The LOGGIC/FIREFLY-2 study evaluating the efficacy and safety of tovorafenib vs SoC chemotherapy in pediatric patients with low-grade glioma requiring first-line systemic therapy

This summary is based on the **peer-reviewed manuscript** published in *BMC Cancer* in January 2024 entitled:

LOGGIC/FIREFLY-2: A phase 3, randomized trial of tovorafenib versus chemotherapy in pediatric and young adult patients with newly diagnosed low-grade glioma harboring an activating *RAF* alteration

Click here to view this peer-reviewed publication

Study start date: February 27, 2023

Study number: NCT05566795

Study end date: (estimated) March 2030

Other study names: DAY101-002

Click to view more information on the LOGGIC/FIREFLY-2 study:
https://www.clinicaltrials.gov/study/NCT05566795

Who is conducting the LOGGIC/FIREFLY-2 study?
Day One is conducting the study in collaboration with the Low-Grade Glioma in Children (LOGGIC) consortium, a group of internationally recognized experts in pLGG research, with an extensive network of pediatric oncology centers across Europe

Background

What is pediatric low-grade glioma (pLGG)?

- pLGGs are a group of slow growing tumors in the brain and/or spinal cord, and are the most common type of cancer in these areas in children and adolescents and young adults (AYAs)[2,3]
- There are three different RAF genes (ARAF, BRAF, and CRAF);[4] in pLGG, changes in one of these genes and therefore, the RAF protein, may cause tumors to grow[4]
  - **~70%** of pLGGs have changes in the *BRAF* gene[5,6]
  - ***BRAF* fusions** are the most frequent alteration observed in pLGGs[6]

- Depending on where the tumor is located in the brain, pLGGs may cause people to feel tired, have headaches, and have difficulties with concentration, thinking, walking or balance, and sometimes, with vision[1]

Types of gene changes in pLGGs[7-9]

Mutation: is a spontaneous change in a specific part of a gene that makes it work incorrectly (example: BRAF V600E mutation)

Fusion: is when part of a gene rearranges and fuses to part of a different gene and makes it work incorrectly (example: *KIAA1549*::*BRAF* fusions)

Abbreviations: **AYAs**, adolescents and young adults; **pLGG**, pediatric low-grade glioma; **SoC**, standard of care

Pronounciations: **ARAF**, a-raf; **BRAF**, be-raf; **CRAF**, see-raf; **Glioma**, glee-OH-ma; **Tovorafenib**, toe-voe-RAF-uh-nib

Disclaimer: Publishing clinical trial results helps the research community understand both progress and setbacks in medical research. However, plain language summaries (PLS) help the general public understand clinical trial results. This PLS contains information about a therapy that was approved by the US FDA in patients ≥6 months of age with relapsed or refractory pLGG harboring a *BRAF* fusion or rearrangement, or BRAF V600 mutation. However, it is under investigation for use in newly diagnosed *BRAF*-altered pLGG. There is no guarantee that an investigational therapy will be approved or offered for sale in any country. This PLS is intended for informational use only and is not intended to promote any Day One Biopharmaceuticals, Inc. product.

1. Roka K, *et al. EJC Paediatric Oncology.* 2024;4:100169. 2. Ostrum QT, *et al. Neuro Oncol.* 2022;24:iii1–iii38. 3. WebMD. Pediatric Low-Grade Gliomas: An Overview. https://www.webmd.com/children/plgg-overview. Accessed May 29, 2025. 4. Sholl LM. *Precis Cancer Med.* 2020;3:26. 5. Singh S, *et al. Clin Cancer Res.* 2025;31(8):1383–1389. 6. Ryall S, Tabori U, Hawkins C. *Acta Neuropathol.* 2020;8(1):30. 7. National Cancer Institute. Definition of Fusion Gene. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/fusion-gene. Accessed May 29, 2025. 8. National Cancer Institute. Definition of Mutation. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/mutation. Accessed May 29, 2025. 9. Fangusaro J, *et al. Neuro Oncol.* 2024;26(1):25–37.

How are pLGGs treated?[1]

The ideal treatment, when possible, is **surgery** to completely remove the tumor

- When surgery is not possible or incomplete, systemic* anticancer treatments, known as chemotherapy, are often given to shrink the tumor
- Radiation is another type of treatment, but is used less often due to concerns about the long-term effects in growing children

"Targeted therapies" are a newer type of systemic treatment.[2,3] Many target a key cancer pathway called the MAPK pathway and block proteins responsible for tumors, such as MEK[3] and RAF

Targeted therapies are sometimes combined (**"combination therapy"**) as they can block, or inhibit, specific proteins in the MAPK pathway[3]

- Some targeted therapies (**"MAPK inhibitors"**) target proteins that come from BRAF mutations only; others may target proteins that come from *BRAF* fusions[4,5] and mutations[3]

pLGG is considered a chronic disease, so multiple courses of treatment are often needed over time to prevent tumors from growing[6]

What is tovorafenib?

- Tovorafenib is a targeted treatment taken as a pill or liquid once a week.[7] It is designed to treat children as young as 6 months old and older who have a type of low-grade brain tumor (called pLGG) with specific changes in a gene called BRAF[7]
- It is in a class of molecules known as "type II RAF inhibitors"[7]
- Was granted accelerated approval by the US Food and Drug Administration (FDA) on April 23, 2024 for patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (pLGG) harboring a *BRAF* fusion or rearrangement, or BRAF V600 mutation[8,†]
  - Was the first FDA approval of a systemic therapy for the treatment of patients with pLGG with either type of change in the *BRAF* gene[8]

FIREFLY-1 study

- FIREFLY-1 (NCT04775485) is an ongoing phase 2 study of tovorafenib in children and AYAs with relapsed/recurrent pLGG (Arms 1 & 2) with changes in the *BRAF* gene who have previously received systemic anticancer treatment[9]
- The FIREFLY-1 analysis found that tumors decreased in size in approximately 1 out of 2 participants with pLGG in Arm 1, the group used to evaluate the efficacy of tovorafenib[9]
  - In Arms 1 and 2, the groups used to evaluate the safety of tovorafenib, most of the common side effects were mild to moderate in severity and most participants were able to continue treatment[9]

*Systemic treatments are any type of drug therapy that spreads throughout the entire body. They can be given as an injection, infusion, or as a pill. For example, chemotherapy moves through the blood to help tumors shrink or disappear.

†This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Click here to view this peer-reviewed publication

Abbreviations: MAPK, mitogen-activated protein kinase; **pLGG**, pediatric low-grade glioma

Pronounciations: MAPK, map-kay

1. Roka K, *et al. EJC Paediatric Oncology.* 2024;4:100169. 2. National Cancer Institute. Targeted Therapy to Treat Cancer. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies. Accessed May 29, 2025. 3. Bahar ME, *et al. Signal Transduct Target Ther.* 2023;18;8(1):455. 4. Sheikh SR, *et al. Front Oncol.* 2024;14:1503894. 5. Kondyli M, *et al. J Neurooncol.* 2018;140(2):435–444. 6. Goebel AM, *et al. J Cancer.* 2019;10(25):6314–6326. 7. OJEMDA [package insert]. Brisbane CA: Day One Biopharmaceuticals, Ltd; 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218033s000lbl.pdf. Accessed May 2025. 8. US Food and Drink Administration (FDA). FDA grants accelerated approval to tovorafenib for patients with relapsed or refractory BRAF-altered pediatric low-grade glioma. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tovorafenib-patients-relapsed-or-refractory-braf-altered-pediatric?sf187932196=1. Accessed May 29, 2025. 9. Kilburn LB, *et al. Nat Med.* 2024;30(1):207–217.

LOGGIC/FIREFLY-2 study design

What is the LOGGIC/FIREFLY-2 study?[1]

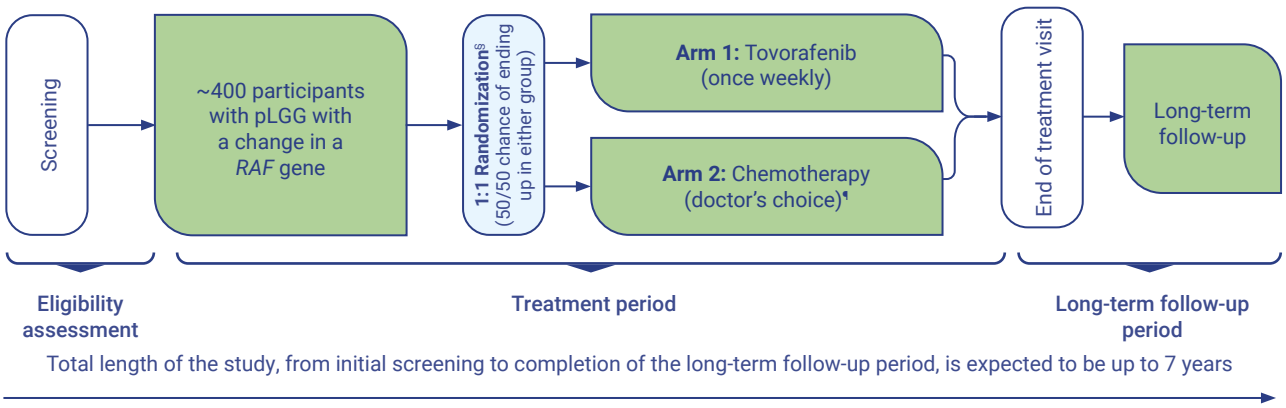
- An ongoing two-arm, randomized, open-label phase 3* study being conducted at ~100 sites†[2] in children and AYAs younger than 25 years of age with newly diagnosed pLGG with a change in the *RAF* gene requiring systemic therapy
- It is comparing once-weekly[1] tovorafenib (Arm 1) with standard of care chemotherapy‡ (Arm 2)

Who is eligible to participate?[1]

A detailed list of criteria for what makes someone eligible or ineligible to participate in this study is available online and a participating doctor would determine eligibility; generally, eligible participants should:

- Be younger than 25 years of age and diagnosed with pLGG
- Have changes in the *RAF* gene and have a tumor that is growing based on a type of brain imaging called magnetic resonance imaging (MRI)
- Have not received any prior systemic anticancer treatment for pLGG

What does the study entail?



§Randomization will factor in certain participant characteristics, such as **tumor location** and **type of change in the *RAF* gene**, in order to ensure balanced groups

†The doctor's choice of chemotherapy will be chosen prior to randomization.

Options for chemotherapy are one of the following current standard of care treatments for pLGG: 1) Children's Oncology Group - Vincristine/Carboplatin, 2) International Society for Paediatric Oncology - Low-Grade Glioma Vincristine/Carboplatin, or 3) Vinblastine

How long will participants receive treatment?

Arm 1 tovorafenib

Up to 5 years, including long-term follow-up[3]

- Option to continue tovorafenib if their tumor worsens or their doctor thinks they are benefiting from continuing

Arm 2 chemotherapy

1 – 1.5 years (depending on the chemotherapy selected)[4], and then long-term follow-up (up to 5 years)

- Option to receive tovorafenib if their tumor worsens while on chemotherapy or after finishing chemotherapy[3]

Treatment will continue until completion or any of the following occurs: the tumor worsens, unacceptable toxicity, study withdrawal, or end of study

*Phase 3 studies compare how well a new treatment works and how safe it is compared with a treatment that is considered the current standard of care.

†In Europe, the Asia Pacific region (Singapore, South Korea, Australia, and New Zealand), and North America (US and Canada).

‡Doctor's choice from a defined selection of chemotherapy options considered current standard of care

Abbreviations: **AYA**, adolescents and young adults; **MRI**, magnetic resonance imaging; **pLGG**, pediatric low-grade glioma

1. van Tilburg CM, *et al. BMC Cancer.* 2024;24(1):147. 2. Clinicaltrials.gov (NCT05566795). https://www.clinicaltrials.gov/study/NCT05566795. Accessed May 29, 2025. 3. Day One Biopharmaceuticals, Inc. Clinical Protocol DAY101-002 (date). Data on file. 4. Kilburn LB, *et al. J Clin Oncol.* 2023;41:16_suppl, TPS10067.

What is LOGGIC/FIREFLY-2 evaluating?[1,2]

The goal of the study is to determine how tovorafenib compares with chemotherapy*, as a safe and effective treatment, in children and AYAs with newly diagnosed pLGG with a change in the *RAF* gene who require systemic anticancer treatment.

- The primary objective is to assess the **objective response rate** (ORR) of tovorafenib compared to standard of care chemotherapy. The ORR is the sum of patients who had **complete response** (tumor disappeared) and **partial response** (tumor significantly decreased)
- Other important key secondary objectives will further assess the impact after the start of treatment and will compare tovorafenib and chemotherapy:

Progression-free survival (PFS)
Average length of time a participant's cancer does not grow or spread during their lifetime

Duration of response (DOR)
Average length of time (while on treatment) that a tumor does not grow or spread

Overall survival (OS)
Average length of time participants live

Safety and tolerability
Type, frequency, and severity of side effects

- Other secondary and exploratory objectives will utilize other measures to compare outcomes of participants in the 2 treatment arms

What else will LOGGIC/FIREFLY-2 evaluate?

Other select assessments†

What is measured and when are they measured?	These measures assess changes in:
MRI scan Every 12 weeks	Tumor size
Visual acuity (eye) test At every MRI visit (if needed)	Ability to see
Neurological functioning and adaptive behaviors 1, 2, and 5 years after the start of treatment	Brain function such as memory and thinking
Quality of life‡ 1, 2, and 5 years after the start of treatment	Ability to participate in and enjoy daily activities
Safety monitoring§ Throughout the study (various timepoints)	How someone feels or if certain chemicals in their blood (or other tests) are changing, indicating side effects
Pharmacokinetics‖,¶ Day 1 of cycles 1, 2, and 4: before each dose and 2 hours after Day 1 of cycles 7, 10, and 13: before each dose When there is a serious side effect: any time	Ability to detect, monitor, and treat tumors

*Doctor's choice from a defined selection of chemotherapy options considered current standard of care. †All measures will be assessed at baseline before the start of study treatment. ‡In participants over 2 years of age. For children under 4 years of age, caregiver(s)/parent(s) will complete the proxy-reporting quality of life assessment. For children above 5 years of age, both the child and parent will complete a self-report and parent proxy report version of the assessment, if applicable. Quality of life assessments will only be conducted if local language translation is available. §Includes assessments of vital signs, skin and bone health. ‖Study of how a drug acts in the body over a period of time, including how it is absorbed, distributed, metabolized, and excreted. ¶For cycles 2, 4, 7, 10, and 13, blood can be collected on Day 1 or up to 3 days before or after. Samples taken before a dose will be collected 0–1 hours before. Samples taken 2 hours after a dose will be collected between 1–3 hours afterwards

1. Clinicaltrials.gov (NCT05566795). https://www.clinicaltrials.gov/study/NCT05566795. Accessed May 29, 2025. 2. van Tilburg CM, *et al. BMC Cancer.* 2024;24(1):147.

When will the LOGGIC/FIREFLY-2 study be completed?[1]

March 2030 (estimated); however, some early results may be available earlier as the estimated completion of the primary endpoint portion (assessment of the impact of tovorafenib on tumors and in comparison with chemotherapy) is February 2026.

Conclusions from this publication[1,2]

The results from the LOGGIC/FIREFLY-2 study aim to:

- Inform if tovorafenib shrinks tumors in participants and by how much, how many participants' tumors shrink, and how it compares with chemotherapy*
- Provide information on the side effects of tovorafenib, how severe they may be, and if they impact participants from continuing treatment
- Provide additional support for the evaluation of tovorafenib as a potential treatment in children and AYAs newly diagnosed with pLGG with a change in a *RAF* gene

Overall summary[2]

The ongoing LOGGIC/FIREFLY-2 study, is trying to find out whether an anticancer treatment, tovorafenib, is safe and effective in treating children and AYAs under 25 years of age who have been diagnosed with pLGG and have not yet received treatment.

- The type of pLGG of interest includes changes in a *RAF* gene
- Once-weekly tovorafenib (pill or liquid form) is being compared with chemotherapy*
- Participants must not have already received chemotherapy or systemic anticancer treatments for pLGG
- Results aim to support the evaluation of tovorafenib as a potential treatment in children and AYAs newly diagnosed with pLGG with a change in a *RAF* gene
- The trial is currently enrolling participants

*Doctor's choice from a defined selection of chemotherapy options considered current standard of care.

Abbreviations: **AYAs**, adolescents and young adults; **pLGG**, pediatric low-grade glioma

Day One Biopharmaceuticals, Inc.
1800 Sierra Point Pkwy #200
Brisbane, CA 94005, USA

Day One, the study sponsor, is extremely grateful to all patients, families, caregivers, and clinical investigators for their participation in the LOGGIC/FIREFLY-2 study.

Click here to view more information on the LOGGIC/FIREFLY-2 study

Click here to view more information on clinical trials in general

Click here to view more information on clinical trials childhood cancer

1. Clinicaltrials.gov (NCT05566795). https://www.clinicaltrials.gov/study/NCT05566795. Accessed May 29, 2025.
2. van Tilburg CM, *et al. BMC Cancer.* 2024;24(1):147.

Writing support for this summary was provided by Day One Biopharmaceuticals, Inc. and the Bioscript Group, funded by Day One Biopharmaceuticals, Inc.

MED-0062, May 2025

Day One BIOPHARMACEUTICALS