Novartis Clinical Trial Results

Sponsor

Novartis

Name of Active Ingredient

BAF312

Trial Indication(s)

No applicable.

Protocol Number

CBAF312A2104

Protocol Title

An open label, single oral dose study to investigate the absorption, pharmacokinetics, distribution, metabolism, and elimination of 10 mg of [^{14}C]BAF312 in healthy male subjects

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

23-Jun-2009 to 11-Aug-2009

Reason for Termination

Not applicable.

Study Design/Methodology

A single-center, open-label study in healthy male subjects administered a single oral ^{14}Cradiolabeled dose of 10 mg BAF312.

Centers

1 center in 1 country: Netherlands (1)

Objectives:

Primary objective(s)

- To identify and quantify the metabolites of BAF312 in plasma, urine and feces and to compare the human metabolite patterns to those obtained from animal species used in toxicology studies
- To determine the rate and routes of excretion and the mass balance by total radioactivity in urine and feces.
- To evaluate the absorption of unchanged drug and total radioactivity as feasible, from available urinary and fecal excretion data.
- To elucidate the key biotransformation pathways and clearance mechanisms of BAF312 in man.
- To determine the pharmacokinetics of total radioactivity of BAF312, and of any important metabolites in plasma

Secondary objective(s)

Not applicable.

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

The radiolabeled drug in solid from was provided by Novartis Pharma (Isotope Laboratory) in individual glass bottles each containing a dose of 10 mg/2 mL [14C]BAF312 as a concentrate for oral solution.

Statistical Methods

Summary statistics (including mean and SD) for demographic and baseline characteristics, safety assessments, pharmacokinetic and ADME measurements. No formal inferential statistical analysis was performed. The number of subjects with adverse events were counted by body system and preferred term.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

This study was performed in four healthy, male volunteers aged 18 – 55 years who were CYP2C9 wild-type (CYP2C9*1*1 carriers i.e. subjects without a *2 or *3 allele).

Exclusion criteria

• Subjects who refused genotype testing at screening or who were homo- or heterozygote for CYP2C9*3 and CYP2C9*2.
• Hemoglobin levels below 8.1 mmol/L at screening.
• Absence of regular defecation pattern (subjects producing stools every second or third day).
• Subjects who were subject to relevant radiation exposure (>0.2 mSv) within 12 months prior to scheduled dosing with [^{14}C]BAF312, e.g. due to systemic administration of radioactive substances, or to external irradiation (e.g. by X-rays), for diagnostic, therapeutic or research purposes (for comparison: standard thorax or mammary X-rays cause 0.1-0.2 mSv).

Participant Flow Table

	[^{14}C]BAF312 10mg
Patients	
Randomized	4
Completed	4
Discontinued	0

NOVARTIS

Baseline Characteristics

Demographic summary

		[^{14}C]BAF312 10mg N=4
Age (years)	Mean (SD)	35.8 (18.37)
	Range	18-54
Gender-n(%)	Male	4 (100.0%)
Race-n(%)	Caucasian	4 (100.0%)
Ethnicity-n(%)	Other	4 (100.0%)
Weight (kg)	Mean (SD)	77.5 (8.11)
	Median	78.7
	Range	67.2-85.5
Height (cm)	Mean (SD)	183.0 (6.48)
	Median	183.5
	Range	176-189
BMI (kg/m^2)	Mean (SD)	23.11 (1.487)
	Median	23.60
	Range	20.97-24.28

BMI = body mass index

NOVARTIS

Primary Outcome Result(s)

Main pharmacokinetic parameters of radioactivity and BAF312 in blood and plasma

Means * (SD) of N=4 subjects, based on non-compartmental analysis.

PK Parameter		Blood radioactivity	Plasma radioactivity	Plasma BAF312
Tmax	[h] (median; range)	6; all	6; all	4; 4-6
Cmax	[ng/mL] *	86.6	131	80.4
Tlast	[h] (range)	216-480	312-480	216-480
AUClast	[ng·h/mL] [b, c]	4900	7650	3196
T1/2	[h]	156	171	56.6
typical time interval	[h]	192-312	240-482	144-216
AUCinf [d]	[ng·h/mL] [b, c]	5530	8270	3226
	[% of ^{14}C-AUCinf plasma]	67	--	38
AUC%Extrap	[% of AUCinf]	12.5	8.26	0.952
Vz/F	L	--	--	291
CL/F	[L/h]	--	--	3.97

a: for radioactivity: [ng-eq/mL]
b: for radioactivity: [ng-eq·h/mL].
c: AUClast were calculated using the linear trapezoidal rule.
d: AUCinf= AUClast+ AUCt-inf ; AUCt-inf = Clast ·T1/2/ ln2.
e: mean values are means of individual values.
-- : not calculable, not meaningful.

Mean excretion of radioactivity in urine and feces

Means (SD) of N=4 subjects

Time Period	^{14}C-Excretion [% of dose]					
[h]	Urine		Feces		Total	
0 - 216	3.61	(0.37)	84.1	(3.47)	87.7	(3.69)
0 - 312	3.70	(0.35)	86.7	(2.46)	90.4	(2.71)

AUC0-120h of BAF312 and its metabolites in plasma

Peak	Compound / Metabolite	AUC0-120h Min (nmol·h/L)	Max (nmol·h/L)	mean ± SD, N=4 [a,b] (nmol·h/L)		(% of total ^{14}C)	
P29.6	Unknown	267	491	378	± 103	3.72	±1.49
P30.5	Unknown	111	244	192	± 57.4	1.82	±0.467
M3	Glucuronide of M5	1690	2260	1850	± 268	18.4	±5.11
M5	Formed by hydroxylation	122	188	156	± 29.0	1.51	±0.343
M6	Formed by hydroxylation	135	213	170	± 39.9	1.63	±0.326
M7	Formed by hydroxylation	175	361	282	± 87.8	2.75	±1.11
BAF312	Parent drug	4350	10600	6320	± 2920	57.1 [c]	±5.91
P73.0	Formed during sample processing	91.0	275	190	± 91.7	1.74	±0.623
	Sum of unknown trace metabolites	176	231	204	± 29.8	2.02	±0.592
	Lost during sample processing and HPLC	622	1900	1040	± 578	9.30	±2.10
Total ^{14}C (total of radiolabeled components)		8200	16100	10800	± 3700	100	–

a: mean values of N=4 subjects.
b: mean values are means of individual values.
c: 58.8%, incl.P73 formed by methyl-esterification of parent drug during sample preparation.
--: not calculable, not meaningful.

Relative exposure of metabolites in comparison to BAF312

Peak	AUCinf [a,b] (nmol·h/L)	Percentage of parent drug AUC (%)	T1/2 , mean [a] (h)
P29.6 [c]	378	5.8	–
P30.5 [c]	192	2.9	–
M3	1998	27.6	29.3
M5	173	2.4	34.0
M6	180	2.5	31.6
M7	320	4.4	35.2
BAF312 [d]	7240	100.0	33.3

a: mean values of N=4 subjects.
b: AUCinf= AUClast+ AUCt-∞ ; AUCt-∞ = Clast ·T1/2/ ln2.
c: AUC0-120h used for metabolite and parent drug [d], AUCinf and T1/2 not calculable due to high percentage of extrapolation.
d: BAF312 and P73.0 summarized.
--: not calculable, not meaningful.

Secondary Outcome Result(s)

Not applicable.

NOVARTIS

Safety Results

Serious Adverse Events by System Organ Class

No deaths and no serious adverse events were reported in the study.

Summary of number of subjects with adverse events by treatment

	[14C]BAF312 10mg N=4	
Body system/ Preferred Term	**n**	**(%)**
-Any body system		
-Total	3	(75.0)
GASTROINTESTINAL DISORDERS		
-Total	1	(25.0)
Diarrhea	1	(25.0)
Vomiting	1	(25.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
-Total	2	(50.0)
Asthenia	2	(50.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
-Total	1	(25.0)
Arthropod Bite	1	(25.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
-Total	1	(25.0)
Myalgia	1	(25.0)
NERVOUS SYSTEM DISORDERS		
-Total	3	(75.0)
Headache	3	(75.0)
Somnolence	2	(50.0)

Conclusion:

• The tolerability of BAF312 10 mg was in line with the known safety profile at that dose level. Intermittent bradycardia and one episode on AV block second degree have been clinically well tolerated.
• Peak concentrations of BAF312 and total radiolabeled components (radioactivity) after oral dosing of 10 mg [14C]BAF312 showed substantial systemic availability of BAF312.
• The extent of oral absorption was estimated to be higher than 70% of the administered dose.
• The apparent terminal half-lifes of total radiolabeled components (radioactivity) and BAF312 in plasma were 171 and 56.6 hours, respectively. For the metabolites M3, M5, M6, and M7 the apparent elimination half-lifes ranged between 29.3 and 35.2 hours. Hence, unexpectedly high accumulation of BAF312 and/or its metabolites M3, M5, M6, and M7 is not anticipated following once daily oral dosing of BAF312 in patients.
• The most abundant radioactive component in plasma was unchanged BAF312 (57.1% of the radioactivity AUC0-120). The metabolite M3 (formed by glucuronidation of the hydroxylated metabolite M5) was the main metabolite and accounted for 18.4% of the radioactivity AUC0-120h (27.6% of the exposure to BAF312).
• The pharmacokinetic parameters of radioactivity and BAF312 in plasma and blood displayed moderate variabilities (≦59%).
• The apparent distribution volume of BAF312 was moderate (mean 291 L).
• BAF312 and its metabolites were mainly confined with the plasma compartment. BAF312 and/or its metabolites displayed no special affinity to erythrocytes.
• The biotransformation of BAF312 occurred by essentially by the following pathways: The phase I metabolic reactions involved C-hydroxylations (M5, M6 and M7), cleavage/hydrolysis at the oxime ether bound (M1, M2) and further reduction yielding metabolite M8. Phase II reactions involved sulfation (M4) and glucuronidation (M3 and M12) of hydroxylated metabolites.
• The apparent clearance of BAF312 was low (mean CL/f = 4.0 L/h).
• BAF312 was eliminated from the systemic circulation mainly due to metabolism, and subsequent biliary/fecal excretion.
• Renal excretion of radioactivity was mainly in the form of hydroxylated glucuronide M3 (2.1% of the dose).
• Excretion of radioactivity was close to complete after 13 days (88.2% - 93.3% of the dose).

Date of Clinical Trial Report

01-Feb-2010

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230
Swissmedic Approval Date: 22-Oct-2020

Novartis Study Code

CBAF312A2104

EudraCT Number

2009-010820-24

Planned and Actual Number of Patients

Planned: 4 subjects

Enrolled: 4 subjects

Batch Numbers

Batch no. Y113 0609

Information on comparators drug dosage, route of administration, batch numbers

Not applicable.

Publication(s)

Glaenzel U, Jin Y, Nufer R, Li W, Schroer K, Adam-Stitah S, van Marle SP, Legangneux E, Borell H, James AD, Meissner A, Camenisch G, Gardin A. Metabolism and Disposition of Siponimod, a Novel Selective S1P 1/S1P 5 Agonist, in Healthy Volunteers and In Vitro Identification of Human Cytochrome P450 Enzymes Involved in Its Oxidative Metabolism. Drug Metab Dispos. 2018 Jul;46(7):1001-1013. doi: 10.1124/dmd.117.079574. Epub 2018 May 7.

NOVARTIS

Investigators & Information on Study Centers

Investigator	**Facility Name** **Address** **Country**
Dr Sjoerd van Marle	Pharmaceutical research Associates group B.V. Zuidlaren, The Netherlands