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ClinicalTrials.gov ID: NCT05303519

Study Identification

Unique Protocol ID: AB-218-G203

Brief Title: SIGMA (Safusidenib in IDH1 Mutant Glioma Maintenance)

Official Title: A Phase 3, Multicenter, Clinical Study to Evaluate the Efficacy and Safety of Safusidenib Erbumine in Participants With Isocitrate Dehydrogenase 1 (IDH1)-Mutant Glioma

Secondary IDs:

Study Status

Record Verification: December 2025

Overall Status: Recruiting

Study Start: June 5, 2023 [Actual]

Primary Completion: December 1, 2028 [Anticipated]

Study Completion: December 1, 2030 [Anticipated]

Sponsor/Collaborators

Sponsor: Nuvation Bio Inc.

Responsible Party: Sponsor

Collaborators: AnHeart Therapeutics Inc.

Oversight

U.S. FDA-regulated Drug: Yes

U.S. FDA-regulated Device: No

U.S. FDA IND/IDE: Yes

IND/IDE Information: FDA Center: CDER
IND/IDE Number: 157873
Serial Number:
Has Expanded Access: No

Human Subjects Review: Board Status: Approved
Board Name: Advarra
Board Affiliation: Advarra, Inc
Phone: 410-884-2900
Email:
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6100 Merriweather Dr., Suite 600
Columbia, MD 21044

Data Monitoring: Yes

FDA Regulated Intervention: Yes

Section 801 Clinical Trial: Yes

Study Description

Brief Summary: This is a 3-part study. The purpose of Part 1 of the study is to evaluate the efficacy, safety, and pharmacokinetic (PK) characteristics of safusidenib in participants with recurrent/progressive IDH1-mutant World Health Organization (WHO) Grade 2 or Grade 3 glioma.

The purpose of Part 2 will be to evaluate the efficacy of maintenance safusidenib treatment versus placebo in IDH1-mutant Grade 2 or Grade 3 astrocytoma with high-risk features or IDH1-mutant Grade 4 astrocytoma, following standard-of-care radiation or chemoradiation and adjuvant temozolomide. Part 2 will be randomized, double-blind, and placebo-controlled.

The purpose of Part 3 will be to evaluate the efficacy of safusidenib in participants with residual or recurrent IDH1-mutant Grade 3 oligodendroglioma who have received surgery as their only treatment. Part 3 will be an open-label single-arm cohort and will enroll participants concurrently with Part 2.

Detailed Description: Part 1 of this study will enroll up to 25 patients that will be randomized 1:1:1:1:1 (5 patients per group) to receive one of the daily oral doses of safusidenib at 125 mg twice a day (BID), 250 mg BID, 500 mg once daily (QD), 375 mg BID, or 500 mg BID. The PK characteristics and safety and initial efficacy data will be assessed in Part 1.

Part 1 was fully enrolled as of 19 Dec 2023 and participants are currently ongoing.

Part 2 will include approximately 300 participants with IDH1-mutant Grade 2 or Grade 3 astrocytoma with high-risk features or IDH1-mutant Grade 4 astrocytoma, following standard-of-care radiation or chemoradiation and adjuvant temozolomide. Participants will be randomized (1:1) after their last dose of adjuvant temozolomide to receive either oral safusidenib 250 mg BID or placebo in 28-day continuous cycles. Patients will continue treatment until progression of disease or until other discontinuation criteria are met. The tumor response evaluation will be conducted on a regular basis until progression of disease per Blinded Independent Central Review (BICR), consent withdrawal, or death, whichever occurs first. Long-term survival follow-up will be conducted as well.

Part 3 will include approximately 40 participants with residual or recurrent IDH1-mutant Grade 3 oligodendroglioma with measurable disease who have undergone surgery as their only treatment and are not in need of immediate chemotherapy or radiotherapy. Participants will receive oral safusidenib 250 mg BID in 28-day continuous cycles until disease progression or another reason for discontinuation occurs.

Conditions

Conditions: Glioma
Astrocytoma, Grade IV
IDH1-mutant Glioma
Astrocytoma, IDH-Mutant, Grade 2
Astrocytoma, IDH-Mutant, Grade 3
Astrocytoma, IDH-Mutant, Grade 4
Oligodendroglioma
Oligodendroglioma, IDH-Mutant and 1p/19q-Codeleted

Keywords: safusidenib

IDH1-mutant glioma
astrocytoma

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	8
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Allocation:	Randomized
Enrollment:	365 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: safusidenib 125mg bid (part 1) safusidenib 125mg bid administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with safusidenib until disease progression or development of other unacceptable toxicity.	Drug: safusidenib safusidenib administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with agent safusidenib until disease progression or development of other unacceptable toxicity. Other Names: • DS-1001b • safusidenib • AB-218
Experimental: safusidenib 250mg bid (part 1) safusidenib 250mg bid administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with safusidenib until disease progression or development of other unacceptable toxicity.	Drug: safusidenib safusidenib administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with agent safusidenib until disease progression or development of other unacceptable toxicity. Other Names: • DS-1001b • safusidenib • AB-218
Experimental: safusidenib 500mg qd (part 1) safusidenib 500mg qd administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with safusidenib until disease progression or development of other unacceptable toxicity.	Drug: safusidenib safusidenib administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with agent safusidenib until disease progression or development of other unacceptable toxicity. Other Names: • DS-1001b • safusidenib

Arms	Assigned Interventions
	• AB-218
Experimental: safusidenib 375mg bid (part 1) safusidenib 375mg bid administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with safusidenib until disease progression or development of other unacceptable toxicity.	Drug: safusidenib safusidenib administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with agent safusidenib until disease progression or development of other unacceptable toxicity. Other Names: • DS-1001b • safusidenib • AB-218
Experimental: safusidenib 500mg bid (part 1) safusidenib 500mg bid administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with safusidenib until disease progression or development of other unacceptable toxicity.	Drug: safusidenib safusidenib administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with agent safusidenib until disease progression or development of other unacceptable toxicity. Other Names: • DS-1001b • safusidenib • AB-218
Experimental: safusidenib 250mg bid (Part 2) safusidenib administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment until disease progression or another reason for discontinuation occurs.	Drug: safusidenib safusidenib administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with agent safusidenib until disease progression or another reason for discontinuation occurs. Other Names: • DS-1001b • safusidenib • AB-218
Placebo Comparator: placebo (Part 2) Placebo administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with placebo until disease progression or another reason for discontinuation occurs.	Drug: Placebo Placebo administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with placebo until disease progression or another reason for discontinuation occurs.
Experimental: safusidenib 250mg bid (Part 3) safusidenib administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment until disease progression or another reason for discontinuation occurs.	Drug: safusidenib safusidenib administered continuously as dosed single agent orally on Days 1 to 28 of a 28-day cycle. Subjects may continue treatment with agent safusidenib until disease progression or another reason for discontinuation occurs. Other Names:

Arms	Assigned Interventions
	• DS-1001b • safusidenib • AB-218

Outcome Measures

Primary Outcome Measure:

1. Part 1: Incidence of adverse events (AEs) and serious adverse events (SAEs)
   calculate Percentage and numbers of participants with treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) assessed by CTCAE 5.0

   [Time Frame: From participants sign ICF to 30 days after last dose, average 2 years]
2. Part 2: Progression-free survival (PFS) assessed by Blinded Independent Central Review (BICR) per Response Assessment in Neuro-Oncology (RANO) 2.0
   PFS is defined as the time from randomization to the date of the first documented disease progression assessed by BICR per RANO 2.0 or death (by any cause in the absence of disease progression).

   [Time Frame: From randomization until the date of first documented disease progression, average 2 years]

3. Part 3: Objective Response Rate (ORR) (Complete Response (CR), Partial Response (PR) and Minor Response (MR)) assessed by Blinded Independent Central Review (BICR) per Response Assessment in Neuro-Oncology (RANO) 2.0

   [Time Frame: From the first dose of study drug until the date of first documented disease progression, average 18 months]

Secondary Outcome Measure:

3. Part 1: Cmax of safusidenib
   Peak Plasma Concentration (Cmax)

   [Time Frame: on Cycle 1 Day 1 and Day 8 (every cycle is 28 days)]
4. Part 1: Tmax of safusidenib
   the time for safusidenib to reach Cmax

   [Time Frame: on Cycle 1 Day 1 and Day 8 (every cycle is 28 days)]
5. Part 1: AUC8h of safusidenib
   Area under the plasma concentration curve (AUC) from time 0 to 8 hours

   [Time Frame: on Cycle 1 Day 1 and Day 8 (every cycle is 28 days)]
6. Part 1 : AUC12h of safusidenib
   Area under the plasma concentration curve (AUC) from time 0 to 12 hours

   [Time Frame: on Cycle 1 Day 1 and Day 8 (every cycle is 28 days)]
7. Part 1: AUC24h [QD only] of safusidenib
   Area under the plasma concentration curve (AUC) from time 0 to 24h hours for 500mg qd cohort

   [Time Frame: on Cycle 1 Day 1 and Day 8 (every cycle is 28 days)]
8. Part 1 : Ctrough of safusidenib
   Lowest plasma concentration reached after AB-218 administration

   [Time Frame: on Days 2, 3, 4, 6, 8, 9 of Cycle 1 and Day 1 of Cycles 2, 3, 4, 6 and 8 (every cycle is 28 days)]
9. Part 1: Overall Response Rate (ORR) assessed by the investigator
   ORR (defined as the proportion of participants with the best overall confirmed response of Complete Response (CR), Partial Response (PR) or Minor Response (MR)[for RANO-HGG/RANO LGG] according to the appropriate tumor response criteria) as assessed by the Investigator

   [Time Frame: from the first dose of study drug until the date of first documented disease progression, average 2 years]
10. Part 1: Duration of Response (DOR) assessed by the Investigator
    DOR, defined as the time from the first documentation of objective response (CR, PR, or MR) to the date of the first documentation of disease progression per RANO-HGG/RANO-LGG as applicable, or death (by any cause in the absence of progression), for participants with confirmed objective response, as assessed by the Investigator

    [Time Frame: from the first dose of study drug until the date of first documented disease progression, average 2 years]

11. Part 1: Disease control rate (DCR) assessed by the Investigator
DCR, defined as the proportion of patients with a best overall response of CR, PR, Stable Disease (SD), or Minor Response (MR) per RANO-HGG/RANO-LGG as applicable, as assessed by the Investigator

[Time Frame: from the first dose of study drug until the date of first documented disease progression, average 2 years]

12. Part 1: Progression free survival (PFS) assessed by the Investigator
PFS, defined as the time from the first dose of study drug to the date of the first documented disease progression per RANO-HGG/RANO-LGG as applicable, or death (by any cause in the absence of disease progression), as assessed by the Investigator

[Time Frame: from the first dose of study drug until the date of first documented disease progression, average 2 years]

13. Part1: Time to Response (TTR) assessed by the Investigator.
TTR, the time from the first dose of study drug to the first documentation of objective response (CR, PR, or MR) per RANO-HGG/RANO-LGG as applicable, for participants with confirmed objective response, as assessed by the Investigator.

[Time Frame: From the first dose of study drug until the date of first documented objective response, average 2 years]

14. Part 1: Overall Survival (OS)
OS, defined as the time from randomization to death from any cause. Participants without death information at the analysis cutoff date will be censored at last date known to be alive.

[Time Frame: from the first dose of study drug to date of death, average 7 years]

15. Part 2: Overall Survival (OS)
OS, defined as the time from randomization to death from any cause.

[Time Frame: from randomization to date of death, average 7 years]

16. Part 2: PFS assessed by the Investigator.
PFS, defined as the time from randomization to the date of the first documented disease progression per RANO 2.0, or death (by any cause in the absence of disease progression), as assessed by the Investigator.

[Time Frame: from randomization until the date of first documented disease progression, average 2 years]

17. Part 2: Time to Next Intervention (TTNI)
TTNI, defined as the time from randomization to initiation of the first subsequent anticancer therapy.

[Time Frame: From randomization until the date of next treatment, average 2 years]

18. Part 2: DCR assessed by BICR and by the Investigator
DCR, defined as the proportion of participants with a best overall response of CR, PR, MR, or SD per RANO 2.0, as assessed by the Investigator and BICR

[Time Frame: from randomization until the date of first documented disease progression, average 2 years]

19. Part 2: ORR, assessed by BICR and the Investigator
ORR, defined as the proportion of participants with the confirmed best overall response of CR, PR, or MR per RANO 2.0, as assessed by BICR and the Investigator.

[Time Frame: from randomization until the date of first documented disease progression, average 2 years]

20. Part 2: DOR, assessed by BICR and the Investigator
DOR, the time from the first documentation of objective response (CR, PR, or MR) to the date of the first documentation of disease progression per RANO 2.0, or death (by any cause in the absence of progression), as assessed by the BICR and the Investigator.

[Time Frame: from randomization until the date of first documented disease progression, average 2 years]

21. Part 2: Time to Response (TTR) assessed by BICR and by the Investigator
TTR, defined as the time from randomization to the first documentation of objective response (CR, PR, or MR) per RANO 2.0, as assessed by the BICR and the Investigator.

[Time Frame: From randomization until the date of first documented objective response, average 2 years]

22 Part 2: Health-related quality of life
The Functional Assessment of Cancer Therapy-Brain (FACT-Br) and the Quality of Life in Epilepsy (QOLIE-10-P) questionnaires

[Time Frame: From the first dose of study drug to treatment discontinuation, average 2 years]

23. Part 2: Safety and tolerability
AEs graded by NCI CTCAE v5.0, laboratory abnormalities as graded by NCI CTCAE v5.0, vital signs, physical examinations, and ECGs.

[Time Frame: from the first dose of study drug until 30 days after treatment discontinuation, average 2 years]

24. Part 2: Seizure Activity
Defined as seizure frequencies and severity including type of seizure, seizure-related AEs, and changes in anti-epileptic medications.

[Time Frame: from the first dose of study drug until the date of first documented disease progression, average 2 years]

25. Part 2: Safusidenib PK Profile
Defined as safusidenib concentrations and PK parameters.

[Time Frame: from the first dose of study drug through 20 weeks]

26. Part 3: ORR, assessed by the Investigator
ORR, defined as the proportion of participants with the confirmed best overall response of CR, PR, or MR per RANO 2.0, as assessed by the Investigator.

27. Part 3: DOR, assessed by BICR and the Investigator
DOR, the time from the first documentation of objective response (CR, PR, or MR) to the date of the first documentation of disease progression per RANO 2.0, or death (by any cause in the absence of progression), as assessed by the BICR and the Investigator.

28. Part 3: Time to Next Intervention (TTNI)
TTNI, defined as the time from the first dose of study drug to initiation of the first subsequent anticancer therapy.

29. Part 3: PFS assessed by BICR and the Investigator.
PFS, defined as the time from the first dose of study drug to the date of the first documented disease progression per RANO 2.0, or death (by any cause in the absence of disease progression), as assessed by BICR and the Investigator.

30. Part 3: DCR assessed by BICR and by the Investigator
DCR, defined as the proportion of participants with a best overall response of CR, PR, MR, or SD per RANO 2.0, as assessed by the Investigator and BICR

31. Part 3: Time to Response (TTR) assessed by BICR and by the Investigator
TTR, defined as the time from the first dose of study drug to the first documentation of objective response (CR, PR, or MR) per RANO 2.0, as assessed by the BICR and the Investigator.

32. Part 3: Overall Survival (OS)
OS, defined as the time from the first dose of study drug to death from any cause.

33. Part 3: Safety and tolerability
AEs graded by NCI CTCAE v5.0, laboratory abnormalities as graded by NCI CTCAE v5.0, vital signs, physical examinations, and ECGs.

34. Part 3: Safusidenib PK Profile
Defined as safusidenib concentrations and PK parameters.[Time Frame: from the first dose of study drug through 20 weeks]

35. Part 3: Health-related quality of life
The Functional Assessment of Cancer Therapy-Brain (FACT-Br) and the Quality of Life in Epilepsy (QOLIE-10-P) questionnaires.

36. Part 3: Seizure Activity
Defined as seizure frequencies and severity including type of seizure, seizure-related AEs, and changes in anti-epileptic medications.

[Time Frame: from the first dose of study drug until the date of first documented disease progression, average 2 years]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Sex: All

Gender Based: No

Accepts Healthy Volunteers: No

Criteria: Key Inclusion Criteria for Part 1:

1. Patient must be ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Patient must have histologically confirmed recurrent or progressive WHO Grade 2 glioma or Grade 3 glioma with IDH1 R132H or R132C mutation confirmed by immunohistochemistry or molecular genetic testing.
3. The IDH mutation, and other applicable gene/molecular alterations (see Table 10-2) are determined by a validated assay as performed in Clinical Laboratory Improvement Amendments (CLIA)-certified/College of American Pathologists (CAP)-accredited or locally equivalent clinical laboratories. Prior clinical pathology report fulfilling the diagnosis criteria prior to screening with tumor samples collected is acceptable for patient enrollment in both Part 1 and Part 2.
4. Patient has received no more than 2 prior therapies for disease recurrence/progression.
5. Patient has disease recurrence or progression or cannot tolerate the most recent therapy.
6. Patient must have a measurable lesion(s) as per the RANO-HGG criteria for primarily enhancing lesions or RANO-LGG criteria for primarily non-enhancing lesions. The lesion (s) must be visible on 2 or more axial slices and have perpendicular diameters of at least 10 × 10 mm. The definition of primarily enhancing lesions or primarily non-enhancing lesions is referred to Section 8.3.1.

Key Inclusion Criteria for Part 2 and 3:

1. Must be ≥18 years old at the time of signing the ICF.
2. Must agree to submit sufficient tumor tissue for retrospective biomarker and histological analyses. This requirement may be waived in rare circumstances with approval by the Sponsor.
3. Has adequate hematologic and organ function

Key Inclusion Criteria for Part 2:

1. Diagnosis of histologically confirmed IDH1-mutant Grade 2, Grade 3 with high risk features or Grade 4 astrocytoma, per WHO 2021 classification and Investigator Assessment.
2. Have an IDH1 mutation (R132H/C/G/S/L) based on IHC (R132H only), polymerase chain reaction (PCR), or next-generation sequencing (NGS). CDKN2A/B status and at least 1 of the following must be confirmed: absence of 1p19q co-deletion by fluorescence in situ hybridization, array comparative genomic hybridization, or NGS; presence of an ATRX loss of function mutation by NGS; or loss of normal ATRX expression by IHC. A validated assay performed in a CLIA-certified/CAP-accredited (or local equivalent) clinical laboratory must be used for all of the aforementioned results. Documentation of biomarker status, including redacted molecular pathology and NGS reports, must be provided during Screening.
3. Must not have experienced tumor recurrence or progression between first day of radiotherapy and randomization by local assessment per RANO 2.0.

4. Participants must have completed radiation therapy with a minimum of 80% of planned treatment completed (with or without concurrent temozolomide) and between 6 and 12 cycles of adjuvant . Randomization must occur at least 28 days and not more than 75 days after the final dose of temozolomide.

Key Inclusion Criteria for Part 3:

1. Have had at least 1 prior surgery for glioma (biopsy, sub-total resection, or gross total resection), with the most recent surgery having occurred at least 90 days and no longer than 5 years before the date of enrollment, have not had any other prior anticancer therapy, including chemotherapy and radiotherapy, and are not in need of immediate chemotherapy or radiotherapy in the opinion of the Investigator.
2. Have histologically confirmed Grade 3 IDH-mutant oligodendroglioma according to WHO 2021 criteria per local assessment.
3. Have residual or recurrent measurable disease per RANO 2.0 and confirmed by BICR, at the time of enrollment.
4. Have an IDH1 mutation (R132H/C/G/S/L). The presence of 1p19q co-deletion must also be confirmed. All results must be generated using a validated assay performed in a CLIA-certified/CAP-accredited (or local equivalent) clinical laboratory.

Key Exclusion Criteria for Part 1:

1. Prior anti-cancer therapy, within the applicable periods shown below, before the start of the protocol treatment:
2. Systemic drug therapies: within 3 weeks (lomustine within 6 weeks)
3. Surgery: within 3 weeks
4. Radiation therapy: within 12 weeks
5. Investigational agents: within 5 half-lives for other investigational agents
6. Patient did receive the prior therapy targeted to IDH1 mutation..
7. Known hypersensitivity to safusidenib or to any drug with similar chemical structure or to any other excipient present in the pharmaceutical form of safusidenib.

Key Exclusion Criteria for Part 2 and 3:

1. Participants with prior or anticipated treatment with anti-angiogenic agents such as Avastin (bevacizumab), agents known to target IDH1 or IDH2, or investigational agents for glioma are excluded.
2. Have brainstem or spinal cord involvement either as primary location, site of multifocal involvement, or by significant tumor extension.
3. Significant functional or neurocognitive deficits, including uncontrolled seizures, that would preclude participation in protocol-defined study activities, as assessed by Investigator.
4. Evidence of diffuse leptomeningeal disease.
5. History of significant cardiac disease within 12 months prior to randomization (if applicable) or first dose of study drug (if randomization does not apply).
6. If taking corticosteroids, must be on a stable or decreasing dose for the 14 days prior to randomization (if applicable) or first dose of study drug (if randomization does not apply).
7. Participants with other malignancies must have received curative treatment and been disease-free for at least 3 years. Curatively resected skin cancer or curatively treated carcinoma in situ is allowed.
8. Have a condition that would interfere with, or increase the risk of, study participation.

Key Exclusion Criteria for Part 2

1. Participants may not have received any anticancer treatments other than surgery, radiation, concurrent/adjuvant temozolomide, and

tumor-treating fields. Tumor-treating fields must be discontinued prior to randomization.

Key Exclusion Criteria for Part 3:

1. Participants may not have received any prior anticancer therapy other than surgery (biopsy, sub-total, or gross total resection) for treatment of glioma, including radiotherapy.

Contacts/Locations

Central Contact Person: Clinical Trials at Nuvation Bio
Telephone: 332-208-6102
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IPD Sharing

Plan to Share IPD: No

References

Citations:

Links:

Available IPD/Information: