Clinical trial results:
An open-label, randomized three period cross-over relative bioavailability study to compare the pharmacokinetic parameters of a lower dose formulation of ambrisentan (GSK1325760) with marketed ambrisentan in healthy adult participants

Summary

EudraCT number	2019-001699-12
Trial protocol	GB
Global end of trial date	17 December 2019

Results information

Result version number	v1 (current)
This version publication date	06 August 2020
First version publication date	06 August 2020

Trial information

Trial identification

Sponsor protocol code	205019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@GSK.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000434-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the relative bioavailability of ambrisentan (AMB, [1 milligram (mg) x 5 tablets] administered as tablets dispersed in water or administered orally, with marketed AMB (5 mg x 1 tablet) administered orally, in healthy adult participants under fasted conditions

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	29
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a single center, open-label, randomized, single dose, 3-period crossover study in healthy participants that compared the pharmacokinetics (PK) of a new lower dose formulation (dispersed in water and administered intact orally) of ambrisentan (AMB) tablet with the reference marketed AMB tablet (administered orally).

Pre-assignment

Screening details:

A total of 29 participants were enrolled at a single center in the United Kingdom.

Period 1

Period 1 title	Period 1 (4 days) + Washout (7days)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AMB dispersed in water/AMB oral tablet/reference AMB

Arm description:

Participants received a single oral dose of 5 milligram (mg) (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single oral dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Arm title	AMB oral tablet/reference AMB/AMB dispersed in water

Arm description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Arm title	Reference AMB/AMB dispersed in water/AMB oral tablet

Arm description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Arm title	AMB dispersed in water/reference AMB/AMB oral tablet

Arm description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Arm title	AMB oral tablet/AMB dispersed in water/reference AMB

Arm description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5

intact tablets of 1 mg unit dose.

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Arm title	Reference AMB/AMB oral/AMB dispersed in water

Arm description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Number of subjects in period 1	AMB dispersed in water/AMB oral tablet/reference AMB	AMB oral tablet/reference AMB/AMB dispersed in water	Reference AMB/AMB dispersed in water/AMB oral tablet
Started	4	5	5
Completed	3	4	4
Not completed	1	1	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	-	1
Met Protocol defined Stopping Criteria	-	1	-

Number of subjects in period 1	AMB dispersed in water/reference AMB/AMB oral tablet	AMB oral tablet/AMB dispersed in water/reference AMB	Reference AMB/AMB oral/AMB dispersed in water
Started	5	5	5
Completed	5	5	5
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Met Protocol defined Stopping Criteria	-	-	-

Period 2

Period 2 title	Period 2 (4 days) + Washout (7days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AMB dispersed in water/AMB oral tablet/reference AMB

Arm description:

Participants received a single oral dose of 5 milligram (mg) (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single oral dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Arm title	AMB oral tablet/reference AMB/AMB dispersed in water

Arm description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Arm title	Reference AMB/AMB dispersed in water/AMB oral tablet

Arm description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Arm title	AMB dispersed in water/reference AMB/AMB oral tablet

Arm description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Arm title	AMB oral tablet/AMB dispersed in water/reference AMB

Arm description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Arm title	Reference AMB/AMB oral/AMB dispersed in water

Arm description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Number of subjects in period 2	AMB dispersed in water/AMB oral tablet/reference AMB	AMB oral tablet/reference AMB/AMB dispersed in water	Reference AMB/AMB dispersed in water/AMB oral tablet
Started	3	4	4
Completed	3	4	2
Not completed	0	0	2
Adverse event, non-fatal	-	-	-
Met Protocol defined Stopping Criteria	-	-	2

Number of subjects in period 2	AMB dispersed in water/reference AMB/AMB oral tablet	AMB oral tablet/AMB dispersed in water/reference AMB	Reference AMB/AMB oral/AMB dispersed in water
Started	5	5	5
Completed	5	4	5
Not completed	0	1	0
Adverse event, non-fatal	-	1	-
Met Protocol defined Stopping Criteria	-	-	-

Period 3

Period 3 title	Period 3 (4 days) + Follow-up (14 days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	AMB dispersed in water/AMB oral tablet/reference AMB

Arm description:

Participants received a single oral dose of 5 milligram (mg) (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single oral dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Arm title	AMB oral tablet/reference AMB/AMB dispersed in water

Arm description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5

tablets of 1 mg unit dose dispersed in water.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Arm title	Reference AMB/AMB dispersed in water/AMB oral tablet

Arm description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Arm title	AMB dispersed in water/reference AMB/AMB oral tablet

Arm description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

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Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
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Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Arm title	AMB oral tablet/AMB dispersed in water/reference AMB

Arm description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Arm title	Reference AMB/AMB oral/AMB dispersed in water

Arm description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet

during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Arm type	Experimental
Investigational medicinal product name	AMB oral tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were orally administered with 5 intact tablets of 1 mg unit dose.

Investigational medicinal product name	AMB dispersed in water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB tablets were available at a unit dose strength of 1 mg. Participants were administered with 5 tablets of 1 mg unit dose dispersed in water.

Investigational medicinal product name	Reference AMB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AMB reference tablet were available as film-coated tablet at unit dose strength of 5 mg. Participants were orally administered with 1 tablet of 5 mg unit dose

Number of subjects in period 3	AMB dispersed in water/AMB oral tablet/reference AMB	AMB oral tablet/reference AMB/AMB dispersed in water	Reference AMB/AMB dispersed in water/AMB oral tablet
Started	3	4	2
Completed	3	4	2

Number of subjects in period 3	AMB dispersed in water/reference AMB/AMB oral tablet	AMB oral tablet/AMB dispersed in water/reference AMB	Reference AMB/AMB oral/AMB dispersed in water
Started	5	4	5
Completed	5	4	5

Baseline characteristics

Reporting groups	
Reporting group title	Period 1 (4 days) + Washout (7days)
Reporting group description:	
Participants received a single oral dose of AMB tablet (administered as 5 x 1 mg tablet) dispersed in water (F1) or a single dose of AMB oral tablet (administered as 5 x 1 mg tablet)administered intact (F2) or a single oral dose of reference AMB tablet (R) administered as 1 x 5 mg tablet in the following six sequences F1/F2/R, F2/R/F1, R/F1/F2, F1/R/F2, F2/F1/R and R/F2/F1.	

Reporting group values	Period 1 (4 days) + Washout (7days)	Total	
Number of subjects	29	29	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	42.3		
standard deviation	± 11.16	-	
Sex: Female, Male Units: Participants			
Female	2	2	
Male	27	27	
Race/Ethnicity, Customized Units: Subjects			
Asian – Central/South Asian Heritage	2	2	
Asian – East Asian Heritage	1	1	
White – Arabic/North African Heritage	1	1	
White – White/Caucasian/European Heritage	25	25	

End points reporting groups

Reporting group title	AMB dispersed in water/AMB oral tablet/reference AMB

Reporting group description:

Participants received a single oral dose of 5 milligram (mg) (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single oral dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB oral tablet/reference AMB/AMB dispersed in water

Reporting group description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	Reference AMB/AMB dispersed in water/AMB oral tablet

Reporting group description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB dispersed in water/reference AMB/AMB oral tablet

Reporting group description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB oral tablet/AMB dispersed in water/reference AMB

Reporting group description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	Reference AMB/AMB oral/AMB dispersed in water

Reporting group description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB dispersed in water/AMB oral tablet/reference AMB

Reporting group description:

Participants received a single oral dose of 5 milligram (mg) (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single oral dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB oral tablet/reference AMB/AMB dispersed in water

Reporting group description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	Reference AMB/AMB dispersed in water/AMB oral tablet

Reporting group description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB dispersed in water/reference AMB/AMB oral tablet

Reporting group description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB oral tablet/AMB dispersed in water/reference AMB

Reporting group description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	Reference AMB/AMB oral/AMB dispersed in water

Reporting group description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB dispersed in water/AMB oral tablet/reference AMB

Reporting group description:

Participants received a single oral dose of 5 milligram (mg) (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single oral dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB tablet in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB oral tablet/reference AMB/AMB dispersed in water

Reporting group description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	Reference AMB/AMB dispersed in water/AMB oral tablet

Reporting group description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB dispersed in water/reference AMB/AMB oral tablet

Reporting group description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water during treatment period 1 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Reporting group title	AMB oral tablet/AMB dispersed in water/reference AMB

Reporting group description:

Participants received a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 2 followed by a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet in treatment period 3. The treatment periods were

separated by a washout period of minimum 7 days.

Reporting group title	Reference AMB/AMB oral/AMB dispersed in water

Reporting group description:

Participants received a single dose of reference 5 mg (administered as 1 x 5 mg tablet) AMB oral tablet during treatment period 1 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB oral tablet administered intact in treatment period 2 followed by a single dose of 5 mg (administered as 5 x 1 mg tablet) AMB tablet dispersed in water in treatment period 3. The treatment periods were separated by a washout period of minimum 7 days.

Subject analysis set title	AMB dispersed in water
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received a single dose of 5 mg AMB tablet dispersed in water and administered orally

Subject analysis set title	AMB oral tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received a single dose of 5 mg AMB tablet administered intact orally

Subject analysis set title	Reference AMB
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received a single dose of reference 5 mg AMB tablet administered orally

Subject analysis set title	AMB dispersed in water
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received a single dose of 5 mg AMB tablet dispersed in water and administered orally

Subject analysis set title	AMB oral tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received a single dose of 5 mg AMB tablet administered intact orally

Subject analysis set title	Reference AMB
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received a single dose of reference 5 mg AMB tablet administered orally

Subject analysis set title	AMB dispersed in water
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received a single dose of 5 mg AMB tablet dispersed in water and administered orally

Subject analysis set title	AMB oral tablet
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received a single dose of 5 mg AMB tablet administered intact orally

Subject analysis set title	Reference AMB
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received a single dose of reference 5 mg AMB tablet administered orally

Primary: Maximum observed plasma concentration (Cmax) after administration of AMB under fasted condition

End point title	Maximum observed plasma concentration (Cmax) after administration of AMB under fasted condition

End point description:

Blood samples were collected at indicated time-points for PK analysis of AMB. PK parameters were calculated by standard non-compartmental analysis. PK Parameter Population included all participants who provided PK parameter data. Only those participants with data available at the specified data points were analysed.

End point type	Primary

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 18, 24, 36, 48 and 72 hours post-dose

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[1]	25[2]	26[3]	
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)	359.030 (± 15.5)	316.505 (± 19.2)	353.252 (± 29.3)	

Notes:

[1] - PK Parameter Population.

[2] - PK Parameter Population.

[3] - PK Parameter Population.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment comparison between AMB dispersed in water and reference AMB tablet using ratio of adjusted geometric mean and its corresponding 90% confidence interval has been presented

Comparison groups	Reference AMB v AMB dispersed in water
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.11

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Treatment comparison between AMB oral tablet and reference AMB tablet using ratio of adjusted geometric mean and its corresponding 90% confidence interval has been presented

Comparison groups	AMB oral tablet v Reference AMB
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	0.91

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.85
upper limit	0.98

Primary: Time to Cmax (Tmax) after administration of AMB under fasted condition

End point title	Time to Cmax (Tmax) after administration of AMB under fasted condition[4]

End point description:

Blood samples were collected at indicated time-points for PK analysis of AMB. PK parameters were calculated by standard non-compartmental analysis. Only those participants with data available at the specified data points were analysed.

End point type	Primary

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 18, 24, 36, 48 and 72 hours post-dose

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this endpoint.

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[5]	25[6]	26[7]	
Units: Hour				
median (full range (min-max))	1.000 (0.50 to 2.00)	2.000 (1.00 to 4.00)	1.750 (0.50 to 8.00)	

Notes:

[5] - PK Parameter Population.

[6] - PK Parameter Population.

[7] - PK Parameter Population.

Statistical analyses

No statistical analyses for this end point

Primary: Time of last quantifiable concentration (tlast) after administration of AMB under fasted condition

End point title	Time of last quantifiable concentration (tlast) after administration of AMB under fasted condition[8]

End point description:

Blood samples were collected at indicated time-points for PK analysis of AMB. PK parameters were calculated by standard non-compartmental analysis. Only those participants with data available at the specified data points were analysed.

End point type	Primary

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 18, 24, 36, 48 and 72 hours post-dose

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this endpoint.

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[9]	25[10]	26[11]	
Units: Hour				
median (full range (min-max))	72.00 (71.5 to 72.4)	72.00 (71.5 to 72.1)	72.00 (71.5 to 72.2)	

Notes:

[9] - PK Parameter Population.

[10] - PK Parameter Population.

[11] - PK Parameter Population.

Statistical analyses

No statistical analyses for this end point

Primary: Area under the plasma concentration-time curve from time zero extrapolated to infinite time [(AUC(0-inf)] after administration of AMB under fasted condition

End point title	Area under the plasma concentration-time curve from time zero extrapolated to infinite time [(AUC(0-inf)] after administration of AMB under fasted condition

End point description:

Blood samples were collected at indicated time-points for PK analysis of AMB. PK parameters were calculated by standard non-compartmental analysis. Only those participants with data available at the specified data points were analysed.

End point type	Primary

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 18, 24, 36, 48 and 72 hours post-dose

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23[12]	19[13]	22[14]	
Units: Hours*nanogram per milliliter				
geometric mean (geometric coefficient of variation)	3006.443 (± 23.6)	2859.283 (± 21.7)	2963.908 (± 21.6)	

Notes:

[12] - PK Parameter Population.

[13] - PK Parameter Population.

[14] - PK Parameter Population.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Treatment comparison between AMB dispersed in water and reference AMB tablet using ratio of adjusted geometric mean and its corresponding 90% confidence interval has been presented

Comparison groups	AMB dispersed in water v Reference AMB

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.02
upper limit	1.09

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Treatment comparison between AMB oral tablet and reference AMB tablet using ratio of adjusted geometric mean and its corresponding 90% confidence interval has been presented

Comparison groups	AMB oral tablet v Reference AMB
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.08

Primary: Area under the plasma concentration-time curve from time zero to last time of quantifiable concentration [AUC(0-t)] after administration of AMB under fasted condition

End point title	Area under the plasma concentration-time curve from time zero to last time of quantifiable concentration [AUC(0-t)] after administration of AMB under fasted condition

End point description:

Blood samples were collected at indicated time-points for PK analysis of AMB. PK parameters were calculated by standard non-compartmental analysis. Only those participants with data available at the specified data points were analysed.

End point type	Primary

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 18, 24, 36, 48 and 72 hours post-dose

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	25	26	
Units: Hours*nanogram per milliliter				
geometric mean (geometric coefficient of variation)	2844.151 (± 22.1)	2849.378 (± 22.0)	2779.364 (± 21.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Treatment comparison between AMB dispersed in water and reference AMB tablet using ratio of adjusted geometric mean and its corresponding 90% confidence interval has been presented	
Comparison groups	AMB dispersed in water v Reference AMB
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.02
upper limit	1.08

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Treatment comparison between AMB oral tablet and reference AMB tablet using ratio of adjusted geometric mean and its corresponding 90% confidence interval has been presented	
Comparison groups	AMB oral tablet v Reference AMB
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.01
upper limit	1.07

Primary: Apparent terminal phase half-life (t1/2) after administration of AMB under fasted condition

End point title	Apparent terminal phase half-life (t1/2) after administration of AMB under fasted condition[15]

End point description:

Blood samples were collected at indicated time-points for PK analysis of AMB. PK parameters were calculated by standard non-compartmental analysis. Only those participants with data available at the specified data points were analysed.

End point type	Primary

End point timeframe:

Pre-dose, 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, 18, 24, 36, 48 and 72 hours post-dose

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this endpoint.

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	19	22	
Units: Hour				
geometric mean (geometric coefficient of variation)	19.250 (± 15.6)	18.119 (± 19.3)	18.197 (± 16.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Serious Adverse Events (SAEs) and Non-Serious Adverse Events (Non-SAEs >=2%)

End point title	Number of participants with Serious Adverse Events (SAEs) and Non-Serious Adverse Events (Non-SAEs >=2%)

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. Any untoward event resulting in death, life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, congenital anomaly/birth defect, any other situation according to medical or scientific judgment were categorized as SAE. Safety Population comprises of all randomized participants who took at least 1 dose of study intervention. Participants were analyzed according to the intervention actually received. Only those participants with data available at the specified data points were analysed.

End point type	Secondary

End point timeframe:

Up to 40 days

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[16]	25	26	
Units: Participants				
non-SAE (>=2%)	5	7	5	
SAE	0	0	0	

Notes:
[16] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Worst Case Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline

End point title	Number of Participants With Worst Case Vital Sign Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline

End point description:

Vital signs were measured in semi-supine position after 5 minutes rest and included Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Heart rate (HR). Data for number of participants with Post-Baseline worst case Vital Sign results relative to PCI Criteria relative to Baseline has been presented. Participants are counted in worst case category that their value changes to low, within range or high. Participants whose value category was unchanged (e.g., High to High), or whose value became within range, are recorded in "Within Range or No Change" category. Participants with missing baseline value are assumed as within range value. PCI ranges were: SBP [lower: <85, upper: >160 millimeter of mercury (mmHg)]; DBP (lower: <40, upper: >110 mmHg); HR (lower: <45, upper: >100 beats per minute). The value at Day 1 was considered as Baseline. Only those participants with data available at the specified data points were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 40 days

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[17]	25	26	
Units: Participants				
SBP, To Low	0	0	0	
SBP, To High	0	0	0	
DBP, To Low	0	0	0	
DBP, To High	0	0	0	
HR, To Low	2	0	0	
HR, To High	0	0	0	
SBP, Within Range or No Change	27	25	26	
DBP, Within Range or No Change	27	25	26	
HR, Within Range or No Change	25	25	26	

Notes:
[17] - Safety Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with worst case post-Baseline abnormal Electrocardiogram (ECG) Findings

End point title	Number of participants with worst case post-Baseline abnormal Electrocardiogram (ECG) Findings

End point description:

12-lead ECGs were recorded in semi-supine position after 5 minutes rest using an ECG machine that automatically calculated the heart rate and measured PR, QRS, QT and QT duration corrected for heart rate by Fridericia's formula (QTcF) intervals. Data for number of participants with abnormal clinically significant ECG findings for worst case post-Baseline has been presented. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. The value at Day 1 was considered as Baseline. Only those participants with data available at the specified data points were analysed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 40 days

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[18]	25	26	
Units: Participants				
Abnormal, not clinically significant	5	6	5	
Abnormal - clinically significant	0	0	0	

Notes:

[18] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with worst case hematology results relative to PCI criteria post-Baseline relative to Baseline

End point title	Number of participants with worst case hematology results relative to PCI criteria post-Baseline relative to Baseline

End point description:

Blood samples were collected to analyze hemoglobin, hematocrit, lymphocytes, total neutrophils, platelet count, and white blood cell(WBC) counts. PCI ranges were hematocrit (high: >0.54 proportion of red blood cells in blood and low: change from Baseline <0.075); hemoglobin(high: >180 grams per liter[g/L] and low: change from Baseline <25 g/L); lymphocytes (low: <0.8 Giga cells per liter[GI/L]); platelet count (low: <100 GI/L and high: >550 GI/L); neutrophil count (low: <1.5 GI/L); WBC count (low: <3 GI/L and high: >20 GI/L). Participants were counted in worst-case category that their value changed to low, within range or no change, or high unless there was no change in their category. Participants whose value category was unchanged (e.g., High to High), or whose value became within range, were recorded in ''To within Range or No Change' category. Baseline is defined as Day -1. Participants with data available at specified data points were presented as n= X in category titles

End point type	Secondary

End point timeframe:

Baseline (Day -1) and up to 40 days

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[19]	25	26	
Units: Participants				
Hemoglobin, To Low, , n=27, 25, 26	0	0	0	
Hemoglobin, To High, , n=27, 25, 26	0	0	0	
Hematocrit, To Low, n=27, 25, 26	0	0	0	
Hematocrit, To High, n=27, 25, 26	0	0	0	
Lymphocytes, To Low, n=27, 25, 26	0	1	0	
Lymphocytes, To High, n=27, 25, 26	0	0	0	
Neutrophil , To Low, n=27, 25, 26	1	0	1	
Neutrophil , To High, n=27, 25, 26	0	0	0	
Platelet, To Low, n=27, 24, 26	0	0	0	
Platelet, To High, n=27, 24, 26	0	0	0	
WBC, To Low, n=27, 25, 26	0	0	0	
WBC, To High, n=27, 25, 26	0	0	0	
Hemoglobin,To within Range/No Change, n=27, 25,26	27	25	26	
Hematocrit,To within Range/No Change, n=27, 25,26	27	25	26	
Lymphocytes,To within Range/No Change,n=27,25,26	27	24	26	
Neutrophil,To within Range/No Change, n=27,25,26	26	25	25	
Platelet,To within Range/No Change,n=27,24,26	27	24	26	
WBC,To within Range/No Change,n=27,25,26	27	25	26	

Notes:

[19] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with worst case clinical chemistry results relative to PCI criteria post-Baseline relative to Baseline

End point title	Number of participants with worst case clinical chemistry results relative to PCI criteria post-Baseline relative to Baseline

End point description:

Blood samples were collected to analyze PCI ranges for aspartate amino transferase (AST), alanine amino transferase (ALT), & alkaline phosphatase (ALP) (high: >=2 times (*) upper limit of normal [ULN] International units per liter [IU/L]); total bilirubin (high: >=1.5 * ULN micromoles per liter [µmol/L]); calcium (low: <2 millimoles per liter [mmol/L] & high: >2.75 mmol/L); glucose (low: <3 & high: >9 mmol/L); potassium (low: <3 & high: >5.5 mmol/L); sodium (low: <130 & high: >150 mmol/L) & Blood Urea Nitrogen (BUN) (high: >=2 * ULN µmol/L). Participants were counted in worst-case category that their value changed to (low, within range or no change, or high) unless there was no change in their category. Participants whose value category was unchanged (e.g., High to High), or whose value became within range, were recorded in the 'To within Range or No Change' category. Participants with data available at specified data points were presented as n= X in category titles

End point type	Secondary

End point timeframe:

Baseline (Day -1) and up to 40 days

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[20]	25	26	
Units: Participants				
ALP,To Low, n=27, 25, 26	0	0	0	
ALP,To High, n=27, 25, 26	0	0	0	
ALT,To Low, n=27, 25, 26	0	0	0	
ALT,To High, n=27, 25, 26	0	0	0	
AST,To Low, n=26, 25, 26	0	0	0	
AST,To High, n=26, 25, 26	0	0	0	
Bilirubin,To Low, n=27, 25, 26	0	0	0	
Bilirubin,To High, n=27, 25, 26	0	0	0	
Calcium,To Low, n=27, 25, 26	0	0	0	
Calcium,To High, n=27, 25, 26	0	0	0	
Glucose,To Low, n=27, 25, 26	0	0	0	
Glucose,To High, n=27, 25, 26	2	1	1	
Potassium,To Low, n=27, 25, 26	0	0	0	
Potassium,To High, n=27, 25, 26	0	0	0	
Sodium,To Low, n=27, 25, 26	0	0	0	
Sodium,To High, n=27, 25, 26	0	0	0	
BUN,To Low, n=27, 25, 26	0	0	0	
BUN,To High, n=27, 25, 26	0	0	0	
ALP,To within Range/No Change,n=27, 25, 26	27	25	26	
ALT,To within Range/No Change, n=27, 25, 26	27	25	26	
AST,To within Range/No Change, n=26, 25, 26	26	25	26	
Bilirubin,To within Range/No Change, n=27, 25, 26	27	25	26	
Calcium,To within Range/No Change, n=27, 25, 26	27	25	26	
Glucose,To within Range/No Change, n=27, 25, 26	25	24	25	
Potassium,To within Range/No Change, n=27, 25, 26	27	25	26	
Sodium,To within Range/No Change, n=27, 25, 26	27	25	26	
BUN,To within Range/No Change, n=27, 25, 26	27	25	26	

Notes:

[20] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Worst Case Any Increase in Urinalysis Results Post-Baseline Relative to Baseline

End point title	Number of Participants With Worst Case Any Increase in

	Urinalysis Results Post-Baseline Relative to Baseline

End point description:

Urine samples were collected for analysis of cellular casts, granular casts, hyaline casts, red blood cells. WBCs were counted as cells per high-power field (cells/HPF). Participants with worst case any increase in urinalysis results post-Baseline relative to Baseline has been presented. Baseline is defined as Day -1. Only those participants with data available at the specified data points were analysed.

End point type	Secondary

End point timeframe:

Up to 40 days

End point values	AMB dispersed in water	AMB oral tablet	Reference AMB	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3[21]	1	4	
Units: Participants				
Urine Microscopy - Cellular Casts	0	0	0	
Urine Microscopy - Granular Casts	0	0	0	
Urine Microscopy - Hyaline Casts	0	0	0	
Urine Microscopy - Red Blood Cells	0	0	0	
Urine Microscopy-WBCs (1-9 cells/HPF)	1	0	1	

Notes:

[21] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
SAEs and non-SAEs were collected from the start of study treatment until the follow up (Up to 40 days)	
Adverse event reporting additional description:	
SAEs and Non-SAEs were reported for Safety Population which comprised of all participants who received at least one dose of study intervention. Data is presented treatment wise.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	AMB dispersed in water
Reporting group description:	
Participants received a single dose of 5 mg AMB tablet dispersed in water and administered orally	
Reporting group title	Reference AMB
Reporting group description:	
Participants received a single dose of reference 5 mg AMB tablet administered orally	
Reporting group title	AMB oral tablet
Reporting group description:	
Participants received a single dose of 5 mg AMB tablet administered intact orally	

Serious adverse events	AMB dispersed in water	Reference AMB	AMB oral tablet
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	AMB dispersed in water	Reference AMB	AMB oral tablet
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 27 (18.52%)	5 / 26 (19.23%)	7 / 25 (28.00%)
Investigations			
Heart rate increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Liver function test abnormal			

subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	3 / 27 (11.11%)	2 / 26 (7.69%)	1 / 25 (4.00%)
occurrences (all)	4	2	2
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Catheter site swelling			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Feeling hot			
subjects affected / exposed	0 / 27 (0.00%)	2 / 26 (7.69%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Malaise			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 26 (7.69%)	3 / 25 (12.00%)
occurrences (all)	0	2	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported