NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Siponimod.

Trial Indication(s)

Intracerebral hemorrhage (ICH)

Protocol Number

CBAF312X2207

Protocol Title

A phase II, patient- and investigator-blinded, randomized, placebo-controlled study to evaluate efficacy, safety and tolerability of BAF312 (siponimod) in patients with stroke due to intracerebral hemorrhage (ICH)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: December 2017 (Actual)
Primary Completion Date: May 2020 (Actual)
Study Completion Date: May 2020 (Actual)

Reason for Termination (If applicable)

The trial was terminated due to lack of potential efficacy.

Study Design/Methodology

Intracerebral hemorrhage (ICH) participants were randomized at 1:1 ratio into either the active treatment or placebo group. Participants were receiving standard of care. Participants received an intravenous infusion (i.v.) treatment within 24 hours of an ICH event and were up titrated for 7 days. Following the i.v. treatment, participants received 10 mg BAF312 or placebo in tablet form (taken daily orally) for an additional 7 days. Participants were followed for an additional 76 days after treatment for neurological and safety conditions during three clinic visits.

Recruitment for the trial was put on hold due to the COVID-19 pandemic. Those patients who had been enrolled in the trial completed the protocol as planned. After nine months of the trial being on hold, an Interim analysis was conducted and reviewed by the Data Monitoring Committee. Novartis terminated the trial due to lack of potential efficacy.

Centers

United States(11)

Objectives:

Primary:

To obtain the first efficacy estimate of 10 mg BAF312 daily (7 days i.v. with titration followed by 7 days p.o.) compared to placebo on reducing absolute perihematoma edema (aPHE) volume on Day 14 after ICH

Secondary:

To evaluate the pharmacokinetics of BAF312 in ICH patients

Test Product (s), Dose(s), and Mode(s) of Administration

BAF312/placebo concentrate for solution for infusion: 4.5/0 mg / 4.5 mL and BAF312/placebo film-coated tablets: 2/0mg

Statistical Methods

For the primary objective, the log-transformed absolute PHE volume on Day 14 was analyzed using analysis of covariance (ANCOVA) model, with treatment as a classification factor and the baseline log-transformed aPHE as covariate. The mean difference (BAF312 vs. placebo) and its 90% CI were calculated, and these estimates were back-transformed to give adjusted geometric mean and the respective CV along with a geometric mean ratio and two-sided 90% CI of BAF312 vs. placebo. One-sided *p-value* was provided to test superiority of BAF312 to placebo.

Descriptive statistics will be presented for plasma concentrations of BAF312 (concentration vs time) when available. summary descriptive

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
ICH patients eligible for inclusion in this study must fulfill all of the following criteria:
1. Male or female patients aged 18 to 85 years (inclusive).
2. Written informed consent obtained before any study assessment is performed. If the patient is not able to give the informed consent personally, consent by a relative or legal representative is acceptable.
3. Spontaneous, supratentorial intracerebral hemorrhage in cerebral cortex or deep brain structures (putamen, thalamus, caudate, and associated deep white matter tracts) with a volume ≥ 10 mL but ≤ 60 mL (calculated by the ABC/2 method, after Kothari et al 1996) determined by routine clinical MRI or CT.
4. Patients with the onset of ICH witnessed and/or last seen healthy no longer than 24 hrs previously.
5. Patients with Glasgow Coma Scale (GCS) best motor score no less than 5 (brings hands above clavicle on stimulus to head or neck).

Exclusion Criteria:
ICH patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline (for biologics), whichever is longer.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g., fingolimod).
3. Current use of concomitant medications with potent CYP2C9/3A4 inhibitory or induction potential.
4. Infratentorial (midbrain, pons, medulla, or cerebellum) ICH.
5. Candidates for surgical hematoma evacuation or other urgent surgical intervention (i.e., surgical relief of increased intracranial pressure) on initial presentation. If during the treatment period surgical hematoma evacuation or surgical intervention to lower intracranial pressure becomes indicated, the investigational treatment should be stopped.
6. Patients with intraventricular hemorrhage (IVH) having a Graeb score of >3 on initial presentation. Patients must not have blood in the 4th ventricle and may only have blood in the 3rd ventricle in the absence of ventricular expansion. Trace or mild hemorrhage in either or both lateral ventricles is permitted. Patients with hydrocephalus determined radiologically on initial presentation are excluded regardless of Graeb score.
7. Secondary ICH due to:
- aneurysm
- brain tumor
- arteriovenous malformation
- thrombocytopenia, defined as platelet count of <150,000/µl
- known history of coagulopathy
- acute sepsis
- traumatic brain injury (TBI)
- disseminated intravascular coagulation (DIC)
8. Prior disability due to other disease compromising mRS evaluation, thereby interfering with the primary outcome, operationally defined as an estimated mRS score (by history) of ≥ 3 before ICH for patients less than or equal to 80 years of age. For ICH patients 81-85 years of age, estimated mRS by history prior to ICH must be less than or equal to 1 (no significant disability despite symptoms).
9. Preexisting unstable epilepsy.
10. Patients with active systemic bacterial, viral or fungal infections.
11. Concomitant drug-related exclusion criteria:
- Intravenous immunoglobulin, immunosuppressive and/or chemotherapeutic medications.
- Moderate immunosuppressives (e.g. azathioprine, methotrexate) and/or fingolimod within 2 months prior to randomization.
- Stronger immunosuppressives (e.g. cyclophosphamide, immunosuppressive mAb) within (minimally) 6 months prior to randomization, or longer with long-lasting immunosuppressive medications as determined by the investigator.
12. Cardiovascular exclusion criteria:
- Cardiac conduction or rhythm disorders including sinus arrest or sino-atrial block, heart rate <50 bpm, sick-sinus syndrome, Mobitz

Type II second degree AV block or higher grade AV block, or preexisting atrial fibrillation (either by history or observed at screening).
- PR interval >220 msec. Long QT syndrome or QTcF prolongation >450 msec in males or >470 msec in females on screening electrocardiogram (ECG).
- Patients receiving treatment with QT-prolonging drugs having a long half-life (e.g., amiodarone).
13. Any of the following abnormal laboratory values prior to randomization:
- White blood cell (WBC) count < 2,000/µl (< 2.0 x 109/L)
- Lymphocyte count < 800/µl (< 0.8 x 109/L)
14. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
15. Patients with any other medically unstable condition or serious laboratory abnormality as determined by the investigator.

Participant Flow Table

Treatment Period

	BAF312	Placebo	Total
Arm/Group Description	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally - matching placebo	
Started	16	13	29
Completed	8	10	18
Not Completed	8	3	11
Withdrawal by Subject	1	1	2
Adverse Event	0	2	2

Protocol deviation	1	0	1
Physician Decision	2	0	2
Subject failed swallow test	4	0	4

Safety Follow-Up Period

	BAF312	Placebo	Total
Arm/Group Description	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally - matching placebo	
Started	16	13	29
Completed	14	12	26
Not Completed	2	1	3
Adverse Event	0	1	1
Protocol deviation	1	0	1
Lost to Follow-up	1	0	1

Baseline Characteristics

	BAF312	Placebo	Total
Arm/Group Description	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally - matching placebo	
Number of Participants [units: participants]	16	13	29
Age Continuous (units: years) Mean ± Standard Deviation			
	58.3±13.6	63.8±9.06	60.8±11.66
Sex: Female, Male (units:) Count of Participants (Not Applicable)			
Female	10	6	16
Male	6	7	13
Race/Ethnicity, Customized (units: Participants)			
Caucasian	8	11	19
Black	5	0	5
Asian	0	1	1
Other	3	1	4
Absolute perihematoma edema (aPHE) volume (units: mL) Mean ± Standard Deviation			

32.927±32.3153	22.825±9.8617	28.237±24.7188

Primary Outcome Result(s)

Absolute perihematoma edema (aPHE) volume measured by Computed Tomography (CT) scan after intracerebral hemorrhage (ICH)

(Time Frame: On Day 14 following ICH)

	BAF312	Placebo
Arm/Group Description	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally - matching placebo
Number of Participants Analyzed [units: participants]	14	13
Absolute perihematoma edema (aPHE) volume measured by Computed Tomography (CT) scan after intracerebral hemorrhage (ICH) (units: mL) Geometric Mean (90% Confidence Interval)		

	55.09 (42.444 to 71.509)	52.50 (40.042 to 68.835)

Statistical Analysis

Groups	BAF312, Placebo
P Value	0.585
Method	ANCOVA
Other Geo-mean ratio	1.05
90 % Confidence Interval 2-Sided	0.717 to 1.535

Secondary Outcome Result(s)

Plasma BAF312 concentrations

(Time Frame: Days 1, 8, and 14)

	BAF312
Arm/Group Description	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally
Number of Participants Analyzed [units: participants]	

Plasma BAF312 concentrations (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)

Safety Results

All-Cause Mortality

	BAF312 N = 16	**Placebo N = 13**	**Total N = 29**
Arm/Group Description	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally - matching placebo	Total
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment (14 days) plus 76 days post treatment, up to approximately of 90 days
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment

	BAF312 N = 16	**Placebo N = 13**	**Total N = 29**
Arm/Group Description	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally - matching placebo	Total
Total participants affected	2 (12.50%)	2 (15.38%)	4 (13.79%)
Cardiac disorders			
Acute myocardial infarction	1 (6.25%)	0 (0.00%)	1 (3.45%)
Cardiomyopathy	1 (6.25%)	0 (0.00%)	1 (3.45%)
Infections and infestations			
Pneumonia	0 (0.00%)	1 (7.69%)	1 (3.45%)
Septic shock	0 (0.00%)	1 (7.69%)	1 (3.45%)
Neoplasms benign, malignant and			

unspecified (incl cysts and polyps)			
Neoplasm	0 (0.00%)	1 (7.69%)	1 (3.45%)
Nervous system disorders			
Ischaemic stroke	1 (6.25%)	0 (0.00%)	1 (3.45%)
Renal and urinary disorders			
Renal failure	1 (6.25%)	0 (0.00%)	1 (3.45%)
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration	1 (6.25%)	0 (0.00%)	1 (3.45%)
Respiratory failure	1 (6.25%)	1 (7.69%)	2 (6.90%)
Vascular disorders			
Hypotension	0 (0.00%)	1 (7.69%)	1 (3.45%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment (14 days) plus 76 days post treatment, up to approximately of 90 days
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	BAF312 N = 16	**Placebo N = 13**	**Total N = 29**

Arm/Group Description	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally	Days 1 – 7, IV up titration; days 8 – 14, 10 mg (5 x 2 mg tablets) taken daily orally - matching placebo	Total
Total participants affected	14 (87.50%)	11 (84.62%)	25 (86.21%)
Blood and lymphatic system disorders			
Anaemia	0 (0.00%)	1 (7.69%)	1 (3.45%)
Leukocytosis	1 (6.25%)	0 (0.00%)	1 (3.45%)
Leukopenia	1 (6.25%)	0 (0.00%)	1 (3.45%)
Lymphopenia	1 (6.25%)	0 (0.00%)	1 (3.45%)
Thrombocytopenia	1 (6.25%)	1 (7.69%)	2 (6.90%)
Cardiac disorders			
Bradycardia	5 (31.25%)	0 (0.00%)	5 (17.24%)
Ventricular tachycardia	1 (6.25%)	0 (0.00%)	1 (3.45%)
Eye disorders			
Dry eye	0 (0.00%)	1 (7.69%)	1 (3.45%)
Gastrointestinal disorders			
Constipation	2 (12.50%)	2 (15.38%)	4 (13.79%)
Dyspepsia	0 (0.00%)	1 (7.69%)	1 (3.45%)
Vomiting	1 (6.25%)	1 (7.69%)	2 (6.90%)

General disorders and administration site conditions			
Infusion site extravasation	2 (12.50%)	0 (0.00%)	2 (6.90%)
Infusion site irritation	0 (0.00%)	1 (7.69%)	1 (3.45%)
Injection site swelling	1 (6.25%)	0 (0.00%)	1 (3.45%)
Pain	1 (6.25%)	0 (0.00%)	1 (3.45%)
Peripheral swelling	1 (6.25%)	0 (0.00%)	1 (3.45%)
Pyrexia	0 (0.00%)	1 (7.69%)	1 (3.45%)
Swelling face	0 (0.00%)	1 (7.69%)	1 (3.45%)
Infections and infestations			
Conjunctivitis	0 (0.00%)	1 (7.69%)	1 (3.45%)
Pneumonia	0 (0.00%)	1 (7.69%)	1 (3.45%)
Urinary tract infection	0 (0.00%)	1 (7.69%)	1 (3.45%)
Investigations			
Blood bicarbonate decreased	1 (6.25%)	0 (0.00%)	1 (3.45%)
Computerised tomogram abnormal	0 (0.00%)	1 (7.69%)	1 (3.45%)
Transaminases increased	1 (6.25%)	0 (0.00%)	1 (3.45%)
Metabolism and nutrition disorders			
Dyslipidaemia	1 (6.25%)	0 (0.00%)	1 (3.45%)
Hypercalcaemia	0 (0.00%)	1 (7.69%)	1 (3.45%)
Hyperchloraemia	0 (0.00%)	1 (7.69%)	1 (3.45%)

Hyponatraemia	1 (6.25%)	0 (0.00%)	1 (3.45%)
Musculoskeletal and connective tissue disorders			
Back pain	1 (6.25%)	0 (0.00%)	1 (3.45%)
Muscular weakness	1 (6.25%)	0 (0.00%)	1 (3.45%)
Pain in extremity	1 (6.25%)	0 (0.00%)	1 (3.45%)
Nervous system disorders			
Aphasia	1 (6.25%)	0 (0.00%)	1 (3.45%)
Cerebral haemorrhage	1 (6.25%)	0 (0.00%)	1 (3.45%)
Dizziness	1 (6.25%)	0 (0.00%)	1 (3.45%)
Facial paralysis	1 (6.25%)	0 (0.00%)	1 (3.45%)
Headache	1 (6.25%)	2 (15.38%)	3 (10.34%)
Hydrocephalus	1 (6.25%)	0 (0.00%)	1 (3.45%)
Psychiatric disorders			
Agitation	0 (0.00%)	2 (15.38%)	2 (6.90%)
Confusional state	1 (6.25%)	0 (0.00%)	1 (3.45%)
Depression	2 (12.50%)	0 (0.00%)	2 (6.90%)
Hallucination, visual	1 (6.25%)	0 (0.00%)	1 (3.45%)
Insomnia	0 (0.00%)	2 (15.38%)	2 (6.90%)
Restlessness	1 (6.25%)	0 (0.00%)	1 (3.45%)
Sleep disorder	2 (12.50%)	0 (0.00%)	2 (6.90%)
Renal and urinary disorders			
Acute kidney injury	0 (0.00%)	1 (7.69%)	1 (3.45%)
Azotaemia	1 (6.25%)	1 (7.69%)	2 (6.90%)

Urinary retention	1 (6.25%)	2 (15.38%)	3 (10.34%)
Respiratory, thoracic and mediastinal disorders			
Atelectasis	1 (6.25%)	0 (0.00%)	1 (3.45%)
Pneumonia aspiration	0 (0.00%)	1 (7.69%)	1 (3.45%)
Pulmonary oedema	1 (6.25%)	0 (0.00%)	1 (3.45%)
Respiratory failure	0 (0.00%)	1 (7.69%)	1 (3.45%)
Rhonchi	0 (0.00%)	1 (7.69%)	1 (3.45%)
Skin and subcutaneous tissue disorders			
Rash	1 (6.25%)	0 (0.00%)	1 (3.45%)
Rash papular	0 (0.00%)	1 (7.69%)	1 (3.45%)
Vascular disorders			
Hypertension	1 (6.25%)	0 (0.00%)	1 (3.45%)

Other Relevant Findings

Conclusion:

Recruitment for the trial was put on hold due to the COVID-19 pandemic. Patients that were enrolled in the trial completed the protocol as planned. After nine months of the trial being on hold, an Interim analysis was conducted and reviewed by the Data Monitoring Committee. Novartis terminated the trial due to low probability of observing benefit for the patient population. There were no new safety issues raised for BAF312

Date of Clinical Trial Report

Draft May 11, 2021