	1 (1.7)	20 (14.6)	1 (0.7)
Arthralgia	11 (14.3)	0	8 (13.3)	0	19 (13.9)	0
Rhinorrhoea	6 (7.8)	0	13 (21.7)	0	19 (13.9)	0
Conjunctivitis	8 (10.4)	0	10 (16.7)	0	18 (13.1)	0
Dizziness	7 (9.1)	0	11 (18.3)	0	18 (13.1)	0
Nasal congestion	10 (13.0)	0	8 (13.3)	0	18 (13.1)	0
Stomatitis	8 (10.4)	0	10 (16.7)	0	18 (13.1)	0
Oropharyngeal pain	12 (15.6)	0	5 (8.3)	0	17 (12.4)	0
Tumour haemorrhage	8 (10.4)	2 (2.6)	9 (15.0)	3 (5.0)	17 (12.4)	5 (3.6)
Muscle spasms	12 (15.6)	0	4 (6.7)	0	16 (11.7)	0
Pericardial effusion	9 (11.7)	1 (1.3)	7 (11.7)	0	16 (11.7)	1 (0.7)
Viral infection	10 (13.0)	4 (5.2)	6 (10.0)	0	16 (11.7)	4 (2.9)
Abdominal pain upper	11 (14.3)	0	4 (6.7)	0	15 (10.9)	0
Hydrocephalus	9 (11.7)	8 (10.4)	6 (10.0)	5 (8.3)	15 (10.9)	13 (9.5)
Rash erythematous	9 (11.7)	1 (1.3)	6 (10.0)	0	15 (10.9)	1 (0.7)
Flushing	10 (13.0)	0	4 (6.7)	0	14 (10.2)	0
Influenza like illness	9 (11.7)	0	5 (8.3)	0	14 (10.2)	0
Weight increased	6 (7.8)	2 (2.6)	8 (13.3)	3 (5.0)	14 (10.2)	5 (3.6)

Abbreviations: LGG = low-grade glioma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
MedDRA Version 23.1; Common Terminology Criteria for Adverse Events Version 5.0.
Data cutoff date: 10 May 2024.

Table 35: Treatment-related Adverse Events (Excluding Laboratory Abnormalities) Reported in ⩾ 10% of All Patients (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

MedDRA Preferred Term Number of Patients, n (%)	Arm 1 (LGG) N=77		Arm 2 (LGG) N=60		Arm 1 + Arm 2 N=137	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any treatment-related TEAE	76 (98.7)	48 (62.3)	60 (100)	41 (68.3)	136 (99.3)	89 (65.0)
Hair colour changes	64 (83.1)	0	42 (70.0)	0	106 (77.4)	0

MedDRA Preferred Term Number of Patients, n (%)	Arm 1 (LGG) N=77		Arm 2 (LGG) N=60		Arm 1 + Arm 2 N=137	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	39 (50.6)	3 (3.9)	29 (48.3)	3 (5.0)	68 (49.6)	6 (4.4)
Rash maculo-papular	38 (49.4)	8 (10.4)	25 (41.7)	3 (5.0)	63 (46.0)	11 (8.0)
Growth retardation	31 (40.3)	22 (28.6)	27 (45.0)	22 (36.7)	58 (42.3)	44 (32.1)
Dry skin	28 (36.4)	0	24 (40.0)	0	52 (38.0)	0
Dermatitis acneiform	20 (26.0)	1 (1.3)	23 (38.3)	0	43 (31.4)	1 (0.7)
Paronychia	23 (29.9)	1 (1.3)	15 (25.0)	1 (1.7)	38 (27.7)	2 (1.5)
Pruritus	23 (29.9)	2 (2.6)	12 (20.0)	0	35 (25.5)	2 (1.5)
Constipation	13 (16.9)	0	21 (35.0)	0	34 (24.8)	0
Decreased appetite	19 (24.7)	3 (3.9)	12 (20.0)	1 (1.7)	31 (22.6)	4 (2.9)
Headache	20 (26.0)	0	11 (18.3)	0	31 (22.6)	0
Vomiting	18 (23.4)	3 (3.9)	12 (20.0)	0	30 (21.9)	3 (2.2)
Eczema	16 (20.8)	2 (2.6)	13 (21.7)	1 (1.7)	29 (21.2)	3 (2.2)
Epistaxis	19 (24.7)	0	9 (15.0)	0	28 (20.4)	0
Nausea	15 (19.5)	0	12 (20.0)	0	27 (19.7)	0
Alopecia	16 (20.8)	0	10 (16.7)	0	26 (19.0)	0
Weight decreased	16 (20.8)	0	9 (15.0)	0	25 (18.2)	0
Face oedema	11 (14.3)	0	12 (20.0)	0	23 (16.8)	0
Photosensitivity reaction	8 (10.4)	0	12 (20.0)	1 (1.7)	20 (14.6)	1 (0.7)
Erythema	12 (15.6)	0	7 (11.7)	1 (1.7)	19 (13.9)	1 (0.7)
Pyrexia	11 (14.3)	1 (1.3)	7 (11.7)	0	18 (13.1)	1 (0.7)
Rash	13 (16.9)	0	4 (6.7)	0	17 (12.4)	0
Rash erythematous	9 (11.7)	1 (1.3)	6 (10.0)	0	15 (10.9)	1 (0.7)
Stomatitis	6 (7.8)	0	9 (15.0)	0	15 (10.9)	0
Myalgia	11 (14.3)	0	4 (6.7)	0	15 (10.9)	0
Tumour haemorrhage	8 (10.4)	2 (2.6)	7 (11.7)	1 (1.7)	15 (10.9)	3 (2.2)
Diarrhoea	5 (6.5)	0	9 (15.0)	1 (1.7)	14 (10.2)	1 (0.7)

Abbreviations: LGG = low-grade glioma; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
MedDRA Version 23.1; Common Terminology Criteria for Adverse Events Version 5.0.
Data Cutoff Date: 10 May 2024.

5.4.3.1. Adverse drug reactions

The ADRs were identified from consideration of all the reported TEAEs in FIREFLY-1.

A sponsor assessment was performed taking into consideration:

• the frequency of reporting

• the extent to which the adverse event is consistent with the pharmacology of the drug

- the timing of the event relative to the time of drug exposure
- the existence of dechallenge and rechallenge experience
- the known safety profile of the class
- the events leading to drug discontinuation or dose modification
- the plausibility of physio-pathological mechanism.

Tabulated list of adverse reactions

Adverse reactions reported in patients treated with tovorafenib monotherapy in FIREFLY-1 (n=137) are listed in the table below. ADRs proposed for inclusion by the applicant in the SmPC Adverse reactions are listed below by MedDRA body system organ class and the following frequency convention: very common (≥ 1/10) and common (≥ 1/100 to < 1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 36: ADRs proposed for inclusion by the applicant in the SmPC

System organ class	MedDRA preferred term	Adverse reactions n (%); N=137
Infections and infestations	Upper respiratory tract infection	Very common 49 (35.8)
	Paronychia	Very common 41 (29.9)
	Viral infection	Very common 16 (11.7)
Blood and lymphatic system disorders	Anaemia[a]	Very common 84 (61.3)
Metabolism and nutrition disorders	Decreased appetite	Very common 41 (29.9)
	Hypokalaemia	Very common 39 (28.5)
	Hypoalbuminemia	Very Common 20 (14.6)
	Hyponatraemia	Very Common 19 (13.9)
Nervous systems disorders	Headache	Very Common 72 (52.6)
Eye disorders	Blepharitis	Common 10 (7.3)
	Dry eye	Common 7 (5.1)
Vascular disorders	Haemorrhage[b]	Very Common 55 (40.1)
	Intratumoural haemorrhage[c]	Very Common 19 (13.9)
	Flushing	Very Common 14 (10.2)
Gastrointestinal disorders	Vomiting	Very common 77 (56.2)

System organ class	MedDRA preferred term	Adverse reactions n (%); N=137
	Nausea	Very common 51 (37.2)
	Constipation	Very common 50 (36.5)
	Abdominal pain[d]	Very common 40 (29.2)
	Stomatitis[e]	Very common 39 (28.5)
	Diarrhoea[f]	Very common 36 (26.3)
Skin and subcutaneous tissue disorders	Rash[g]	Very common 114 (83.2)
	Hair colour changes	Very common 106 (77.4)
	Dry skin[h]	Very common 65 (47.4)
	Dermatitis acneiform[i]	Very common 52 (38.0)
	Pruritus	Very common 38 (27.7)
	Skin discolouration[j]	Very common 28 (20.4)
	Alopecia	Very common 28 (20.4)
	Photosensitivity reaction	Very common 20 (14.6)
Musculoskeletal and connective tissue disorders	Growth retardation[k]	Very common 61 (44.5)
	Pain in extremity	Very common 28 (20.4)
	Myalgia	Very common 22 (16.1)
	Arthralgia	Very common 19 (13.9)
General disorders	Fatigue	Very common 83 (60.6)
	Pyrexia	Very common 64 (46.7)
	Oedema[l]	Very common 46 (33.6)
Investigations	Blood phosphorus decreased[m]	Very common 76 (55.5)
	Blood creatine phosphokinase increased	Very common 85 (62.0)
	Blood lactate dehydrogenase increased	Very common 52 (38.0)

System organ class	MedDRA preferred term	Adverse reactions n (%); N=137
	Aspartate aminotransferase increased	Very common 52 (38.0)
	Alanine aminotransferase increased	Very common 34 (24.8)
	Blood bilirubin increased	Very common 20 (14.6)
	Lymphocyte count decreased	Very common 23 (16.8)
	Weight decreased	Very common 35 (25.5)
	White blood cell count decreased	Very common 16 (11.7)
	Eosinophilia	Common 11 (8.0)

a Includes term haemoglobin decreased
b Includes terms epistaxis, contusion, gingival bleeding, haematoma, petechiae, gastrointestinal haemorrhage, haematemesis, haematochezia, lower gastrointestinal haemorrhage, purpura, subdural haemorrhage, vaginal haemorrhage
c Includes terms tumour haemorrhage, intracranial tumour haemorrhage
d Includes term abdominal pain upper
e Includes terms aphthous ulcer, mouth ulceration, cheilitis, angular cheilitis, lip ulceration
f Includes term enterocolitis
g Includes terms rash maculo-papular, eczema, rash erythematous, rash papular, rash pustular, dermatitis, drug eruption, skin exfoliation, dermatitis bullous, rash follicular, rash macular, rash pruritic, erythema multiforme, rash vesicular
h Includes terms chapped lips, lip dry, xeroderma
i Includes term acne
j Includes terms skin depigmentation, skin hyperpigmentation, skin hypopigmentation, melanocytic nevus
k Includes term growth failure
l Includes terms face oedema, swelling face, periorbital oedema, eye swelling, oedema peripheral, peripheral swelling, lip oedema, vulval oedema
m Includes term hypophosphataemia

Description of selected adverse reactions

Intratumoural haemorrhage (ITH)

In FIREFLY-1, intratumoural haemorrhage (Including terms tumour haemorrhage and intracranial tumour haemorrhage) were observed in 13.9% patients, 3.6% patients reported grade ≥3 events, 0.7% patient reported a grade 5 event. Tovorafenib was permanently discontinued due to ITH events in 2.9% of patients. The mean time to onset since initiating treatment with tovorafenib was 239.2 days (median: 206.0 days; range 23.0-671.0 days) and the mean duration of the initial occurrence of ITH was 30.8 days (median: 19.5 days; range: 1.0 days to 88.0 days).

Other haemorrhage events

In FIREFLY-1, other haemorrhage events were observed in 40.1% of paediatric patients, with Grade ≥3 events occurring in 2.2%. The most frequent haemorrhagic event (epistaxis) was reported in 32.1% of patients and the majority were Grade 1. 1 patient had a Grade 3 event of epistaxis. The

mean time to onset since initiating treatment with tovorafenib was 124.5 days (median: 77.0 days; range 4.0 days- 617.0 days), and the mean duration of the initial occurrence of haemorrhage was 78.1 days (median: 9.0 days; range: 1.0 day - 428.0 days).

Growth retardation

Patients treated with tovorafenib for up to 24 months showed reductions from baseline in Z-scores for height compared to age and sex-matched normative data, although children with paediatric LGG may be expected to have altered growth rates compared to children without cancer. In FIREFLY-1, growth retardation was reported in 44.5% of patients 18 years of age or younger. Growth retardation resulted in dose interruption in 5.1% of patients and dose reduction in 2.2% of patients. Among those patients who experienced growth retardation who had hand radiographs taken to assess bone age, there was no evidence of premature closure of the epiphyseal growth plates or advancement of bone age. Growth retardation resulted in permanent discontinuation in 2.9% of patients. Patients followed after interruption of treatment with tovorafenib showed recovery of growth velocity and increase in Z-scores.

Liver related events

In FIREFLY-1, increased ALT was reported in 24.8% of patients taking tovorafenib. Increased AST occurred in 38% of patients taking tovorafenib. Grade ≥3 elevations in ALT and AST were observed in 5.8% and 2.9% of patients, respectively. Additionally, increased bilirubin was reported in 14.6% of patients. The mean time to onset of increased ALT was 215.3 days (range 1.0–672.0 days), increased AST was 123.4 days (range 12.0–813.0 days), and increased bilirubin was 79.6 days (range 13.0–645.0 days). Increased ALT leading to dose interruption occurred in 5.1% of patients and dose reduction in 1.5% of patients, and increased AST leading to dose interruption occurred in 2.9% of patients, and dose reduction in 0.7% of patients. Increased bilirubin leading to dose interruption occurred in 0.7% of patients, with no dose reduction required in any patients.

Blood creatinine phosphokinase increased

In FIREFLY1, 62% of patients reported events of blood creatine phosphokinase increased. 12.4% of patients reported grade ≥3 events. All events were non-serious. Of those who reported an increase in CPK, the majority (61.2%), reported an increase within the first 4 weeks of initiation of tovorafenib. Some patients had multiple episodes. Increased CPK led to a dose interruption in 3.6% of patients. The mean time to onset since initiating treatment with tovorafenib was 98.5 days (median: 29.0 days; range: 4 days to 701 days). The mean duration of the of the initial occurrence of the event was 238.4 days (median: 122.0 days; range: 8 days - 926 days).

Anaemia

In FIREFLY1, anaemia was reported in 61.3% of patients. 13.1% of patients reported anemia events grade ≥ 3. The majority of these patients (54.8%) reported an event of anaemia within 60 days of tovorafenib initiation. One patient experienced a serious event. No patients discontinued treatment due to anaemia; 2.2% of patients reported anaemia which required dose interruption or dose modification. The mean time to onset since initiating treatment with tovorafenib was 107.4 days (median: 57.0 days; range 8.0 days-737.0 days) The mean duration of the initial occurrence of the anaemia was 207.1 days (median 89.5 days; range 1.0 day - 826.0 days).

Skin toxicity, including photosensitivity

In FIREFLY-1, rash occurred in 83.2% of patients. Most events were mild, with Grade ≥3 events reported in 12.4% of patients. Rash resulted in dose interruption in 16.1% of patients and dose reduction in 8.8% of patients, and 1 (0.7 %) patient discontinued treatment due to rash pruritic. The mean time to onset of rash since initiating treatment with tovorafenib was 87.6 days (median:

14.5 days; range 1.0 day - 617.0 days), and the mean duration of the initial occurrence of rash was 103 days (median: 43 days; range: 1 days-777 days). Photosensitivity occurred in 14.6% of patients, including one Grade 3 event in a single patient (0.7%) and resulted in dose interruption in one patient (0.7%).

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Deaths

There were no treatment-related deaths. As of the data cutoff date of 10 May 2024, a total of eight unrelated deaths occurred across Arms 1, 2, and 3, including two deaths > 30 days after the last dose of study treatment.

• One 4-year-old patient in Arm 1 with a cerebellum tumor and leptomeningeal dissemination had a Grade 5 (fatal) TEAE of brain death. The patient had an SAE of Grade 4 neurological decompensation due to progressive disease on Day 33, which worsened to Grade 5 brain death on Day 35, 5 days after the last dose of tovorafenib.

• One 18-year-old patient in Arm 1 with a disseminated spinal and posterior fossa tumor first diagnosed at the age of 5 years had a Grade 5 (fatal) non-treatment emergent AE of hydrocephalus. The patient had a serious AE of Grade 4 hydrocephalus on Day 362, 55 days after the last dose of tovorafenib. After multiple shunt revisions and drain externalization, the family elected to withdraw care on Day 382.

• One 2-year-old patient in Arm 1 with a localized optic pathway tumor had a Grade 5 (fatal) TEAE of death (verbatim: unexplained death) on Day 737, 1 day after the last dose of tovorafenib. This patient with a history of adrenal insufficiency had been hospitalized previously with multiple sepsis and hypovolemic shock events and had an unremarkable immune work up. No stress dose steroids were administered on the night prior to the patient's death when parents reported abdominal cramping and pallor. The autopsy results found no cause of death, and the investigator attributed the event to the patient's multiple chronic medical problems.

• One 7-year-old patient in Arm 1 with a disseminated cerebral hemisphere tumor died due to PD on Day 1112, 782 days after the last dose of tovorafenib.

• One 14-year-old patient in Arm 2 with a mixed glial-neuronal tumor with leptomeningeal dissemination had a Grade 5 (fatal) TEAE of tumor hemorrhage. The patient had a serious TEAE of Grade 4 tumor hemorrhage 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.

• One 13-year-old patient in Arm 2 with localized mixed glial-neuronal tumor with brainstem components and history of worsening swallowing dysfunction and aspiration had a Grade 5 (fatal) TEAE of pneumonia on Day 612, 5 days after the last dose of tovorafenib.

Table 37: Serious Adverse Events Reported in ⩾2 Patients (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

MedDRA Preferred Term Number of Patients, n (%)	Arm 1 (LGG) N=77	Arm 2 (LGG) N=60	Arm 1 + Arm 2 N=137
Any serious TEAE	41 (53.2)	35 (58.3)	76 (55.5)
Pyrexia	7 (9.1)	8 (13.3)	15 (10.9)
Hydrocephalus	6 (7.8)	4 (6.7)	10 (7.3)
Growth retardation	7 (9.1)	2 (3.3)	9 (6.6)
Seizure	2 (2.6)	7 (11.7)	9 (6.6)
Vomiting	5 (6.5)	4 (6.7)	9 (6.6)
Tumour haemorrhage	3 (3.9)	4 (6.7)	7 (5.1)
Headache	5 (6.5)	1 (1.7)	6 (4.4)
Pneumonia	1 (1.3)	5 (8.3)	6 (4.4)
Viral infection	4 (5.2)	2 (3.3)	6 (4.4)
Appendicitis	3 (3.9)	2 (3.3)	5 (3.6)
Hyponatraemia	2 (2.6)	3 (5.0)	5 (3.6)
Sepsis	4 (5.2)	1 (1.7)	5 (3.6)
Device related infection	2 (2.6)	2 (3.3)	4 (2.9)
Hypernatraemia	1 (1.3)	3 (5.0)	4 (2.9)
Shunt infection	1 (1.3)	3 (5.0)	4 (2.9)
Cellulitis	0	3 (5.0)	3 (2.2)
Constipation	1 (1.3)	2 (3.3)	3 (2.2)
Decreased appetite	2 (2.6)	1 (1.7)	3 (2.2)
Erysipelas	2 (2.6)	1 (1.7)	3 (2.2)
Hypothermia	0	3 (5.0)	3 (2.2)
Otitis media	2 (2.6)	1 (1.7)	3 (2.2)
Rhinovirus infection	2 (2.6)	1 (1.7)	3 (2.2)
Shunt malfunction	2 (2.6)	1 (1.7)	3 (2.2)
Vascular device infection	2 (2.6)	1 (1.7)	3 (2.2)
Abdominal pain	1 (1.3)	1 (1.7)	2 (1.5)
Acute kidney injury	1 (1.3)	1 (1.7)	2 (1.5)
Adrenal insufficiency	0	2 (3.3)	2 (1.5)
Anxiety	1 (1.3)	1 (1.7)	2 (1.5)
Ascites	2 (2.6)	0	2 (1.5)
Dehydration	1 (1.3)	1 (1.7)	2 (1.5)
Device malfunction	0	2 (3.3)	2 (1.5)
Enterovirus infection	1 (1.3)	1 (1.7)	2 (1.5)
Hypoxia	1 (1.3)	1 (1.7)	2 (1.5)
Respiratory failure	0	2 (3.3)	2 (1.5)
Upper respiratory tract infection	0	2 (3.3)	2 (1.5)

MedDRA Preferred Term Number of Patients, n (%)	Arm 1 (LGG) N=77	Arm 2 (LGG) N=60	Arm 1 + Arm 2 N=137
Viral upper respiratory tract infection	2 (2.6)	0	2 (1.5)

Abbreviations: LGG = low-grade glioma; MedDRA = Medical Dictionary for Regulatory Activities TEAE = treatment-emergent adverse event.
MedDRA Version 23.1.
Data Cutoff Date: 10 May 2024.

Adverse Events of Special Interest

Rhabdomyolysis/Myopathy

As of the clinical cutoff date, no patients had events meeting rhabdomyolysis/myopathy (Narrow scope) criteria.

Secondary Primary Malignancy

As of the clinical cutoff date, no patients had events meeting "non-hematological malignant tumors" search criteria. No patients had any events of squamous cell carcinoma or keratoacanthomas.

Severe Anaemia

As of the clinical cutoff date, a total of 18 (13.1%) patients in Arms 1 and 2 have reported events of severe anaemia One (0.7%) patient had Grade 4 anaemia (serious, considered related to tovorafenib by investigator), which led to interruption of tovorafenib treatment and hospitalization for transfusion. This patient had iron studies and red cell indices suspicious for a mixed nutritional deficiency and was placed on iron therapy with subsequent stabilization of hemoglobin. Review by the Sponsor concluded that while chronic anemia is common with tovorafenib treatment, nutritional deficiencies were a major contributor to the severity of this acute event.

Two additional patients had dose interruption due to severe anaemia; no patients had dose reduction or tovorafenib discontinuation due to severe anaemia.

Fourteen (10.2%) patients required blood transfusions for anaemia. The majority of patients requiring transfusion had an acute event (e.g. haemolysis due to an antibiotic, gastrointestinal bleed due to *Clostridium difficile* infection, iatrogenic loss due to blood draws, post-operative bleeding, other intercurrent infection, etc.) or nutritional deficiencies exacerbating anaemia. No patients had adverse clinical sequelae as a result of the blood transfusions and in all cases of severe anaemia, the patient's haemoglobin resolved from Grade 3 following treatment with iron, transfusion, or no intervention.

Table 38: Adverse Events of Special Interest of Severe Anaemia (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

Category Preferred Term	Arm 1 + Arm 2 (N=137) n (%)			
	Grade ≥ 3	Grade 3	Grade 4	Grade 5
Severe anaemia	18 (13.1)	17 (12.4)	1 (0.7)	0
Anaemia	18 (13.1)	17 (12.4)	1 (0.7)	0

Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1; Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Ophthalmologic Events

Optic atrophy or impingement-associated visual changes were most often attributable to underlying tumor with only 1 patient with an adjudicated event of vision blurred (Grade 1, event resolved) that did not recur in a patient without an optic pathway tumor. There were no events of uveitis and no events involving the retina such as events of serious retinopathy or retinal vein occlusion. As of the clinical cutoff date, a total of 10 (7.3%) patients in Arms 1 and 2 have reported events that were positively adjudicated as AESIs of ophthalmologic events. All ophthalmologic events were Grade 1 or Grade 2, and none led to discontinuation of tovorafenib.

Table 39: Positively Adjudicated Adverse Events of Special Interest of Ophthalmologic Events (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

Category Preferred Term	Arm 1 + Arm 2 (N=137) n (%)			
	All Grades	Grade 3	Grade 4	Grade 5
Ophthalmologic events	10 (7.3)	0	0	0
Dyschromatopsia	4 (2.9)	0	0	0
Vision blurred	1 (0.7)	0	0	0
Corneal lesion	1 (0.7)	0	0	0
Corneal oedema	1 (0.7)	0	0	0
Glaucoma	1 (0.7)	0	0	0
Photopsia	1 (0.7)	0	0	0
Episcleritis	1 (0.7)	0	0	0
Intraocular pressure increased	1 (0.7)	0	0	0

Abbreviations: AESI = adverse event of special interest; TEAE = treatment-emergent adverse event.
Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1; Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
Note: Only events positively adjudicated as AESIs of ophthalmologic events are presented.
Note: One patient had TEAEs of dyschromatopsia and intraocular pressure increased reported.
Data Cutoff Date: 10 May 2024.

Ventricular Arrhythmias

As of the clinical cutoff date, a total of 3 (2.2%) patients in Arms 1 and 2 have reported events of ventricular arrhythmias, all of them asymptomatic premature ventricular contractions (PVCs).

One 8-year-old patient had an SAE of Grade 2 ventricular extrasystoles that began on Day 15. The patient had no symptoms and continued to have normal vital signs. Subsequent to the ECG finding, the patient was hospitalized for continuous cardiac monitoring, and the tovorafenib dose was 50% reduced. Following dose reduction, the patient continued to have a higher than baseline percent of PVC on Holter (asymptomatic) monitoring and review of the event by the institutional ethics board concluded that tovorafenib should be discontinued (date of last dose Day 22). The ventricular extrasystoles improved to Grade 1 and resolved on Day 46. The event was considered related to tovorafenib treatment by the investigator and the Sponsor. At the time of data cutoff, the patient remained on study in follow up.

One 5-year-old patient experienced a non-serious AE of Grade 1 ventricular arrhythmia (PVCs per ECG findings) on Day 438 considered not related to tovorafenib, 1 year and 2 months after starting tovorafenib (Listing 16.2.7.7). During a polysomnography, the patient was found to have mild

obstructive sleep apnea, elevated transcutaneous carbon dioxide, an abnormal electroencephalogram, and rare PVCs. The patient and mother denied any symptoms associated with the PVCs. On Holter monitor, the patient had rare, isolated PVCs and otherwise normal heart rates and rhythm for age. No clinically significant structural abnormalities and normal systolic function were observed on serial echocardiograms. No action was taken with tovorafenib, and no symptoms were reported. Repeat ECG performed on Day 587 showed normal sinus rhythm with no PVCs, and the event was considered resolved. The investigator considered the event likely associated with the patient's underlying comorbidities, including sleep apnea. The patient discontinued tovorafenib treatment on Day 722 due to progressive disease and at the time of data cutoff remained on study in follow up.

One 9-year-old patient with a medical history notable for a right heart thrombus prior to initiation of tovorafenib had a Grade 1 AE of ventricular arrhythmia (PVCs per ECG findings). During the Cycle 25 (Day 682) echocardiogram, irregular beats were observed by the provider. On the same day, the patient's potassium was 6.0 mmol/L (< 5.1), phosphorous 3.8 mg/dL (3.5 to 5.5), and magnesium 1.9 mg/dL (1.6 to 2.6). PVCs were observed on the rhythm strip, and the patient was referred to cardiology. A Holter monitor was placed that revealed 11% PVCs, and tovorafenib was held pending follow-up. The patient had no symptoms or changes in vital signs. During the dose interruption, the patient was withdrawn from study treatment at the request of the parents (i.e. not investigator decision), and the investigator considered the ventricular arrhythmia as related to tovorafenib. Follow-up ECG performed 36 days after the final dose of tovorafenib showed normal sinus rhythm, and a Holter monitor placed 82 days after the last dose of tovorafenib showed 6% PVCs. The patient had no evidence of impairment of systolic function on echocardiogram. Given the persistence of PVCs on Holter beyond the patient having exposure to study treatment, it is likely that this patient had baseline factors contributing to their PVCs. At the time of data cutoff, the patient remained on study in follow up.

No association was observed between tovorafenib exposure and ECG parameters including QTc, and there were no clinically meaningful changes in cardiac function.

Intra-tumoral hemorrhage (ITH)

As of the clinical cutoff date, 19 (13.2%) patients in Arms 1 and 2 have reported events that were positively adjudicated as AESIs of ITH. No patients had dose reduction, 5 (3.6%) patients had dose interruption, and 4 (2.9%) patients, including 3 patients with Grade 1 ITH, permanently discontinued tovorafenib treatment due to ITH events.

Fourteen (10.2%) patients had ITH events that were maximum CTCAE Grade 1 or 2. Onset of first ITH event ranged from Day 57 to Day 671. Thirteen of the 14 patients had their events considered by the investigator as related to tovorafenib.

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). Onset of first ITH event for these patients was Day 23 and Day 37, respectively; the events for both patients resolved.

Two (1.5%) patients had maximum CTCAE Grade 4 serious events. Onset of first ITH event for these patients was Day 206, and Day 402, respectively. Both patients had their events considered by the investigator as related to tovorafenib, and the events resolved. In addition, 1 (0.7%) patient in Arm 2 had a Grade 4 serious event on Day 226 that worsened to Grade 5 and was noted by the investigator as attributable to disease progression.

Of the 19 patients with positively adjudicated ITH events, 9 (6.6%) patients had cystic tumors; 6 of the 19 had an ITH event requiring surgical intervention for shunt placement or revision, 2 (1.5%) patients required only treatment with steroids, and 11 patients (8.0% of patients in Arm 1 and Arm 2)

had events that were asymptomatic and required no medical or surgical intervention. Among the 6 patients with symptomatic ITH requiring surgical intervention, 2 patients had ITH prior to initiation of tovorafenib, 3 had notably cystic tumors known to be prone to bleeding, and 4 had leptomeningeal or metastatic disease.

At the time of data cutoff, events for 3 of the 19 patients were reported as not resolved while most were resolved or resolved (including both Grade 2 serious events and the Grade 3 events). Overall, the observed rate of symptomatic ITH requiring medical or surgical intervention of 5.8% in these patients with heavily pre-treated relapsed refractory disease was found to be consistent with rates of haemorrhage reported in the literature for patients with newly diagnosed pilocytic astrocytoma.

Table 40: Positively Adjudicated Adverse Events of Special Interest of Intra-tumoural Hemorrhage (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

Category Preferred Term	Arm 1 + Arm 2 (N=137) n (%)			
	All Grades	Grade 3	Grade 4	Grade 5
Intra-tumoural haemorrhage	19 (13.9)	2 (1.5)	2 (1.5)	1 (0.7)
Tumour haemorrhage	17 (12.4)	2 (1.5)	2 (1.5)	1 (0.7)
Intracranial tumour haemorrhage	3 (2.2)	0	0	0

Abbreviations: AESI = adverse event of special interest; TEAE = treatment-emergent adverse event.
Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1; Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
Note: Only events positively adjudicated as AESIs of intra-tumoural haemorrhage are presented.
Note: One patient had TEAEs of tumour haemorrhage (Grade 3) and intracranial tumour haemorrhage (Grade 2) reported.

Decrease in Growth Velocity

As of the data cutoff date, 61 (44.5%) patients in Arms 1 and 2 have reported TEAEs of decrease in growth velocity. Three (2.2%) patients had dose reduction, 7 (5.1%) patients had dose interruption, and 4 (2.9%) patients permanently discontinued tovorafenib treatment due to decrease in growth velocity.

Decrease in growth velocity was reported in patients with baseline age from 1 through 14 years of age and in more males than females (36 vs. 25). Of the 61 patients with treatment-emergent decrease in growth velocity, 24 (39.3%) patients also had a neuromuscular comorbidity such as spastic hemiplegia that could affect linear growth. Thirty-five (57.4%) of the 61 patients had an underlying endocrinopathy including 20 patients with baseline precocious puberty being treated with a gonadotropin-releasing hormone (GnRH) analogue. Fifteen (24.6%) patients had neither a neuromuscular nor endocrine comorbidity at baseline. Eight (13.1%) patients had baseline heights either 2 standard deviations above or below average height for age and sex indicating they were significant outliers for growth prior to initiating tovorafenib.

Tumor location varied and generally reflected the overall treatment population. Of the 61 patients, 30 (49.2%) had optic pathway tumors, 14 (23.0%) had deep midline tumors, 6 (9.8%) had cerebral hemisphere tumors, 3 (4.9%) had leptomeningeal tumors, and 8 (13.1%) patients had tumors in other locations including suprasellar tumors (2 patients) and tumors of the brain stem, cerebellum, spine, optic/brainstem/thalamus, multiple brain nodules, and right thymus/brainstem (1 patient each).

Among the 35 patients with on-treatment bone age provided, 13 patients also had a baseline bone age provided. No patients with both baseline and on-treatment bone age showed an advancement from baseline in bone age relative to chronological age and 1 patient showed a delayed bone age relative to

normal bone age at baseline. Among the remaining patients with only on-treatment bone age, 2 patients had bone age read as advanced (1 with precocious puberty at baseline), 3 patients had bone age read as delayed or slightly delayed, and the remaining were read as normal bone age. There was no evidence of premature closure of growth plates, and there were no reports of osteopenia or abnormal fractures. In cases where endocrine laboratory evaluations were provided, including IGF-1 (insulin-like growth factor-1) and IGFBP-3 (insulin-like growth factor binding protein-3) to assess growth hormone, there was no association between growth velocity changes and treatment-emergent hypothalamic-pituitary axis function (4 patients had tumor-associated growth failure or growth hormone deficiency at baseline), and among patients with Tanner stage provided, there was no evidence of inappropriate pubertal advancement.

Twenty-one patients who remained on-study after discontinuing tovorafenib had height measures followed via the safety database for at least 90 days post last study treatment date. All 21 patients had increase in growth velocity during the off-treatment period relative to the on-treatment period. Seventeen of the 21 patients showed sufficient recovery in growth velocity to demonstrate partial catch-up growth (increase from end of treatment in height percentiles/z-scores). Among the 4 patients where growth velocity recovered to a lesser degree, 1 patient was a 6-year old female with scoliosis and baseline height > 3 standard deviations below normal, 1 was a 10-year-old male with hemiparesis and baseline height 2 standard deviations below normal, 2 were 10-year-old females: 1 with precocious puberty at baseline and treatment with triptorelin and the other with a hypothalamic tumor and no diagnosis of precocious puberty but was Tanner stage 4 at study entry. Decrease in growth velocity was considered by the investigator to be resolving or resolved in 17 of the 21 patients with sufficient off-treatment follow-up.

Table 41: Adverse Events of Special Interest of Decrease in Growth Velocity (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

Category Preferred Term	Arm 1 + Arm 2 (N=137) n (%)			
	All Grades	Grade 3	Grade 4	Grade 5
Decrease in growth velocity	61 (44.5)	45 (32.8)	1 (0.7)	0
Growth retardation	59 (43.1)	44 (32.1)	0	0
Growth failure	3 (2.2)	1 (0.7)	1 (0.7)	0

Abbreviation: TEAE = treatment-emergent adverse event.
Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1; Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
Note: One patient had TEAEs of growth failure (Grade 3) and growth retardation (Grade 2) reported (Listing 16.2.7.7).
Data Cutoff Date: 10 May 2024.

A majority of patient's heights remained within 1 to 2 StDs of their baseline height during the first 18 months of tovorafenib treatment. By Cycle 25 of treatment, the median change from baseline height z-score was –1.1, and among 44 patients who completed 24 months of treatment and had baseline heights within ± 2 StDs, 9 (20.5%) had absolute height z-scores ≥ 2 StDs below the mean, consistent with temporary growth failure. Post-treatment AGVs among patients in the off-treatment analysis set described below and in Table 43 support the reversibility of this growth effect, and on-treatment bone age assessments reported to the safety database suggest preservation of growth potential. Loss in percentiles and z-scores over time on treatment was slightly greater among patients 2 to < 6 years of age (Table 42).

Table 42: Growth Velocity by Patient Age Group During Tovorafenib Treatment (Safety Analysis Set; Arms 1 and 2)

Time of Tovorafenib Treatment	Median (minimum, maximum) Growth Velocity, cm/year				
	Patient Age at Start of Tovorafenib Treatment				
	6M to <2Y	2 to <6Y	6 to <12Y	12 to <16Y	16 to ≤25Y
Cycle 7 (~6 months)	8.6 (3.2, 9.4) (n=3)	0.9 (-4.8, 9.3) (n=25)	1.1 (-3.7, 9.7) (n=59)	0.4 (-2.2, 4.2) (n=23)	-0.2 (-4.7, 3.7) (n=11)
Cycle 13 (~12 months)	2.8 (-0.2, 6.1) (n=3)	2.6 (-3.8, 6.8) (n=25)	1.7 (-6.3, 6.7) (n=55)	0.0 (-4.0, 9.3) (n=20)	0.0 (-6.3, 2.6) (n=8)
Cycle 19 (~18 months)	6.3 (4.3, 8.3) (n=2)	2.2 (-4.0, 10.2) (n=24)	1.3 (-3.2, 11.3) (n=46)	0.2 (-9.3, 19.2) (n=16)	-0.3 (-4.3, 2.8) (n=6)
Cycle 25 (~24 months)	-- (n=0)	2.4 (-3.9, 6.5) (n=14)	2.2 (-7.8, 24.9) (n=25)	0.0 (-5.7, 1.9) (n=9)	-0.5 (-2.6, 1.5) (n=2)

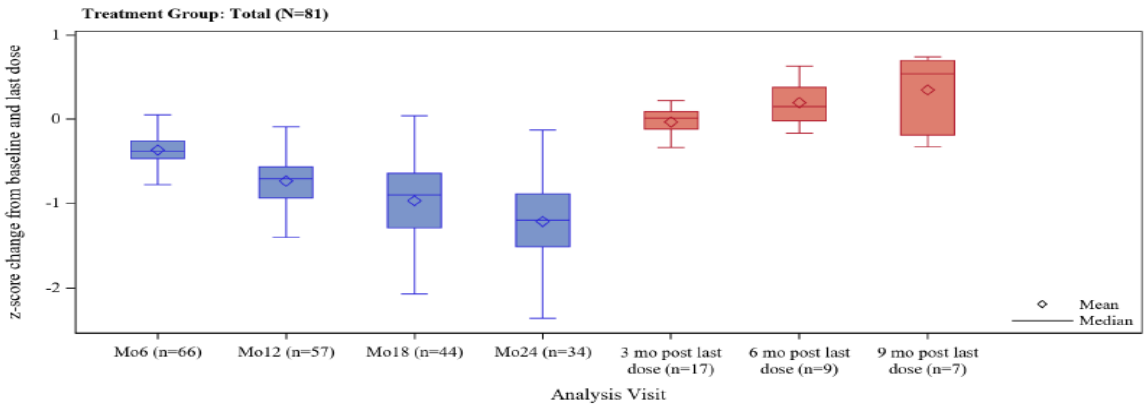
Abbreviations: M = months; Y = years.
Note: Negative values were the result of measurement error given the protocol did not mandate a stadiometer or other calibrated tool for height measurement.
Data Cutoff Date: 10 May 2024.

Table 43: Growth Velocity by Patient Age Group from Last Dose of Tovorafenib (Off-treatment/Drug Holiday Population Set; Arms 1 and 2)

Duration Post Last Dose	Median (minimum, maximum) Growth Velocity, cm/year				
	Patient Age at Start of Off-treatment Period[a]				
	6M to <2Y	2 to <6Y	6 to <12Y	12 to <16Y	16 to ≤25Y
3 months	-- (n=0)	8.5 (4.8, 12.2) (n=2)	-0.6 (-8.2, 11.2) (n=8)	3.2 (-0.4, 9.9) (n=6)	5.8 (-, -) (n=1)
6 months	-- (n=0)	12.8 (-, -) (n=1)	10.5 (6.3, 18.7) (n=4)	6.8 (0, 21.6) (n=4)	-- (n=0)
9 months	-- (n=0)	-- (n=0)	8.7 (1.4, 11.6) (n=5)	2.9 (0, 5.8) (n=2)	-- (n=0)

Abbreviations: M = months; Y = years.
Note: Negative values were the result of measurement error given the protocol did not mandate a stadiometer or other calibrated tool for height measurement.

Figure 7: Box Plot for Height Z-score Change from Baseline and from Last Dose of Tovorafenib (Off-treatment/Drug Holiday Population Set; Arms 1 and 2)



Abbreviation: Mo = month of primary tovorafenib treatment; mo = months.
Note: Mo6 to Mo24 are change from baseline during treatment.
Note: Three months to 9 months post last dose are change from the last height data collected before end of treatment.
Note: Excluding patients age 18 years or older at the last height collection before end of treatment.
Data Cutoff Date: 10 May 2024.

5.4.5. Discontinuation due to adverse events

Adverse Events Leading to Treatment Discontinuation

Table 44: Treatment-emergent Adverse Events Leading to Discontinuation of Study Treatment (Safety Analysis Set; FIREFLY-1 Arms 1 and 2)

MedDRA Preferred Term Number of Patients, n (%)	Arm 1 (LGG) N=77	Arm 2 (LGG) N=60	Arm 1 + Arm 2 N=137
Any TEAE leading to discontinuation of study treatment	8 (10.4)	7 (11.7)	15 (10.9)
Growth retardation	2 (2.6)	2 (3.3)	4 (2.9)
Tumour haemorrhage	3 (3.9)	1 (1.7)	4 (2.9)
Autoimmune haemolytic anaemia	1 (1.3)	0	1 (0.7)
Bone marrow failure	0	1 (1.7)	1 (0.7)
Haemolysis	0	1 (1.7)	1 (0.7)
Death	1 (1.3)	0	1 (0.7)
Fatigue	0	1 (1.7)	1 (0.7)
Ventricular extrasystoles	1 (1.3)	0	1 (0.7)
Shunt malfunction	1 (1.3)	0	1 (0.7)
Cerebrospinal fluid circulation disorder	0	1 (1.7)	1 (0.7)
Rash pruritic	0	1 (1.7)	1 (0.7)

Abbreviations: LGG = low-grade glioma; TEAE = treatment-emergent adverse event.
Medical Dictionary for Regulatory Activities Version 23.1.
Note: Adverse events leading to discontinuation of treatment based on both primary and other action taken.

Adverse Events Leading to Dose Reduction

Table 45: Treatment-emergent Adverse Events Leading to Dose Reduction (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

MedDRA Preferred Term Number of Patients, n (%)	Arm 1 (LGG) N=77	Arm 2 (LGG) N=60	Arm 1 + Arm 2 N=137
Any TEAE leading to dose reduction	25 (32.5)	19 (31.7)	44 (32.1)
Rash maculo-papular	5 (6.5)	2 (3.3)	7 (5.1)
Fatigue	2 (2.6)	4 (6.7)	6 (4.4)
Decreased appetite	3 (3.9)	1 (1.7)	4 (2.9)
Anaemia	1 (1.3)	2 (3.3)	3 (2.2)
Growth retardation	2 (2.6)	1 (1.7)	3 (2.2)
Dermatitis acneiform	1 (1.3)	1 (1.7)	2 (1.5)
Dermatitis bullous	1 (1.3)	1 (1.7)	2 (1.5)
Pruritus	2 (2.6)	0	2 (1.5)
Alanine aminotransferase increased	0	2 (3.3)	2 (1.5)
Weight decreased	2 (2.6)	0	2 (1.5)
Eczema	1 (1.3)	0	1 (0.7)
Erythema	1 (1.3)	0	1 (0.7)

MedDRA Preferred Term Number of Patients, n (%)	Arm 1 (LGG) N=77	Arm 2 (LGG) N=60	Arm 1 + Arm 2 N=137
Rash erythematous	1 (1.3)	0	1 (0.7)
Rash follicular	1 (1.3)	0	1 (0.7)
Face oedema	1 (1.3)	0	1 (0.7)
Hyponatraemia	1 (1.3)	0	1 (0.7)
Left ventricular hypertrophy	1 (1.3)	0	1 (0.7)
Pericardial effusion	1 (1.3)	0	1 (0.7)
Ventricular extrasystoles	1 (1.3)	0	1 (0.7)
Aspartate aminotransferase increased	0	1 (1.7)	1 (0.7)
Folliculitis	0	1 (1.7)	1 (0.7)
Impetigo	0	1 (1.7)	1 (0.7)
Localised infection	1 (1.3)	0	1 (0.7)
Otitis media	0	1 (1.7)	1 (0.7)
Paronychia	0	1 (1.7)	1 (0.7)
Skin infection	0	1 (1.7)	1 (0.7)
Headache	0	1 (1.7)	1 (0.7)
Lethargy	1 (1.3)	0	1 (0.7)
Seizure	0	1 (1.7)	1 (0.7)
Periorbital oedema	1 (1.3)	0	1 (0.7)
Abdominal pain upper	0	1 (1.7)	1 (0.7)
Diarrhoea	0	1 (1.7)	1 (0.7)
Depression	1 (1.3)	0	1 (0.7)

Abbreviations: LGG = low-grade glioma; Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
MedDRA Version 23.1.
Note: Adverse events leading to dose reduction based on both primary and other action taken.

Adverse Events Leading to Dose Interruption

Table 46: Treatment-emergent Adverse Events Leading to Dose Interruption Occurring in ≥ 2 Patients (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

	Arm 1 (LGG) N=77 n (%)	Arm 2 (LGG) N=60 n (%)	Arm 1 + Arm 2 N=137 n (%)
Any TEAE leading to dose interruption	51 (66.2)	39 (65.0)	90 (65.7)
Pyrexia	11 (14.3)	8 (13.3)	19 (13.9)
Rash maculo-papular	9 (11.7)	5 (8.3)	14 (10.2)
Vomiting	10 (13.0)	4 (6.7)	14 (10.2)
Fatigue	5 (6.5)	3 (5.0)	8 (5.8)
Hydrocephalus	6 (7.8)	2 (3.3)	8 (5.8)
Nausea	5 (6.5)	2 (3.3)	7 (5.1)
Alanine aminotransferase increased	4 (5.2)	3 (5.0)	7 (5.1)
Headache	7 (9.1)	0	7 (5.1)

	Arm 1 (LGG) N=77 n (%)	Arm 2 (LGG) N=60 n (%)	Arm 1 + Arm 2 N=137 n (%)
Growth retardation	4 (5.2)	2 (3.3)	6 (4.4)
COVID-19	3 (3.9)	2 (3.3)	5 (3.6)
Pneumonia	1 (1.3)	4 (6.7)	5 (3.6)
Blood creatine phosphokinase increased	4 (5.2)	1 (1.7)	5 (3.6)
Decreased appetite	3 (3.9)	2 (3.3)	5 (3.6)
Appendicitis	2 (2.6)	2 (3.3)	4 (2.9)
Otitis media	1 (1.3)	3 (5.0)	4 (2.9)
Sepsis	3 (3.9)	1 (1.7)	4 (2.9)
Shunt infection	1 (1.3)	3 (5.0)	4 (2.9)
Eczema	3 (3.9)	1 (1.7)	4 (2.9)
Aspartate aminotransferase increased	3 (3.9)	1 (1.7)	4 (2.9)
Tumour haemorrhage	2 (2.6)	2 (3.3)	4 (2.9)
Rhinovirus infection	2 (2.6)	1 (1.7)	3 (2.2)
Viral infection	2 (2.6)	1 (1.7)	3 (2.2)
Pruritus	2 (2.6)	1 (1.7)	3 (2.2)
Anaemia	1 (1.3)	2 (3.3)	3 (2.2)
Cellulitis	0	2 (3.3)	2 (1.5)
Device related infection	1 (1.3)	1 (1.7)	2 (1.5)
Enterovirus infection	1 (1.3)	1 (1.7)	2 (1.5)
Erysipelas	1 (1.3)	1 (1.7)	2 (1.5)
Respiratory syncytial virus infection	1 (1.3)	1 (1.7)	2 (1.5)
Upper respiratory tract infection	1 (1.3)	1 (1.7)	2 (1.5)
Viral upper respiratory tract infection	0	2 (3.3)	2 (1.5)
Dermatitis bullous	1 (1.3)	1 (1.7)	2 (1.5)
Rash erythematous	1 (1.3)	1 (1.7)	2 (1.5)
Face oedema	1 (1.3)	1 (1.7)	2 (1.5)
Hypothermia	0	2 (3.3)	2 (1.5)
Abdominal pain	1 (1.3)	1 (1.7)	2 (1.5)
Abdominal pain upper	0	2 (3.3)	2 (1.5)
Diarrhoea	1 (1.3)	1 (1.7)	2 (1.5)
Weight decreased	2 (2.6)	0	2 (1.5)
Seizure	0	2 (3.3)	2 (1.5)
Somnolence	2 (2.6)	0	2 (1.5)
Hypernatraemia	1 (1.3)	1 (1.7)	2 (1.5)
Hyponatraemia	2 (2.6)	0	2 (1.5)
Shunt malfunction	2 (2.6)	0	2 (1.5)
Acute kidney injury	1 (1.3)	1 (1.7)	2 (1.5)

	Arm 1 (LGG) N=77 n (%)	Arm 2 (LGG) N=60 n (%)	Arm 1 + Arm 2 N=137 n (%)
Adrenal insufficiency	0	2 (3.3)	2 (1.5)

Abbreviations: LGG = low-grade glioma; TEAE = treatment-emergent adverse event.
Medical Dictionary for Regulatory Activities Version 23.1.
Note: Adverse events leading to dose interruption based on both primary and other actions taken.
Data Cutoff Date: 10 May 2024.

5.4.6. Safety in special populations

Safety Analyses by Age: Pivotal Study FIREFLY-1

Most of the frequently reported TEAEs generally occurred with comparable frequency across age groups though the youngest age cohort (6 months to < 2 years) was not considered in this comparison due to the small group (N = 3). TEAEs more frequently reported among younger patients included vomiting (70.4%, 60.6%, 38.5%, and 33.3% among patients ages 2 to < 6 years, 6 to < 12 years, 12 to < 16 years, and 16 to ≤ 25 years, respectively), rash maculo papular (70.4%, 56.1%, 26.9%, and 26.7%, respectively), pyrexia (66.7%, 48.5%, 34.6% and 26.7%, respectively), decrease in growth velocity (PT: growth retardation) (63.0%, 50.0%, 26.9%, and 0%, respectively), upper respiratory tract infection (40.7%, 37.9%, 30.8%, and 20.0%, respectively), cough (48.1%, 25.8%, 15.4%, and 13.3%, respectively), rhinorrhoea (25.9%, 12.1%, 7.7%, and 6.7%, respectively), viral infection (22.2%, 10.6%, 7.7%, and 6.7%, respectively), and weight increased (18.5%, 9.1%, 7.7%, and 6.7%, respectively). Fatigue was more frequently reported among older patients (51.9%, 60.6%, 69.2%, and 73.3%, respectively), as were nausea (22.2%, 37.9%, 46.2%, and 46.7%, respectively), dermatitis acneiform (11.1%, 28.8%, 57.7%, and 60.0%, respectively), myalgia (7.4%, 15.2%, 23.1%, and 26.7%, respectively), and dizziness (7.4%, 12.1%, 19.2%, and 20.0%, respectively), which may be due to reporting by the patient rather than parent/caregiver.

There was a trend toward increasing frequency of patients with maximum Grade 3 events and Grade ≥ 3 events in the younger versus older age groups. The predominant Grade 3 or higher events that occurred in younger patients more frequently than patients 16 years or older were infections (mostly viral and shunt-related infections) and growth-related AEs.

Table 47: Adverse Drug Reactions (All grades) by Category and Preferred Term, by Age GroupAEs by age range

	Arm 1 + Arm 2				
Category Preferred Term	6 months to <2 years (N=3)	2 years to <6 years (N=27)	6 years to <12 years (N=66)	12 years to <16 years (N=26)	16 years to <=25 years (N=15)
Patients with any adverse drug reactions	3 (100)	27 (100)	66 (100)	26 (100)	15 (100)
Rash	3 (100)	26 (96.3)	55 (83.3)	19 (73.1)	11 (73.3)
Rash maculo-papular	2 (66.7)	19 (70.4)	37 (56.1)	7 (26.9)	4 (26.7)
Eczema	1 (33.3)	5 (18.5)	15 (22.7)	8 (30.8)	4 (26.7)
Rash	1 (33.3)	4 (14.8)	10 (15.2)	6 (23.1)	2 (13.3)
Rash pustular	1 (33.3)	0	8 (12.1)	1 (3.8)	0
Rash erythematous	0	5 (18.5)	4 (6.1)	3 (11.5)	3 (20.0)
Rash papular	0	2 (7.4)	6 (9.1)	2 (7.7)	0
Drug eruption	0	2 (7.4)	1 (1.5)	0	1 (6.7)
Skin exfoliation	0	1 (3.7)	2 (3.0)	1 (3.8)	0
Dermatitis	0	1 (3.7)	1 (1.5)	3 (11.5)	0
Dermatitis bullous	0	0	2 (3.0)	1 (3.8)	0
Rash macular	0	0	2 (3.0)	0	0
Rash pruritic	0	0	2 (3.0)	0	0

	Arm 1 + Arm 2				
Category Preferred Term	**6 months to <2 years (N=3)**	**2 years to <6 years (N=27)**	**6 years to <12 years (N=66)**	**12 years to <16 years (N=26)**	**16 years to <=25 years (N=15)**
Rash follicular	0	0	1 (1.5)	1 (3.8)	0
Rash vesicular	0	0	1 (1.5)	0	0
Erythema multiforme	0	0	0	0	1 (6.7)
Vomiting	3 (100)	19 (70.4)	40 (60.6)	10 (38.5)	5 (33.3)
Vomiting	3 (100)	19 (70.4)	40 (60.6)	10 (38.5)	5 (33.3)
Decreased growth velocity	2 (66.7)	17 (63.0)	35 (53.0)	7 (26.9)	0
Growth retardation	2 (66.7)	17 (63.0)	33 (50.0)	7 (26.9)	0
Growth failure	0	0	3 (4.5)	0	0
Diarrhoea	2 (66.7)	12 (44.4)	15 (22.7)	4 (15.4)	3 (20.0)
Diarrhoea	2 (66.7)	12 (44.4)	15 (22.7)	3 (11.5)	3 (20.0)
Enterocolitis	0	0	2 (3.0)	1 (3.8)	0
Upper respiratory tract infection	2 (66.7)	11 (40.7)	25 (37.9)	8 (30.8)	3 (20.0)
Upper respiratory tract infection	2 (66.7)	11 (40.7)	25 (37.9)	8 (30.8)	3 (20.0)
Hair colour changes	1 (33.3)	19 (70.4)	53 (80.3)	22 (84.6)	11 (73.3)
Hair colour changes	1 (33.3)	19 (70.4)	53 (80.3)	22 (84.6)	11 (73.3)
Anaemia	1 (33.3)	18 (66.7)	46 (69.7)	11 (42.3)	8 (53.3)
Anaemia	1 (33.3)	18 (66.7)	45 (68.2)	11 (42.3)	8 (53.3)
Haemoglobin decreased	0	0	3 (4.5)	0	0
Blood creatine phosphokinase increased	1 (33.3)	18 (66.7)	38 (57.6)	18 (69.2)	10 (66.7)
Blood creatine phosphokinase increased	1 (33.3)	18 (66.7)	38 (57.6)	18 (69.2)	10 (66.7)
Pyrexia	1 (33.3)	18 (66.7)	32 (48.5)	9 (34.6)	4 (26.7)
Pyrexia	1 (33.3)	18 (66.7)	32 (48.5)	9 (34.6)	4 (26.7)
Dry skin	1 (33.3)	14 (51.9)	34 (51.5)	9 (34.6)	7 (46.7)
Dry skin	1 (33.3)	11 (40.7)	30 (45.5)	8 (30.8)	6 (40.0)
Lip dry	0	2 (7.4)	5 (7.6)	3 (11.5)	1 (6.7)
Chapped lips	0	1 (3.7)	1 (1.5)	0	0
Xeroderma	0	0	3 (4.5)	0	0
Blood phosphate decreased	1 (33.3)	13 (48.1)	36 (54.5)	18 (69.2)	8 (53.3)
Hypophosphataemia	1 (33.3)	13 (48.1)	33 (50.0)	17 (65.4)	8 (53.3)
Blood phosphorus decreased	0	0	4 (6.1)	2 (7.7)	1 (6.7)
Constipation	1 (33.3)	11 (40.7)	21 (31.8)	11 (42.3)	6 (40.0)
Constipation	1 (33.3)	11 (40.7)	21 (31.8)	11 (42.3)	6 (40.0)
Oedema	1 (33.3)	9 (33.3)	27 (40.9)	5 (19.2)	4 (26.7)
Oedema	1 (33.3)	0	0	0	0
Face oedema	0	5 (18.5)	16 (24.2)	3 (11.5)	2 (13.3)
Oedema peripheral	0	2 (7.4)	1 (1.5)	0	1 (6.7)
Periorbital oedema	0	1 (3.7)	9 (13.6)	0	2 (13.3)
Swelling face	0	1 (3.7)	2 (3.0)	0	1 (6.7)
Eye swelling	0	1 (3.7)	2 (3.0)	0	0
Peripheral swelling	0	0	2 (3.0)	0	0
Lip oedema	0	0	0	1 (3.8)	0
Vulval oedema	0	0	0	1 (3.8)	0
Nausea	1 (33.3)	6 (22.2)	25 (37.9)	12 (46.2)	7 (46.7)
Nausea	1 (33.3)	6 (22.2)	25 (37.9)	12 (46.2)	7 (46.7)
Stomatitis	1 (33.3)	4 (14.8)	25 (37.9)	6 (23.1)	3 (20.0)
Mouth ulceration	1 (33.3)	0	1 (1.5)	0	0
Stomatitis	0	2 (7.4)	11 (16.7)	3 (11.5)	2 (13.3)
Cheilitis	0	2 (7.4)	9 (13.6)	1 (3.8)	0
Angular cheilitis	0	0	6 (9.1)	4 (15.4)	1 (6.7)

	Arm 1 + Arm 2				
Category Preferred Term	**6 months to <2 years (N=3)**	**2 years to <6 years (N=27)**	**6 years to <12 years (N=66)**	**12 years to <16 years (N=26)**	**16 years to <=25 years (N=15)**
Aphthous ulcer	0	0	2 (3.0)	0	0
Lip ulceration	0	0	2 (3.0)	0	0
Dermatitis acneiform	1 (33.3)	4 (14.8)	21 (31.8)	15 (57.7)	11 (73.3)
Dermatitis acneiform	1 (33.3)	3 (11.1)	19 (28.8)	15 (57.7)	9 (60.0)
Acne	0	2 (7.4)	2 (3.0)	0	2 (13.3)
Weight decreased	1 (33.3)	3 (11.1)	20 (30.3)	7 (26.9)	4 (26.7)
Weight decreased	1 (33.3)	3 (11.1)	20 (30.3)	7 (26.9)	4 (26.7)
Photosensitivity reaction	1 (33.3)	2 (7.4)	11 (16.7)	4 (15.4)	2 (13.3)
Photosensitivity reaction	1 (33.3)	2 (7.4)	11 (16.7)	4 (15.4)	2 (13.3)
Fatigue	0	14 (51.9)	40 (60.6)	18 (69.2)	11 (73.3)
Fatigue	0	14 (51.9)	40 (60.6)	18 (69.2)	11 (73.3)
Headache	0	12 (44.4)	38 (57.6)	15 (57.7)	7 (46.7)
Headache	0	12 (44.4)	38 (57.6)	15 (57.7)	7 (46.7)
Blood lactate dehydrogenase increased	0	11 (40.7)	27 (40.9)	7 (26.9)	7 (46.7)
Blood lactate dehydrogenase increased	0	11 (40.7)	27 (40.9)	7 (26.9)	7 (46.7)
Aspartate aminotransferase increased	0	10 (37.0)	29 (43.9)	6 (23.1)	7 (46.7)
Aspartate aminotransferase increased	0	10 (37.0)	29 (43.9)	6 (23.1)	7 (46.7)
Haemorrhage	0	10 (37.0)	26 (39.4)	13 (50.0)	6 (40.0)
Epistaxis	0	7 (25.9)	20 (30.3)	13 (50.0)	4 (26.7)
Haematoma	0	1 (3.7)	2 (3.0)	0	0
Gastrointestinal haemorrhage	0	1 (3.7)	0	0	0
Haematemesis	0	1 (3.7)	0	0	0
Lower gastrointestinal haemorrhage	0	1 (3.7)	0	0	0
Gingival bleeding	0	0	8 (12.1)	1 (3.8)	0
Contusion	0	0	6 (9.1)	2 (7.7)	2 (13.3)
Petechiae	0	0	1 (1.5)	0	1 (6.7)
Subdural haemorrhage	0	0	1 (1.5)	0	0
Vaginal haemorrhage	0	0	1 (1.5)	0	0
Haematochezia	0	0	0	1 (3.8)	0
Purpura	0	0	0	0	1 (6.7)
Decreased appetite	0	7 (25.9)	26 (39.4)	6 (23.1)	2 (13.3)
Decreased appetite	0	7 (25.9)	26 (39.4)	6 (23.1)	2 (13.3)
Pruritus	0	7 (25.9)	17 (25.8)	9 (34.6)	5 (33.3)
Pruritus	0	7 (25.9)	17 (25.8)	9 (34.6)	5 (33.3)
Alopecia	0	7 (25.9)	9 (13.6)	8 (30.8)	4 (26.7)
Alopecia	0	7 (25.9)	9 (13.6)	8 (30.8)	4 (26.7)
Hypoalbuminemia	0	7 (25.9)	9 (13.6)	2 (7.7)	2 (13.3)
Hypoalbuminaemia	0	7 (25.9)	9 (13.6)	2 (7.7)	2 (13.3)
Paronychia	0	6 (22.2)	22 (33.3)	9 (34.6)	4 (26.7)
Paronychia	0	6 (22.2)	22 (33.3)	9 (34.6)	4 (26.7)
Alanine aminotransferase increased	0	6 (22.2)	21 (31.8)	3 (11.5)	4 (26.7)
Alanine aminotransferase increased	0	6 (22.2)	21 (31.8)	3 (11.5)	4 (26.7)
Lymphocyte count decreased	0	6 (22.2)	12 (18.2)	2 (7.7)	3 (20.0)
Lymphocyte count decreased	0	6 (22.2)	12 (18.2)	2 (7.7)	3 (20.0)
Pain in extremity	0	4 (14.8)	17 (25.8)	5 (19.2)	2 (13.3)
Pain in extremity	0	4 (14.8)	17 (25.8)	5 (19.2)	2 (13.3)

	Arm 1 + Arm 2				
Category Preferred Term	**6 months to <2 years (N=3)**	**2 years to <6 years (N=27)**	**6 years to <12 years (N=66)**	**12 years to <16 years (N=26)**	**16 years to <=25 years (N=15)**
White blood cell count decreased	0	4 (14.8)	9 (13.6)	0	3 (20.0)
White blood cell count decreased	0	4 (14.8)	9 (13.6)	0	3 (20.0)
Arthralgia	0	4 (14.8)	8 (12.1)	5 (19.2)	2 (13.3)
Arthralgia	0	4 (14.8)	8 (12.1)	5 (19.2)	2 (13.3)
Skin discoloration	0	3 (11.1)	17 (25.8)	6 (23.1)	2 (13.3)
Skin hyperpigmentation	0	2 (7.4)	4 (6.1)	0	0
Melanocytic naevus	0	1 (3.7)	4 (6.1)	3 (11.5)	2 (13.3)
Skin discolouration	0	0	7 (10.6)	0	0
Skin hypopigmentation	0	0	4 (6.1)	3 (11.5)	0
Skin depigmentation	0	0	1 (1.5)	0	0
Flushing	0	3 (11.1)	8 (12.1)	0	3 (20.0)
Flushing	0	3 (11.1)	8 (12.1)	0	3 (20.0)
Blood bilirubin increased	0	2 (7.4)	12 (18.2)	3 (11.5)	3 (20.0)
Blood bilirubin increased	0	2 (7.4)	12 (18.2)	3 (11.5)	3 (20.0)
Myalgia	0	2 (7.4)	10 (15.2)	6 (23.1)	4 (26.7)
Myalgia	0	2 (7.4)	10 (15.2)	6 (23.1)	4 (26.7)
Intratumoural haemorrhage	0	1 (3.7)	9 (13.6)	6 (23.1)	3 (20.0)
Intracranial tumour haemorrhage	0	1 (3.7)	2 (3.0)	0	0
Tumour haemorrhage	0	0	8 (12.1)	6 (23.1)	3 (20.0)
Abdominal pain	0	0	12 (18.2)	2 (7.7)	1 (6.7)
Abdominal pain upper	0	0	12 (18.2)	2 (7.7)	1 (6.7)
Eosinophil count increased	0	0	6 (9.1)	3 (11.5)	2 (13.3)
Eosinophilia	0	0	6 (9.1)	3 (11.5)	2 (13.3)
Hypokalemia	0	0	3 (4.5)	1 (3.8)	0
Blood potassium decreased	0	0	3 (4.5)	1 (3.8)	0

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
MedDRA version 23.1.
Data cut off: 10 May 2024 (FIREFLY-1 2-Year CSR Data cut off)

Table 48: AE by special population

	Patients with Mild Hepatic Impairment[a] N=14	**Patients with Mild Renal Impairment[a] N=10**	**Overall (excluding Patients with Renal and Hepatic Impairment) N=114**
Patients with TEAEs			
Patients with Any TEAEs	14 (100)	10 (100)	114 (100)
Number of patients with dose interruption	8 (57.1)	6 (60.0)	76 (66.7)
Number of patients with dose reduction	5 (35.7)	0	39 (34.2)
Number of patients with drug withdrawn	3 (21.4)	3 (30.0)	9 (7.9)
Patients with Any Grade 3 and Above TEAEs	11 (78.6)	10 (100.0)	92 (80.7)
Patients with Any Serious TEAEs	8 (57.1)	6 (60.0)	62 (54.4)
Patients with ADRs[b]			
Skin and subcutaneous tissue disorders	14 (100)	10 (100)	109 (95.6)
Skin toxicity	12 (85.7)	8 (80.0)	95 (83.3)
Dry skin	4 (28.6)	7 (70.0)	55 (48.2)
Hair colour changes	12 (85.7)	6 (60.0)	89 (78.1)
Dermatitis acneiform	8 (57.1)	4 (40.0)	41 (36.0)
Pruritus	6 (42.9)	2 (20.0)	30 (26.3)
Alopecia	4 (28.6)	2 (20.0)	23 (20.2)
Skin discoloration	3 (21.4)	1 (10.0)	24 (21.1)
Photosensitivity reaction	2 (14.3)	1 (10.0)	17 (14.9)

	Patients with Mild Hepatic Impairment[a] N=14	Patients with Mild Renal Impairment[a] N=10	Overall (excluding Patients with Renal and Hepatic Impairment) N=114
General disorders and administration site conditions	9 (64.3)	10 (100)	97 (85.1)
Fatigue	5 (35.7)	6 (60.0)	73 (64.0)
Pyrexia	7 (50.0)	4 (40.0)	54 (47.4)
Oedema	2 (14.3)	4 (40.0)	40 (35.1)
Infections and infestations	6 (42.9)	9 (90.0)	68 (59.6)
Upper respiratory tract infection	4 (28.6)	5 (50.0)	41 (36.0)
Paronychia	2 (14.3)	5 (50.0)	34 (29.8)
Viral infection	0	2 (20.0)	14 (12.3)
Gastrointestinal disorders	14 (100)	8 (80.0)	96 (84.2)
Vomiting	7 (50.0)	5 (50.0)	66 (57.9)
Diarrhoea	4 (28.6)	5 (50.0)	28 (24.6)
Nausea	7 (50.0)	3 (30.0)	42 (36.8)
Constipation	3 (21.4)	3 (30.0)	44 (38.6)
Stomatitis	4 (28.6)	2 (20.0)	33 (28.9)
Abdominal pain	5 (35.7)	1 (10.0)	34 (29.8)
Investigations	12 (85.7)	8 (80.0)	104 (91.2)
Blood phosphorus decreased	4 (28.6)	7 (70.0)	66 (57.9)
Blood creatine phosphokinase increased	9 (64.3)	6 (60.0)	71 (62.3)
Blood lactate dehydrogenase increased	5 (35.7)	4 (40.0)	43 (37.7)
Aspartate aminotransferase increased	4 (28.6)	4 (40.0)	45 (39.5)
Alanine aminotransferase increased	1 (7.1)	4 (40.0)	29 (25.4)
Weight decreased	4 (28.6)	2 (20.0)	30 (26.3)
Blood bilirubin increased	3 (21.4)	2 (20.0)	16 (14.0)
Eosinophilia	0	2 (20.0)	9 (7.9)
White blood cell count decreased	1 (7.1)	1 (10.0)	14 (12.3)
Lymphocyte count decreased	0	1 (10.0)	22 (19.3)
Vascular disorders	8 (57.1)	7 (70.0)	57 (50.0)
Haemorrhage	5 (35.7)	4 (40.0)	47 (41.2)
Intratumoral haemorrhage	3 (21.4)	2 (20.0)	14 (12.3)
Flushing	1 (7.1)	2 (20.0)	11 (9.6)
Blood and lymphatic system disorders	10 (71.4)	6 (60.0)	69 (60.5)
Anaemia	10 (71.4)	6 (60.0)	69 (60.5)
Metabolism and nutrition disorders	7 (50.0)	6 (60.0)	71 (62.3)
Hypokalaemia	2 (14.3)	4 (40.0)	33 (28.9)
Decreased appetite	3 (21.4)	3 (30.0)	36 (31.6)
Hypoalbuminaemia	3 (21.4)	1 (10.0)	17 (14.9)
Hyponatraemia	1 (7.1)	1 (10.0)	17 (14.9)
Nervous system disorders	11 (78.6)	4 (40.0)	58 (50.9)
Headache	11 (78.6)	4 (40.0)	58 (50.9)
Musculoskeletal and connective tissue disorders	7 (50.0)	4 (40.0)	82 (71.9)
Arthralgia	2 (14.3)	3 (30.0)	14 (12.3)
Growth retardation	3 (21.4)	2 (20.0)	56 (49.1)
Pain in extremity	3 (21.4)	2 (20.0)	23 (20.2)
Myalgia	2 (14.3)	1 (10.0)	19 (16.7)

5.4.7. Immunological events

NA.

5.4.8. Safety related to drug-drug interactions and other interactions

Please refer to the overall discussion on clinical pharmacology in section 4.3.

5.4.9. Vital signs and laboratory findings

Hematology

Table 49: Shift Summary of Selected Hematology Results by Maximum CTCAE Grade (Safety Analysis Set; Arms 1 and 2)

Laboratory Test	Baseline Grade	Arm 1 + Arm 2 (Low-grade Glioma)				
		Maximum Postbaseline Grade,[a] n (%)				
		0	1	2	3	4
Hemoglobin (low)	0	6 (4.4)	32 (23.4)	56 (40.9)	16 (11.7)	0
	1	0	4 (2.9)	18 (13.1)	5 (3.6)	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	4	0	0	0	0	0
Leukocytes (low)	0	74 (54.0)	40 (29.2)	5 (3.6)	2 (1.5)	0
	1	2 (1.5)	14 (10.2)	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	4	0	0	0	0	0
Lymphocytes (high)	0	85 (62.0)	0	43 (31.4)	0	0
	1	0	0	0	0	0
	2	0	0	5 (3.6)	0	0
	3	0	0	0	0	0
	4	0	0	0	0	0
Lymphocytes (low)	0	59 (43.1)	55 (40.1)	10 (7.3)	2 (1.5)	2 (1.5)
	1	0	3 (2.2)	1 (0.7)	0	0
	2	0	0	0	0	0
	3	0	1 (0.7)	0	0	0
	4	0	0	0	0	0
Neutrophils (low)	0	93 (67.9)	5 (3.6)	22 (16.1)	6 (4.4)	0
	1	1 (0.7)	1 (0.7)	2 (1.5)	2 (1.5)	0
	2	2 (1.5)	0	2 (1.5)	1 (0.7)	0
	3	0	0	0	0	0
	4	0	0	0	0	0
Platelets (low)	0	102 (74.5)	26 (19.0)	2 (1.5)	1 (0.7)	0
	1	1 (0.7)	5 (3.6)	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	4	0	0	0	0	0

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.
[a] Includes all on-treatment assessments (after the first dose administration of study treatment and up to and including 30 days following discontinuation of treatment).
Baseline is defined as the last available assessments prior to start of tovorafenib on Cycle 1 Day 1.
For each laboratory parameter, patients are included only once based on the maximum post-baseline severity.
CTCAE Version 5.0.
Data Cutoff Date: 10 May 2024.

Chemistry

Table 50: Chemistry Abnormalities Reported as Adverse Events in ≥ 2 Patients (Safety Analysis Set; Arms 1 and 2)

	Arm 1 + Arm 2 (N=137), n (%)			
	All TEAEs		Related to Study Treatment	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood creatine phosphokinase increased	85 (62.0)	17 (12.4)	82 (59.9)	16 (11.7)
Hypophosphataemia	72 (52.6)	1 (0.7)	57 (41.6)	1 (0.7)
Blood lactate dehydrogenase increased	52 (38.0)	0	47 (34.3)	0
Aspartate aminotransferase increased	52 (38.0)	4 (2.9)	45 (32.8)	4 (2.9)
Hypokalaemia	39 (28.5)	6 (4.4)	21 (15.3)	3 (2.2)
Alanine aminotransferase increased	34 (24.8)	8 (5.8)	25 (18.2)	7 (5.1)
Hypocalcaemia	24 (17.5)	2 (1.5)	14 (10.2)	1 (0.7)
Blood bilirubin increased	20 (14.6)	1 (0.7)	17 (12.4)	1 (0.7)
Hypoalbuminaemia	20 (14.6)	1 (0.7)	13 (9.5)	0
Hyponatraemia	19 (13.9)	3 (2.2)	5 (3.6)	1 (0.7)
Hypernatraemia	17 (12.4)	4 (2.9)	6 (4.4)	0
Hyperglycaemia	12 (8.8)	0	1 (0.7)	0
Hypoglycaemia	10 (7.3)	1 (0.7)	3 (2.2)	0
Blood phosphorus decreased	7 (5.1)	1 (0.7)	5 (3.6)	1 (0.7)
Hypomagnesaemia	6 (4.4)	0	2 (1.5)	0
Blood bicarbonate decreased	5 (3.6)	0	1 (0.7)	0
Blood cholesterol increased	5 (3.6)	0	2 (1.5)	0
Hyperkalaemia	5 (3.6)	0	1 (0.7)	0
Blood potassium decreased	4 (2.9)	0	0	0
Hypermagnesaemia	4 (2.9)	0	1 (0.7)	0
Blood creatinine increased	3 (2.2)	0	2 (1.5)	0
Gamma-glutamyltransferase increased	3 (2.2)	1 (0.7)	1 (0.7)	1 (0.7)
Blood alkaline phosphatase decreased	2 (1.5)	0	0	0
Blood chloride increased	2 (1.5)	0	1 (0.7)	0
Blood glucose increased	2 (1.5)	0	0	0
Blood magnesium decreased	2 (1.5)	0	1 (0.7)	0
Blood sodium increased	2 (1.5)	0	0	0
Blood urea increased	2 (1.5)	0	0	0
Hyperphosphataemia	2 (1.5)	0	0	0

Abbreviation: TEAE = treatment-emergent adverse event.
Medical Dictionary for Regulatory Activities Version 23.1; Common Terminology Criteria for Adverse Events Version 5.0 except phosphate, where phosphate (low) is graded based on Version 4.03.
Data Cutoff Date: 10 May 2024.

Thyroid Function

Among the 137 patients in Arms 1 and 2, 16 (11.7%) patients had abnormal thyroid test results reported as TEAEs, including 4 patients with blood thyroid-stimulating hormone (TSH) increased; 3 patients with blood TSH decreased; 2 patients each with thyroxine increased, hypothyroidism, and hyperthyroidism; and 1 patient each with thyroid function test abnormal, tri-iodothyronine decreased, tri-iodothyronine free increased, and hyperparathyroidism.

All these patients, except for 1 patient with Grade 2 blood TSH decreased and 1 patient with Grade 2 hypothyroidism, had events with a maximum severity of Grade 1. All thyroid function test AEs occurred in patients with a baseline history of thyroid dysfunction, occurred concurrent with development of other tumor-related endocrinopathies, or were isolated events and recovered with no change in study treatment or medical intervention. The patient who developed hyperparathyroidism had a history of pontine myelinolysis at baseline.

Hepatic Safety

Table 51: Elevations from Baseline in Aminotransferase and Total Bilirubin (FIREFLY-1 Safety Analysis Set; Arms 1 and 2)

	Arm 1 (LGG) N=77 n (%)	Arm 2 (LGG) N=60 n (%)	Arm 1 + Arm 2 N=137 n (%)
Total bilirubin > 2× ULN concurrent with ALT or AST > 3× ULN and ALP < 2× ULN with no confounding factor	0	0	0
AST or ALT elevation	9 (11.7)	6 (10.0)	15 (10.9)
> 3 × ULN to ≤ 5 × ULN	8 (10.4)	5 (8.3)	13 (9.5)
> 5 × ULN to ≤ 10 × ULN	5 (6.5)	4 (6.7)	9 (6.6)
> 10 × ULN	1 (1.3)	0	1 (0.7)
AST elevation	8 (10.4)	2 (3.3)	10 (7.3)
> 3 × ULN to ≤.5 × ULN	6 (7.8)	2 (3.3)	8 (5.8)
> 5 × ULN to ≤.10 × ULN	3 (3.9)	0	3 (2.2)
> 10 × ULN	0	0	0
ALT elevation	6 (7.8)	6 (10.0)	12 (8.8)
> 3 × ULN to ≤.5 × ULN	5 (6.5)	4 (6.7)	9 (6.6)
> 5 × ULN to ≤.10 × ULN	3 (3.9)	4 (6.7)	7 (5.1)
> 10 × ULN	1 (1.3)	0	1 (0.7)
Total bilirubin elevation			
> 2 × ULN	4 (5.2)	3 (5.0)	7 (5.1)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LGG = low-grade glioma; ULN = upper limit of normal.
If baseline was abnormally high, elevation was defined as magnitude increase from baseline.

Cardiac Safety

Table 52: Absolute Change in Left Ventricular Ejection Fraction/Fractional Shortening During Treatment (Safety Analysis Set; Arms 1 and 2)

	Arm 1 (LGG) N=77 n (%)	Arm 2 (LGG) N=60 n (%)	Arm 1 + Arm 2 N=137 n (%)
LVEF			
Patients with both baseline value and at least 1 post-baseline LVEF assessment	75	59	134
≥ 10 percentage point decrease from baseline and absolute value < 50%	0	0	0
≥ 15 percentage point decrease from baseline and absolute value ≥ 50%	4 (5.3)	1 (1.7)	5 (3.7)
FS			
Patients with both baseline value and at least 1 post-baseline FS assessment	74	55	129
≥ 10 percentage point decrease from baseline and absolute value < 29%	2 (2.7)	3 (5.5)	5 (3.9)
≥ 15 percentage point decrease from baseline and absolute value ≥ 29%	2 (2.7)	1 (1.8)	3 (2.3)

Abbreviations: LGG = low-grade glioma; LVEF = left ventricular ejection fraction; FS=fractional shortening.
Baseline is defined as the last available assessment prior to start of tovorafenib on Cycle 1 Day 1. Percentage is based on patients with both baseline and at least one post-baseline assessment.
Data Cutoff Date: 10 May 2024.

Three of the 5 patients with FS ≥ 10 percentage point decrease from baseline and absolute value < 29% had cardiac AEs reported while on treatment.

One patient reported an AE of cardiac failure (verbatim: heart failure [cardiac imaging abnormalities] mild reduction of FS after temporary stop of study treatment) due to an FS of 27% (baseline 38%) on echocardiogram. LVEF was not recorded. Study treatment had been held for approximately 1 month prior to the event of cardiac failure due to an event of anaemia and was restarted as planned on the day of the echocardiogram. The event was reported as verbatim "*Heart failure (cardiac imaging abnormalities) mild reduction of FS after temporary stop of study treatment,*" and no AEs indicating symptomatic heart failure were reported. Repeat echocardiogram in 7 days showed FS of 35%, and the event was considered resolved and not related to tovorafenib.

The second patient had an asymptomatic pericardial effusion identified on the Cycle 2 echocardiogram. At the time, both FS and LVEF were consistent with baseline. On the subsequent echocardiogram (Cycle 4), the pericardial effusion was resolved, and FS was noted to be 23% (baseline 38%). LVEF was not recorded. The patient remained asymptomatic, no clinical intervention was required, and no change was made to study treatment. Repeat echocardiogram at Cycle 7 was within normal limits and all subsequent results were normal. As of data cutoff the patient remained on treatment at Cycle 22.

The third patient had a brainstem tumor and reported history of swallowing dysfunction and aspiration suspected to be contributory in frequent pulmonary infections. On Day 278 (Cycle 10) following recovery from an AE of pulmonary hypertension felt to be secondary to the patient's multiple pulmonary infections, the patient had a routine echocardiogram with FS 27% and LVEF 53% prompting the reporting of the AE verbatim term as decreased cardiac function. Routine echocardiograms for Cycles 13, 16, and 22 showed FS 28%, 34%, and 34%, respectively, and the AE was considered resolved. The patient continued on treatment and passed away due to pneumonia, likely from an aspiration event and unrelated to cardiac function, on Day 612.

The other 2 patients had isolated reductions in FS that returned to baseline on subsequent echocardiograms and were not associated with any reported cardiac AEs.

5.4.10. Post marketing experience

Tovorafenib is approved and marketed in the US as Ojemda™ since 23 April 2024 for the treatment of patients 6 months of age and older with relapsed or refractory paediatric low-grade glioma harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. Based on the information provided, no significant new safety data were identified that would change the safety profile of Ojemda 380 mg/m^2, in the approved population. No change in the current approved product label in the US was warranted.

5.4.11. In vitro biomarker test for patient selection for safety

Not applicable.

5.4.12. Overall discussion and conclusions on clinical safety

5.4.12.1. Discussion

5.4.12.1.1. Overall assessment of available safety data

The safety evaluation for tovorafenib in both paediatric and adult patients is primarily based on data from a single arm phase 2 study, DAY101 001/PNOC026 (FIREFLY-1). Safety data from the completed phase 1 study (Study C28001) that evaluated tovorafenib in adult patients with advanced solid tumours are considered supportive of the overall safety profile. In addition, 3 other completed studies (QSC205140, DAY 101/103 and C28002) provide further supportive safety data. The collection of safety data and the conduct of safety assessments appear appropriate in the pivotal study. Nevertheless, the absence of a control arm in the main study, limits the ability to establish causality for adverse events, thereby complicating the identification and characterization of tovorafenib-related adverse drug reactions.

Patient exposure

The safety data in the target population are derived mainly from 137 patients with paediatric low-grade glioma (LGG) treated in both arms 1 and 2 of the uncontrolled study FIREFLY-1. 77 patients were enrolled and treated in Arm 1 and 60 patients were enrolled in Arm 2 of the main study.

As of the data cutoff date (10 May 2024) of FIREFLY-1 study, the median duration of treatment with tovorafenib was 21.0 months (range: 0.72 to 32.1 months), with a median of 23 treatment cycles (range: 1 to 35 cycles). At the time of the DCO, 108 (78.8%) patients had ≥ 12 months of primary treatment, and 91 (66.4%) patients had ≥ 18 months of primary treatment. The safety database comprising at least 108 patients treated for one year is considered acceptable in the context of a CMA.

The median age at baseline was 9.0 years (range: 1.0 to 24.0 years). Safety data in paediatric patients aged 6 months to 2 years remain limited (based on only three patients). This information has been reflected in section 4.2 of the SmPC, stating that paediatric clinical experience with tovorafenib is limited, particularly in the specific range 6 months to 2 years and that the safety and efficacy of tovorafenib in children below 6 months of age have not been established. More than half of patients (52.6%) had ≥ 3 prior lines of systemic therapy. Most patients (89.8%) had a Karnofsky or Lansky performance score from 80 to 100 at baseline. Eleven patients discontinued treatment voluntarily, either at their own request or that of their parent or guardian and reasons for these discontinuations were provided.

Adverse events

Among the 137 patients in arms 1 and 2, all patients experienced at least one TEAE, 81.8% experienced at least one Grade ≥ 3 TEAE, and 55.5% had at least one SAE reported. There were 15 patients (10.9%) who experienced TEAEs leading to treatment discontinuation, including 13 (9.5%) with treatment-related events. A total of 44 (32.1%) and 90 (65.7%) of patients experienced TEAEs leading to dose reduction or dose interruption, respectively.

The RP2D was revised during the main study. In version 2 of the protocol, the RP2D was reduced from 530 mg/m² to 420 mg/m². Furthermore, the dose recommended in the SmPC does not correspond to the dose used in the study, having been further reduced to 380 mg/m². A review of safety data by the actual starting dose (≤ 350 mg/m^2 (15 patients), 350-420 mg/m^2 (63 patients), and > 420 mg/m^2 (59 patients)) in the main study showed less frequently Grade ≥ 3 AEs, serious TEAEs, TEAEs leading to dose reduction and TEAEs leading to treatment discontinuation at starting doses of 350 - 420 mg/m^2 compared with > 420 mg/m^2. However, further clarification was requested regarding the impact of the newly proposed dose on the safety profile. The applicant provided an analysis of AESI specifically growth retardation and tumour haemorrhage for patients who received 350 - 420 mg/m^2 compared to the higher dose. The analysis of the AESI of growth retardation showed that the number of patients experiencing these events was lower in the 350 - ≤420 mg/m^2 dose group compared with >420 mg/m^2 dose group, and the number of events of ITH (tumour haemorrhage) was comparable in the 350 - ≤420 mg/m^2 dose group and in >420 mg/m^2 dose group.

Some concerns related to the robustness of ADR identification, particularly in the absence of a control group remain. For instance, all events of amenorrhoea reported in the study (5%, corresponding to 7 patients) were considered related to treatment but this event was not considered an ADR. Given that non-clinical findings did not rule out the extrapolation of ovarian dysfunction in human, and based on the clinical cases, the Applicant will investigate amenorrhoea and other menstrual irregularities as part of the agreed SOB.

Adverse events of special interest (AESI) and of clinical importance

AESIs in the FIREFLY-1 study were selected based on review of early tovorafenib nonclinical and clinical data as well as consideration of similar drug class effects which is supported.

No cases of *rhabdomyolysis/myopathy* or *secondary primary malignancy* were reported in the pivotal study. However, these events should continue to be monitored in the ongoing clinical trials and post-marketing setting.

Haemoglobin decreased was reported as an ADR under the SOC Investigations. However, anaemia occurred frequently (60% of patients), with 13% of cases classified as severe, and 14 patients (10.2%) requiring blood transfusions. Accordingly, anaemia—being a clinically significant condition—was added as an ADR under the SOC Blood and lymphatic system disorders.

Tovorafenib has been associated with both events haemorrhage and cases of severe anaemia. While the applicant acknowledges that tovorafenib has been associated with both ITH and cases of severe anaemia, no plausible association between anaemia and haemorrhagic events can be confirmed to date. In addition, an impact on the clinical management of patients due to co-occurrence of these events cannot be established or concluded.

As of the clinical cutoff date (10 May 2024), a total of 63 (46%) patients have reported *ophthalmologic events*. The majority of these events were associated with patient medical history or underlying disease. A total of 10 (7.3%) patients have been identified with events that were positively adjudicated as AESIs of ophthalmologic events. All were Grade 1 or Grade 2, and none led to discontinuation of tovorafenib. There were no events of uveitis and no events involving the retina such as events of

serious retinopathy or retinal vein occlusion. No clinically significant impact was observed from the reported ophthalmologic events. Table 4 of section 4.8 of the SmPC includes all adverse reactions from clinical trials, for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility. In addition, all ophthalmologic events will be further monitored through collection of detailed data from the FIREFLY-2 study (AESI) and in upcoming PSUR.

With respect to *ventricular arrhythmias/ extrasystoles*, three cases were reported in paediatric patients aged 5, 8, and 9 years. Of these, two events were assessed by the investigator as related to treatment. One case of ventricular extrasystoles led to permanent treatment discontinuation shortly after beginning the treatment and the second case of ventricular arrhythmia led to the withdrawal of treatment, without any clinical sequelae. The applicant proposes to continue to monitor through collection of detailed data from the FIREFLY-2 study (AESIs), and where patients will be monitored with ECG reads throughout the duration of the study treatment at regular intervals. These events will continue to be monitored through routine pharmacovigilance and in future periodic safety reports.

One case of cardiac dysfunction was considered related to treatment by the investigator, and a discussion of this case has been provided. On sponsor review, the long latency to onset and rapid resolution with no change in study drug dose indicated this is not likely to be a study drug related finding.

As of the clinical cut-off (10 May 2024), 13.2% (19) of patients experienced *intratumoral haemorrhage (ITH)* events that were positively adjudicated as AESI. Most cases were mild: 14 patients (10.2%) had grade 1–2 ITH, with 10 being asymptomatic and found via routine MRI and 13 considered treatment related. Three patients with Grade 1 ITH and one with a higher grade discontinued tovorafenib permanently, while 5 had dose interruptions; no dose reductions occurred. Two patients (1.5%) had Grade 3 serious events (one treatment-related), and two others (1.5%) had Grade 4 treatment-related events, all of which resolved. One patient (0.7%) experienced a Grade 4 event that progressed to Grade 5 (death), attributed to disease progression rather than treatment.

Review of severe cases of tumor hemorrhage confirmed that most patients had disease characteristics such as history of prior tumor hemorrhage, leptomeningeal or disseminated disease, aggressive tumor histology, or cystic tumor architecture that likely put them at higher risk for tumor hemorrhage events. However, although some patients with events of hemorrhage had potential confounding factors (e.g., concurrent use of anticoagulants, prior history of intra-tumoral hemorrhage, simultaneous disease progression), a possible attribution to tovorafenib cannot be ruled out and the risk of intra-tumoral bleeding must not be underestimated. Thus, a separate warning regarding intra tumoral hemorrhage was added to section 4.4 of the SmPC, informing that events of intratumoural haemorrhage have been reported, that patients are caregivers should be advised on this risk during treatment with tovorafenib, that the risk may increase with concomitant use of anticoagulants and antiplatelet therapy, that monitoring for signs and symptoms of haemorrhage and evaluation as clinically indicated should be done routinely and that the occurrence of hamorrhagic events should be managed with dose interreption or treatment discontinuation. A detailed description of therisk is also reflected in section 4.8 to the SmPC, to present more information (i.e. incidence, onset, contribution of anticoagulants and outcome of an intra tumoral hemorrhage) to the treating physicians. In addition, the Applicant upgraded intra-tumoral hemorrhage to an identified risk in the safety concerns of the RMP.

The presented data suggest that factors associated with reported on-treatment ITH align with many factors known or suspected to increase risk of ITH in the natural history of CNS tumors. The risk is multifactorial, and influenced by chronology of disease, tumor biology and anatomy, prior type, number and duration of treatments, prior and on treatment procedures and medical history including concomitant medications.

Intratumoral haemorrhage is an identified ADR, with Grade 3 events reported and, in some cases, requiring treatment discontinuation.

Growth retardation is a recognized adverse event associated with tovorafenib which is an adverse event of concern in paediatric patients. A decrease in growth velocity was observed in 43% of patients, with 32% experiencing events classified as Grade ≥3 (≥ 50% reductions in growth velocity over the period of a year), and 1 (0.7%) patient had CTCAE Grade 4 (of note this level of severity grading does not exist in the CTCAE criteria). SAEs related to growth retardation occurred in 6.6% of patients. The incidence of serious and treatment-related decreases in growth velocity was higher among younger patients: 14.8% in those aged 2 to <6 years, 6.1% in those aged 6 to <12 years, 3.8% in those aged 12 to <16 years, and 0% in those aged 16 to ≤25 years. The risk appeared to be age-dependent, with the highest incidence observed in children aged 2 to <6 years. Treatment was discontinued in four patients due to this AE. All four patients demonstrated an increase in growth velocity after discontinuation of therapy, and investigators assessed the events as resolved or resolving. Additionally, three patients required dose reductions, and six patients experienced treatment interruptions due to growth retardation.

Across the population, the data show that growth suppression associated with treatment is reversible with demonstrated growth recovery as evidenced by increased AGV post treatment when compared to the on-treatment period.

A warning is reflected in section 4.4 of the SmPC stating that reductions in growth velocity have been reported very commonly in patients treated with tovorafenib, that patients and caregivers should be advised on this risk during treatment with tovorafenib, and that monitoring for growth and development should be done prior to initiation, routinely during and following discontinuation of treatment with tovorafenib.

With regards to dose reduction, treatment interruption, or discontinuation in the event of persistent or severe growth retardation, the applicant stated that no further specific dose modification guidance in section 4.2 of the SmPC for this risk is warranted at this time based on the available data and recognition of broad diversity of data based on patient individuality. The justification is acknowledged. The Applicant proposes to continue to monitor patients in the FIREFLY-1 and FIREFLY-2 trials to further characterize the risk of growth retardation, which is agreed.

Among patients who had both baseline and post-baseline assessments of *left ventricular ejection fraction* (LVEF), no patients met the predefined criteria for clinically significant cardiac dysfunction – defined as a ≥10 percentage point drop from baseline LVEF combined with an absolute LVEF <50% (the lower limit of normal). While five patients experienced a ≥15 percentage point decrease from their baseline LVEF, their absolute LVEF values remained ≥50%, indicating that the decreases, though notable, did not cross the threshold considered clinically abnormal.

Five patients showed clinically significant decreases in FS, falling below a conservative threshold of 29%. Three additional patients had large relative decreases (≥15%) but maintained absolute FS values within normal range. While some patients experienced reductions in cardiac function (as measured by FS), only a small number crossed the conservative lower limit, suggesting a potential but limited cardiac safety concern that may warrant monitoring. Three of the 5 patients with FS ≥ 10 percentage point decrease from baseline and absolute value < 29% had cardiac AEs reported while on treatment but these were resolved without modifications of treatment. Two events of QT prolongation occurred in the study, and one event was considered related to treatment. Upon request, these cases were discussed. Overall, the two clinical cases are considered relatively reassuring, as only modest variations in the QTc interval were observed. A concentration–QTc (C–QTc) analysis was submitted in the initial submission (report-dot1-pmx-day101ecg-2852). This report provides sufficient evidence that tovorafenib does not cause clinically meaningful QT interval prolongation at the clinical dose (420

mg/m2 [not to exceed 600 mg] QW). The predicted 2-sided 90% CI upper bounds for ΔQTc were below the 10 msec threshold for regulatory concern. Therefore, the present analysis is recommended as a substitute for a TQT study.

The population from Study C28001 comprised patients with advanced cancers that had been heavily pretreated, and many patients had comorbidities and risk factors for cardiovascular disease at baseline. The frequency and severity of cardiac AEs was found to be consistent with the age and comorbidities of the treatment population. Events were tachycardia and atrial fibrillation (7 patients each; 4.7%); cardiac failure, angina pectoris, palpitations, and atrial flutter (2 patients each; 1.3%); and bradycardia and supraventricular extrasystoles (1 patient each; 0.7%). In the SOC of Investigations, 1 patient each experienced an event of ejection fraction decreased (Grade 3) and electrocardiogram QT prolonged (Grade 2).

Ojemda has been associated with *hepatotoxicity* in clinical studies with increased ALT, AST and bilirubin. There was no case that met criteria for Hy's law. A warning has been reflected in section 4.4 of the SmPC about liver related events, specifically indicating that ALT, AST and bilirubin increases have been reported very commonly in patients treated with tovorafenib. A monitoreing requirement of liver function tests for these parameters should be done prior to initiation, one month after initiation and routinely during treatment with tovorafenib. Treatment should be withheld and resumed at the same or reduced dose upon improvement or permanently discontinued based on the severity. A description of the risk in section 4.8 to the SmPC, to present more information (i.e. incidence, onset, and outcome) regarding this issue has been added. A management guidance for liver related events has been added in Table 3 in section 4.2 of the SmPC.

Twenty (14.6%) patients in Arms 1 and 2 have reported events of *photosensitivity*, and 23 (16.8%) events of *rash*. Based on the data presented, a warning about skin toxicity including photosensitivity and rash has been added to section 4.4 of the SmPC, stating that rash, including photosensitivity events, have been reported very commonly in patients treated with tovorafenib. Patients should be monitored for new or worsening skin reactions. Dermatologic consultation and initiation of supportive care should be considered as clinically indicated. Patients and caregivers should be advised of the risk of rash and photosensitivity during treatment with tovorafenib. The use of precautionary measures against ultraviolet exposure such as use of sunscreen (SPF ≥50), sunglasses, and/or protective clothing during treatment with tovorafenib is recommended. Treatment should be withheld, resumed at reduced dose, or permanently discontinued based on severity of adverse reaction. Further information describing the risk has also been added in section 4.8 of the SmPC, under the ADR table.

Special populations

Age

Clinical experience is very limited in the youngest intended population. Indeed, only 3 patients ≤ 2 years received tovorafenib, and youngest patient included in the FIREFLY-1 study was 11 months. This limitation has been reflected in section 4.2 of the SmPC.

Of note, there was a trend toward increasing frequency of patients with maximum Grade 3 events and Grade ≥ 3 events in the younger versus older age groups. In addition, as already mentioned above, decrease in growth velocity (PT: growth retardation) was more commonly reported as serious and treatment related among younger patients.

Sex

No significant differences were observed between male and female patients. A similar trend was observed in terms of type of events and their corresponding frequencies.

Laboratory findings

The most frequently occurring laboratory abnormalities (≥20%) worsening from baseline were decreased haemoglobin, decreased phosphate, increased aspartate aminotransferase (AST), increased creatine phosphokinase (CPK), increased lactate dehydrogenase (LDH), decreased potassium, increase alanine aminotransferase (ALT), and decreased lymphocytes. It is agreed with the Applicant that most laboratory abnormalities were Grade 1 or 2 in severity, had no clinical manifestations, and did not require clinical intervention or modification in administration of tovorafenib. However, there are some aspects that are further discussed here below.

Treatment-related AEs of Hypokalaemia (15.3%), hypocalcaemia (10.2%) and hypoalbuminaemia (9.5%) were highly reported in both arms of the study. Hypokalaemia (frequency 'very common', 28.5%) and hypoalbuminemia (frequency 'very common' 14.6%) are included as ADRs under the SOC Metabolism and nutrition disorders in section 4.8 of the SmPC.

The Applicant does not consider hypocalcaemia an ADR and has provided a justification, which is agreed.

White blood cell count decreased events are known to be associated with MAPK inhibitors and such events considered related to treatment were highly reported in both arms (9%). These events were considered as ADRs and are included in section 4.8 of the SmPC.

In addition, hyponatremia occurred in 14% of patients in Firefly-1 study. The applicant reported that Grade 3 or higher sodium abnormalities were observed primarily in patients with pre-existing conditions such as diabetes insipidus, SIADH, and diencephalic syndrome, and that these events resolved without requiring treatment discontinuation. However, in the supportive study C28001, hyponatremia was the most frequently reported chemistry-related adverse event, affecting 10 patients. Given this context and the consistency of findings across studies, the applicant agreed to add hyponatraemia as an ADR in section 4.8 of the SmPC.

Elevated creatine phosphokinase (CPK) levels were reported in more than 50%. However, no cases of Grade 3 or greater CPK elevation were associated with clinical symptoms, and there were no associated AEs of renal impairment, serious muscle injury, or rhabdomyolysis. However, increased CPK documented in FIREFLY-1 is a clinically important laboratory abnormality for which prescriber must be sensitized as it may prompt a treating physician to evaluate for possible muscle damage in a patient being treated with tovorafenib. Elevated CPK has been included as an ADR in section 4.8 of the SmPC and a description of the risk has been added under the ADR table (i.e. incidence, onset, and outcome of increased CPK level) to treating physicians.

Although pre-clinical studies identified the thyroid as a potential target organ, no association was established between tovorafenib treatment and abnormalities in thyroid function in human studies. There were no apparent clinically significant trends in any mean thyroid function test results over time. All thyroid function test AEs were Grade 1 or 2 and occurred in patients with a baseline history of thyroid dysfunction, concurrent with development of other tumor-related endocrinopathies, or were isolated and resolved with no change in study treatment or medical intervention.

Long-term safety

The long-term safety of tovorafenib is currently limited and additional data are required to further characterise its safety profile. Accoridngly, long-term safety, including the monitoring of growth and potential effects on fertility, is considered missing information in the safety concerns of the RMP. Further long-term safety data will be generated from the ongoing phase III study FIREFLY-2, agreed as an SOB under the conditional marketing authorisation. This study will follow patients for up to 5 years. While this duration is expected to provide information on growth, development and other

medium-term safety outcomes, it may not fully capture very late-onset adverse events like secondary malignancies or long-term effects on fertility. However, the feasibility of substantially longer follow-up in this paediatric population is recognised. Residual uncertainty therefore remains regarding very long-term safety outcomes.

Ojemda (tovorafenib) was approved in the US in April 2024. Post-marketing data reported so far is consistent with the overall established safety profile from clinical studies. One case of rhabdomyolysis was reported in the post-marketing setting. However, given that rhabdomyolysis occurred in the setting of severe cellulitis with increased spasticity and very high fever and resolved with the resolution of cellulitis, rhabdomyolysis was considered more likely attributed to the acute infection and not tovorafenib. Rhabdomyolysis will be continued to be monitored as an AESI through routine pharmacovigilance activities.

5.4.12.1.2. Adverse drug reactions in the SmPC

See Table 36.

5.4.12.2. Conclusions on clinical safety

The overall safety profile of tovorafenib is considered manageable and consistent with its mechanism of action. Some of the most common adverse events include rash, fatigue, gastrointestinal disturbances, pyrexia, transaminases increased and haemorrhage which are generally manageable through dose modifications or supportive care.

However, the safety evaluation is significantly hampered by the limited sample size, the heterogenous study population of the pivotal trial, the absence of a controlled comparator arm and long-term safety data. In this regard, the available safety data are not considered comprehensive to support a full marketing authorisation given the limitations and uncertainties in the safety database. Additional safety data will be generated as part of the agreed SOB under the CMA (FIREFLY-2). A secondary objective of this study is to compare the safety and tolerability of tovorafenib with SoC chemotherapy, with particular emphasis on growth retardation, intratumoral haemorrhage, embryo-foetal toxicity, potential effects on fertility and long-term safety outcomes.

Uncertainties remain regarding the safety profile in the youngest indicated age group, as only 3 patients aged ≤ 2 years were treated with tovorafenib in the pivotal study and the youngest patient included was 11 months of age. This limitation is reflected in section 4.2 of the SmPC.

Overall, the identified safety findings appear manageable in clinical practice. However, given the limited size of the safety database and the potential for prolonged treatment in a paediatric population, further data collection and long-term follow-up are warranted to further characterise the safety profile.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 53: Summary of safety concerns in the proposed RMP

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

6.1.2. Discussion on proposed safety specification

Regarding the safety data provided so far, the list of safety concerns in the RMP provided by the applicant is endorsed.

Following the assessment of safety data related to intra-tumoral haemorrhage, data are sufficiently relevant to consider a reasonable possibility for a causal association with tovorafenib and intra-tumoral haemorrhages. As a result, according to GVP Module V, Risk management systems (Rev 2) (EMA/838713/2011 Rev 2), this risk is proposed to be considered as an important identified risk rather than as an important potential risk in the RMP. Relevant sections of the RMP were updated accordingly.

Decreased fertility risk

Non-clinical data from rodents has indicated that tovorafenib may be associated with decreased fertility.

Considering the small and young patient population, the risk of decreased fertility is not considered to have major public health impact but may have serious impact on the individual patient. The risk of decreased fertility is considered important for inclusion in the safety specification and will be further characterized in the agreed SOB.

Long-term safety

There is currently no available data on long term safety of tovorafenib. In RMP SVII.2.3 the Applicant has indicated that the umbrella term long term safety covers the risks rhabdomyolysis, ventricular tachyarrythmias, haemorrhagic central nervous system vascular conditions, non-haematological malignant tumors and Eye disorders.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

The applicant considers routine pharmacovigilance activities sufficient to monitor the safety profile of tovorafenib. No specific adverse reaction follow-up questionaires are proposed.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

It is agreed that routine pharmacovigilance is considered sufficient to further characterize the risks associated with the use of tovorafenib.

6.2.2.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are required. This is agreed.

6.3. Plans for post-authorisation efficacy studies

Table 54: Planned and on-going 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				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
DAY101-002: LOGGIC/FIREFLY-2: 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. Ongoing	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 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.	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
			Final clinical study report	30 April 2032

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.

Risk minimisation measures

6.3.1. Proposed risk minimisation measures

Table 55: Planned routine risk minimisation measures

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 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.

6.3.2. Discussion on the risk minimisation measures

6.3.2.1. Routine risk minimisation measures

It is agreed that routine risk minimisation measures are considered sufficient to mitigate risks of the product and no additional risk minimization measures are warranted at this stage.

6.3.2.2. Additional risk minimisation measures

No additional risk minimisation measures are proposed. Patients treated with tovorafenib will be under specialised paediatric care and it is considered that routine risk minimisation measures are sufficient to minimise the risks associated with the treatment of tovorafenib.

6.4. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.5. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.0 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

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

7.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The applicant requested alignment of the PSUR cycle with the IBD of 23 April 2024. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

Refer to the SmPC.

8.1.1. SmPC section 4.1 justification

The approved indication is aligned and supported by the results of the pivotal clinical study submitted in the dossier, FIREFLY-1, which evaluated tovorafenib in patients aged 6 months to 25 years, inclusive, with relapsed or progressive low-grade glioma harboring an activating BRAF alteration, including BRAF V600 mutations and BRAF fusions. The target population in the agreed indication is fully aligned with the population studied in the pivotal trial, including disease characteristics. No additional restrictions with respect to age, weight, or other patient-related factors were considered necessary.

8.2. Labelling

8.2.1. Package leaflet (PL)

Refer to the PL.

8.3. User consultation

8.3.1.1. Conclusion from the checklist for the review of user consultation

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

8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ojemda (tovorafenib) is included in the additional monitoring list as it is approved under a conditional marketing authorisation and it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

The agreed indication is:

"Ojemda is indicated as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies (for biomarkers-based patient selection, see section 4.2)."

The proposed recommended dose is 380 mg/m^2 orally once weekly (QW) (with a maximum recommended dose of 600 mg once weekly) according to body surface area.

9.1.2. Available therapies and unmet medical need

Patients with pLGG harboring BRAF fusions or other RAF alterations other than BRAF V600E mutations do not currently have any authorised targeted systemic treatment options in the EU. Management of these patients typically consists of surgery, if feasible, and chemotherapy. In clinical practice, targeted therapy including MAPK inhibitors such as BRAF or MEK inhibitors, may be used off-label. There is no authorised targeted therapy specifically indicated for this molecular subgroup.

The combination of dabrafenib plus trametinib is authorised in the EU for the treatment of paediatric patients aged 1 year and older with LGG with a BRAF V600E mutation who require systemic therapy. Although the indication is line-independent, the pivotal study supporting this approval was conducted in the first-line setting, and use of the combination is expected primarily in that context. Patients with BRAF V600E-mutated pLGG who experience disease progression following treatment with dabrafenib and trametinib represent a population with limited subsequent targeted treatment options.

Given the chronic and potentially recurrent nature of the disease, additional therapeutic options aimed at maintaining long-term disease control while preserving quality of life and reducing the risk of treatment-related and disease-related morbidity remain clinically relevant in this patient population.

9.2. Main clinical studies

The pivotal study for the current application is FIREFLY-1, an ongoing phase 2, multicenter, multi-arm, uncontrolled, open-label study evaluating tovorafenib in patients 6 months to 25 years of age, inclusive, with relapsed or refractory paediatric low-grade glioma (pLGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation (Arm 1 and Arm 2 [expansion cohort of Arm 1]) and advanced solid tumours (Arm 3).

The key efficacy data supporting this conditional marketing authorisation are based on the patients enrolled in Arm 1 (N= 77). Data from patients enrolled in Arm 1 (N= 77) and Arm 2 (N=60) are included in the safety analysis set (N=137).

FIREFLY-1 evaluated tovorafenib administered orally at 420 mg/m^2 once weekly (with a maximum of 600 mg weekly) to be taken with or without food. The recommended dose of tovorabenib in this procedure is now 380 mg/m^2 once per week (not to exceed 600 mg). The evidence supporting the 380 mg/m^2 dose is derived from post-hoc analysis of the FIREFLY-1 study and the modelling, taking into account the totality of clinical and preclinical data.

In FIREFLY-1, patients had to complete at least 26 cycles corresponding to a 2-year treatment period before opting to enter a drug holiday discontinuation period or to continue on tovorafenib treatment.

The pre-specified primary objective of Arm 1 of the FIREFLY 1 study was to evaluate the ORR as determined by an IRC as determined by RANO-HGG criteria. Analysis of the response using RAPNO-LGG criteria was evaluated as secondary endpoint.

9.3. Favourable effects

As of the data cutoff date (10 May 2024):

- The independent radiologic review (IRC)-assessed ORR (CR, PR, or minor response [MR]) based on RAPNO-LGG criteria was 52.6% (95% CI: 40.8, 64.2). No patients had a CR, 29 (38.2%) patients had a PR and 11 (14.5%) patients had MR among 76 evaluable patients.
- The median DOR in patients with best overall confirmed response of CR, PR or MR based on RAPNO-LGG criteria by IRC was 18.0 months (95% CI: 12.0, 22.8) with 70% of events.

9.3.1. Uncertainties and limitations about favourable effects

- The evidence supporting the efficacy claims is derived from a single-arm, open-label study with an exploratory design that underwent major protocol amendments, some of which were implemented after initial data review. The absence of a randomised comparator arm and formal hypothesis testing, limits the interpretation and robustness of the observed treatment effect and introduces potential bias, including patient selection and assessment bias. Furthermore, time to event endpoints such as OS and PFS cannot be contextualised in uncontrolled trials, and the drug effect cannot be isolated. No efficacy claims can be based on PFS and OS data from the pivotal study provided. Data from the ongoing FIREFLY-2 will be submitted as part of the agreed SOB (due date 30 April 2032) and are expected to further support the characterisation of the efficacy of Ojemda, providing comparative data and helping contextualise and address the uncertainty regarding the observed treatment effect.
- The definition of ORR per RAPNO-LGG criteria was amended to include MR (in addition to CR and PR). Although reassurance was provided by the applicant that the inclusion of MR in the FIREFLY-1 was not data-driven, but rather reflecting evolving response assessment

recommendations in paediatric neuro-oncology, uncertainty remains in the contextualisation of the efficacy results.

9.4. Unfavourable effects

The safety assessment is largely based on the pooled data from 137 patients 6 months of age and older with relapsed or refractory pLGG harbouring a BRAF alteration in FIRELY-1 (Arms 1 and 2).

The most frequently reported TEAEs, were hair colour changes (77.4%), blood creatine phosphokinase increased (62.0%), fatigue (60.6%), anaemia (60.6%), vomiting (56.2%), hypophosphataemia (56.2%), headache (52.6%), rash maculo-papular (50.4%), pyrexia (46.7%), growth retardation (43.1%).

The most frequently treatment related AEs (TRAEs) were hair colour changes (77.4%), blood creatine phosphokinase increased (60%), anaemia (50%), fatigue (49.6%), rash maculo-papular (46%), decrease in growth velocity (PT: growth retardation) (42.3%), blood phosphate decreased (hypophosphatemia) (42%), dry skin (38%), blood lactate dehydrogenase increased (34%), AST increased (33%).

The most common serious AEs were pyrexia (11%), hydrocephalus (7%), growth retardation (7%), seizure (7%), vomiting (7%), and tumour haemorrhage (5%). Serious TEAEs considered related to tovorafenib treatment were reported in 29 (21.2%) patients in both arms. The most common serious TRAEs were growth retardation (9 patients, 6.6%); tumour haemorrhage (5 patients 3.6%), hydrocephalus (1.5%), seizure (1.5%), vomiting (1.5%), decreased appetite and hyponatraemia (1.5% each).

10.9% of patients (15 patients) have discontinued tovorafenib treatment due to TEAEs, of which 13 (9.5%) patients discontinued treatment due to events considered by the investigator to be related to tovorafenib. These mainly concern decrease in growth velocity and tumour haemorrhage (4 patients each).

32.1% of patients had TEAEs leading to dose reduction and all considered treatment related. The most common were rash maculo-papular (5%), fatigue (4.4%), decreased appetite (2.9%), anaemia (2.2%), growth retardation (2.2%), acneiform rash (1.5%), dermatitis bullous (1.5%), pruritus (1.5%), ALT increased (1.5%), and weight decreased (1.5%). Cardiac events leading to dose reduction were left ventricular hypertrophy, pericardial effusion and ventricular extra-systoles each in one patient and all were considered related to treatment.

65.7% of patients had a TEAE leading to dose interruption. 43.1% of patients had TEAEs leading to dose interruption considered by the investigator to be related to tovorafenib. The most common events considered related to treatment were rash maculo-papular (9.5%); fatigue (5.1%); ALT increased (4.4%), vomiting (4.4%), growth retardation (5.1%); blood CPK increased (3.6%); eczema, decreased appetite (2.9%); and pruritus (2.2%), AST increased (2.2%), pyrexia (2.2%), hydrocephalus (2.2%), and anaemia (2.2%).

As regards growth retardation, across the population, the data show that growth suppression associated with treatment is reversible with demonstrated growth recovery as evidenced by increased AGV post treatment when compared to the on-treatment period. Over this follow-up period with a median of only 8.4 months, most patients showed signs of catch-up growth (82%), with patients in the pre-pubertal age groups demonstrating that fastest catch-up rates when compared to peri-pubertal age groups. While evidence of recovery and catch-up were observed across both pre- and peri-pubertal age groups in both sexes, males had a faster rate of recovery when compared to females in this early post-treatment snapshot.

In addition, there was a trend toward increasing frequency of patients with maximum Grade 3 events and Grade ≥ 3 events in the younger versus older age groups. Growth retardation was more commonly reported as serious and treatment related among younger patients.

The relationship between intratumoral haemorrhage and treatment is difficult to assess, particularly in the context of a single-arm study, where spontaneous haemorrhage may occur independently of therapy. Nevertheless, 13.2% of patients reported events that were adjudicated as AESIs of ITH. A warning for intratumoural haemorrhage has been reflected in section 4.4 of the SmPC and a detailed description for this safety concern included in section 4.8 of the SmPC.

Review of the related TEAEs (including SAEs and grade ≥3 events), for patients with mild hepatic and renal impairment, did not identify any differences in safety profile compared to non-hepatically or non-renally impaired patients.

Overall, the safety profile of tovorafenib seems to be manageable and consistent with its mechanism of action.

9.4.1. Uncertainties and limitations about unfavourable effects

- The absence of a comparator arm limits the ability to establish causality of adverse events, making it challenging to clearly define ADRs attributable to tovorafenib.
- Long-term safety data are limited and the risk for late-onset ADRs remains largely uncharacterised. This is particularly relevant given the potential for long-term treatment in a paediatric population with a chronic disease, and the impact on growth, development and long-term health outcomes remains incompletely characterised. Long-term safety is reflected as missing information in the RMP. Long-term safety and in particular with respect to growth retardation, pubertal development, intratumoural haemorrhage, embryo-foetal toxicity and potential effects on fertility, will be further characterised as part of the agreed SOB within the CMA, which will support the continued evaluation of the safety profile of tovorafenib.
- Clinical experience in the youngest authorised age group (≤ 2 years) remains very limited. In the pivotal study, only 3 patients ≤ 2 years received tovorafenib and the youngest treated patient was 11 months of age. Consequently, uncertainty remains regarding the safety profile and appropriateness of the dose recommendation in the youngest authorised age group. This limitation is reflected in section 4.2 of the SmPC.

9.5. Effects Table

Table 56: Effects Table for Ojemda as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies; (data cut-off: 10 May 2024).

Effect (short description)	*Treatment Tovorafenib*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable Effects			
	RAPNO-LGG (N=76)		
ORR by IRC– no (CR + PR + MR) / - % (95%CI)	52.6% (95% CI: 40.8, 64.2)	**SoE:** uncontrolled exploratory data; low level of evidence **Unc:** No CR; PR 29 patients (38.2%); MR 11 patients (14.5%).	FIREFLY-1 (Arm 1)

Effect (short description)	Treatment Tovorafenib	Uncertainties/ Strength of evidence	Ref
Median DoR by IRC (months) (95%CI)	18.0 (95% CI: 12.0, 22.8)	**SoE:** uncontrolled exploratory data; low level of evidence **Unc:** only applies to responding patients	FIREFLY-1 (Arm 1)
Unfavourable Effects			
	N=137	**Unc:** single-arm study	FIREFLY-1 (Arm 1 and 2)
Haemorrhage	17 (12.4%)		
Growth retardation	59 (43.1%)		
Rash/rash maculo-papular	92 (67%)		
Photosensitivity reaction	20 (14.6%)		
Pyrexia	64 (46.7%)		
Pyrexia treatment-related SAEs	29 (21.2%)		
TAES leading to drug discontinuation	15 (10.9%)		
TEAEs with Severity Grade 3 or Higher	112 (81.8)		

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; CI=confidence interval; CR=complete response; DOR=duration of response; IRC=Independent Radiology Review Committee; MR=minor response; ORR= overall response rate; PR=partial response; RANO-HGG=Response Assessment in Neuro-Oncology High-grade Glioma; RAPNO=Response Assessment in Pediatric Neuro-Oncology; TAES= Treatment emergent adverse event

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

The pivotal study FIREFLY-1 is an open-label, uncontrolled, multi-centre study in paediatric patients aged 6 months to 25 years, with RAF-altered, recurrent or progressive LGG and advanced solid tumours.

In the absence of a control arm, assessment of clinical benefit relies primarily on tumour response. Although ORR based on RAPNO-LGG criteria was defined as a secondary endpoint according to the protocol, it constitutes the primary measure supporting the assessment of efficacy in this application.

The IRC-assessed ORR (CR, PR, or minor response [MR]) based on RAPNO-LGG criteria was 52.6% (95% CI: 40.8, 64.2). No patients had a CR, 29 (38.2%) patients had a PR, and 11 (14.5%) patients had MR among 76 evaluable patients.

Overall, no significant differences with regards to the subgroup analyses of ORR per RAPNO-LGG criteria by age, sex, race, prior lines of therapy and BRAF alterations (BRAF fusion vs BRAF mutation vs other) were observed. However, uncertainty remains due to the limited clinical data available in patients with BRAF V600E mutation previously treated with the combination of dabrafenib and trametinib.

Due to the non-randomised, uncontrolled, open-label design, the risk of bias (especially selection

bias) cannot be eliminated.

The overall safety profile of tovorafenib is based on data from 137 patients in Arm 1 and Arm 2 and is consistent with its mechanism of action. The most frequently observed adverse events include hair colour changes, rash, fatigue, gastrointestinal disturbances, pyrexia, transaminases increased and haemorrhage, which are generally manageable through dose modifications or supportive care.

However, the evaluation of the safety profile of tovorafenib is significantly hampered by the small sample size of the safety database, the heterogeneous study population of the pivotal trial (FIREFLY-1, Arm 1 and Arm 2, N=137) and the absence of controlled arm and long-term safety data. The currently important identified risks as reflected in the RMP are intra-tumoural haemorrhage and growth retardation, and the important potential risk of decreased fertility.

Of note, although the effect on growth appears reversible in many cases after treatment discontinuation, the evidence base is currently limited in terms of sample size, duration of follow-up, and specific impact in patients at critical pubertal ages (e.g., 9–14 years). Further data collection and long-term follow-up are warranted to address these residual uncertainties. Additionally, uncertainties remain regarding the safety profile and dose recommendations in the youngest authorised population. Indeed, only 3 patients ≤ 2 years received tovorafenib. Of note, the youngest patient included in the FIREFLY-1 study was 11 months. In addition, there was a trend toward increasing frequency of patients with maximum Grade 3 events and Grade ≥ 3 events in the younger versus older age groups.

Further data will be gained from the ongoing phase 3 study FIREFLY-2, agreed as an SOB in the context of the CMA.

The systemic exposure predictions in paediatric patients below 2 years are unreliable due to very limited data (n=3), and current PK models do not adequately predict clearance in this subgroup. Although the observed bias is likely related to data scarcity, a potential shift in clearance cannot be excluded. Additional PK data will be collected in patients under 2 years of age to refine and update the PK model, enabling reliable estimation of systemic exposure and confirmation or adjustment of the dosing recommendations in this subgroup of patients (**SOB**).

9.6.2. Balance of benefits and risks

In patients aged 6 months and older with paediatric low-grade glioma harbouring a BRAF fusion or BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies, tovorafenib demonstrated clinically meaningful antitumour activity as reflected by the ORR and DoR. Although derived from a single-arm study and therefore subject to inherent limitations, the efficacy results support a clinically relevant treatment effect in this population.

The safety profile is characterised by adverse reactions consistent with MAPK pathway inhibition, and while associated with toxicities, it is considered manageable in clinical practice with appropriate monitoring and dose modifications. Residual uncertainties, including those related to the single-arm study design and long-term safety, will be addressed through the agreed SOB in the context of a CMA.

Overall, the benefit-risk balance of tovorafenib in the agreed indication is considered positive.

9.6.3. Additional considerations on the benefit-risk balance

9.6.3.1. Conditional marketing authorisation

9.6.3.1.1. Applicant's request for Conditional Marketing Authorisation

The applicant requested in the initial submission consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

A. **The benefit-risk balance is positive**: The applicant considers that the benefit-risk is positive in the proposed indication of Ojemda as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies.

B. **It is likely that the applicant will be able to provide comprehensive data post-authorisation.** The applicant proposes the confirmatory phase 3 FIREFLY-2 study, currently ongoing, to verify, describe and confirm the clinical benefit of tovorafenib and further characterise the safety profile over an extended period of time. This phase 3 study is a randomized, global, multicenter trial of tovorafenib monotherapy versus standard of care chemotherapy in pLGG harboring an activating RAF alteration requiring first-line systemic therapy. This global study is enrolling patients from Asia, Europe and North America. Approximately 400 treatment-naïve LGG patients are planned to be randomized 1:1 to either tovorafenib (Arm 1) or an Investigator's choice of SoC chemotherapy (Arm 2). The study is ongoing since 08 February 2023 and the first patient was dosed on 03 March 2023. The primary analysis date is targeted in Q2 2027, and as of 15 January 2025, 169 patients out of 400 patients have been recruited. Enrolment of patients is expected to be near complete by the time of the European Commission (EC) decision for tovorafenib.

C. **The medicine fulfils and unmet medical need:** as treatment options available to patients, including chemotherapy are associated with high morbidity and low response rates. In addition, the modes of administration of such treatments, which require IV infusions, are burdensome, which is an important point to consider for the young patients and their caregivers. For patients with pLGG harbouring a BRAF fusion or rearrangement, tovorafenib represents the only targeted treatment as the approved dabrafenib/trametinib combination is restricted to patients with BRAF V600E mutations and therefore is not an option for the other more frequently encountered BRAF alterations, such as BRAF fusion or rearrangement. In the context of BRAF V600E mutation, tovorafenib has a significantly more patient-friendly dosing schedule. The dosage regimen of tovorafenib (once weekly dosage schedule) oral route of administration with or without food, is expected to offer a significant advantage over the once and twice daily administration outside of meals for dabrafenib/trametinib.

D. **The benefit of the medicine's immediate availability to patients is greater than the risks inherent in the fact that additional data are still required**.

   In conclusion, in view of the seriously debilitating nature of pLGG, the unmet medical need in this disease given limited treatment options available for these children, the majority of whom are left with chemotherapy as the only available treatment option, and given the favourable benefit-risk profile shown in the FIREFLY-1 study in previously treated patients with BRAF-altered tumours, the applicant believes that the benefit to public health of immediate availability of tovorafenib outweighs risks associated with the fact that additional data are still required.

9.6.3.1.2. Discussion on the non-comprehensiveness of data in the context of a Conditional Marketing Authorisation

In regard to the request for a conditional marketing authorisation, the CHMP considers that the following is to be accounted in terms of comprehensiveness of the dossier:

Due to the limitations of the pivotal study design, including the lack of a randomised comparator arm and the limited sample size, the available data are not considered comprehensive within the meaning of the CMA legislation.

The main uncertainties relate to the potential for bias inherent to the single-arm design, including patient selection and assessment bias, as well as the limited pharmacokinetic data in the youngest intended population (<2 years), for whom additional data and potential dose refinement are required under the agreed SOB.

With respect to safety, follow-up remains limited and the long-term safety profile, including the risk for late-onset ADRs has not yet been fully characterised. This is particularly relevant given the potential for prolonged treatment in a paediatric population and the possible impact on growth, development and long-term health outcomes.

9.6.3.1.3. Conclusions and recommendation on Conditional Marketing Authorisation

As comprehensive data on the product are not available, as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a(1) of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and potentially life-threatening disease. In addition, the product is designated as an orphan medicinal product.

The CHMP considered that the product fulfils the requirements for a conditional marketing authorisation:

- **The benefit-risk of Ojemda is positive** as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies, as discussed above.
- **It is likely that the applicant will be able to provide comprehensive data post-authorisation:** The RCT FIREFLY-2 can be accepted as SOB to provide comprehensive data post-authorisation, and the proposed due dates are considered realistic and acceptable.

  The confirmatory FIREFLY-2 study is currently enrolling patients globally. Recruitment is progressing according to planned timelines, with a target completion of enrolment by Q1 2026, which is reassuring that the target completion can be achieved and that the interim study report (including the ORR primary analysis and the PFS interim analysis) can be projected to be available for submission in April 2028, with the final study report planned for April 2032.

  The FIREFLY-2 study protocol was amended to adopt the RAPNO-LGG criteria as primary endpoint for treatment response evaluation in paediatric low-grade glioma, replacing RANO-LGG. A detailed justification was given for the change of the primary and key secondary endpoints in phase 3 study FIREFLY-2, which can be followed. Furthermore, the change was implemented after 113/400 patients were recruited, such that the majority of the patients (~290/400) will have been enrolled after the change. Thus, the treatment effect will not mainly be driven by data that could have been known before the change. Nevertheless, further

assessment of the consistency of the treatment effect before and after the change in terms of RAPNO-LGG ORR will be of interest when the final data are available as well as the respective effects for RAPNO-LGG. The firewalls that were implemented by the applicant to safeguard trial integrity in the open-label FIREFLY-2 study are sufficient to ensure appropriate restriction of access to efficacy data to ensure integrity of the ongoing study.

In addition, while the study is conducted in a first-line setting, which differs from the second-line setting to be authorised under the CMA, the mechanism of action of Ojemda is not expected to be line-dependent, the molecular-defined disease target is consistent across treatment lines, and as explained, the study is expected to reduce key uncertainties identified at the time of the CMA. However, there is some uncertainty in the fact that this study excludes patients previously treated with dabrafenib in combination with trametinib.

In summary, the RCT FIREFLY-2 will provide comprehensive data, and the proposed due dates are considered realistic and acceptable.

- **An unmet medical need will be addressed**, as there are no authorised treatments available in the EU for patients with pLGG harboring BRAF fusions or rearrangements, who have progressed after one or more prior systemic therapies.

  Treatment options for relapsed or refractory paediatric LGG include traditional chemotherapy and radiotherapy. However, the evidence supporting chemotherapy regimens in this setting is limited, making meaningful indirect comparisons with tovorafenib difficult. Chemotherapy is also associated with relevant toxicity and typically requires parenteral administration in a hospital setting, which may impact quality of life. Radiotherapy remains an effective option, particularly when surgery is not feasible, but its use is often delayed or avoided in younger children due to substantial short- and long-term side effects, including neurocognitive impairment, learning difficulties, behavioural changes, and endocrine dysfunction.

  With regards to patients with BRAF V600E-mutated disease, tovorafenib offers a significantly more convenient once-weekly oral dosing regimen, compared with the once- or twice-daily administration of the combination of dabrafenib and trametinib. This simplified dosing schedule, without the need for fasting requirements or complex administration, is considered to represent a major improvement to patient care and thus a major therapeutic advantage, particularly relevant in a paediatric population expected to require prolonged treatment.

  Direct comparison of efficacy and safety across trial are considered inherently limited, particularly due to the non-randomised, uncontrolled open-label design of the pivotal study. Therefore, conclusions regarding comparative efficacy or safety cannot be drawn.

- **The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required**. The applicant has sufficiently demonstrated that in light of the limited treatment options in this orphan and debilitating disease, the immediate availability of tovorafenib is expected to deliver meaningful public health benefit by providing an effective treatment option for paediatric patients with BRAF-altered paediatric low-grade glioma who have progressed after one or more prior systemic therapies.

The CHMP considers the following measures necessary to address the missing data in the context of a conditional marketing authorisation:

Table 57: Specific obligations in relation to the CMA

Description	*Due date*
In order to confirm the efficacy and safety of tovorafenib in the treatment of patients 6 months of age and older with paediatric lowgrade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, the MAH shall conduct and submit the final report of the phase III randomised, parallel group, twoarm study (FIREFLY2) to evaluate the efficacy and safety of tovorafenib monotherapy versus standard of care (SoC) chemotherapy in patients with paediatric lowgrade glioma harbouring an activating rapidly accelerated fibrosarcoma gene (RAF) alteration requiring firstline systemic therapy.	30 April 2032
The MAH shall generate additional PK data in paediatrics patients below 2 years of age and submit an updated population PK model incorporating these data, including an assessment of systemic exposure and, if necessary, revised dosing recommendations for this subgroup of patients.	30 April 2032

9.7. Benefit-risk conclusions

9.7.1. At Day 210 – CHMP conclusions

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