Clinical trial results:
A Multi-centre, Randomised, Controlled, Parallel Group, Open-label Study Evaluating the Efficacy, Safety and Tolerability of Three Doses of Colestilan (MCI-196) Compared to Standard Therapy with a Calcium-based Phosphate Binder, in Paediatric Subjects with Chronic Kidney Disease Stage 5 on Dialysis and with Hyperphosphataemia

Summary

EudraCT number	2012-002581-12
Trial protocol	GB DE
Global end of trial date	26 January 2015

Results information

Result version number	v1 (current)
This version publication date	09 March 2016
First version publication date	09 March 2016

Trial information

Trial identification

Sponsor protocol code	MCI-196-E14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01814904
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mitsubishi Tanabe Pharma Corporation
Sponsor organisation address	17-10, Nihonbashi-Koamicho, Chuo-ku, Tokyo, Japan, 103-8405
Public contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd (MTPE), regulatory@mt-pharma-eu.com
Scientific contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd (MTPE), regulatory@mt-pharma-eu.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000878-PIP02-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2015
Global end of trial reached?	Yes
Global end of trial date	26 January 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the initial starting dose of colestilan in paediatric subjects.

Protection of trial subjects:

"1 During the wash-out period subjects had to stop their current CBPB treatment, which was likely to cause a rise in P levels. The increase in P is not dangerous for a short period of time and once the required P level was reached, the subject was randomised and treated either with colestilan (MCI-196) or a calcium-based phosphate binder (CBPB). The wash-out period was a maximum of 4 weeks.
2 When specifying the amount of blood to be drawn the following guidelines were used:
- trial-related blood loss (including loss in the procedure) should not exceed 3% of total blood volume during a period of 4 weeks and should not exceed 1% total blood volume at any single time.
Subjects were enrolled to the study if they could safely provide 8 ml of blood at each visit.
3 When investigating new drugs there is always a risk of unexpected side effects and occasionally allergic reactions. Subjects were closely monitored during the study.
4 Rescue treatment for hyperphosphataemia with CBPB, in addition to the allocated fixed dose of colestilan or CBPB, was allowed as clinically indicated. Rescue treatment for hypocalcaemia with calcium supplements, was allowed as clinically indicated. Adjustment of dosing of vitamin D/analogues was permitted during the study to correct hypocalcaemia.
5 Rescue treatment for hypocalcaemia with calcium supplements, was allowable as clinically indicated. The appropriate dose was to be decided by the Investigator based on his/her clinical experience.
6 Consent/assent process: Enough time was provided to the subject/parent/caregiver to consider participation in the study. In addition to the patient information sheet and consent/assent forms, a study flipchart was provided to all sites, which was used as a tool to help explain/discuss aspects of the study in more detail.
7 Tablet intake - it is known that tablets can be difficult to swallow, especially by very young children. The IMP was made available also in granule formulation.
"

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	30 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Turkey: 5

Worldwide total number of subjects	10
EEA total number of subjects	5

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)	10
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from patients already attending hospital clinics, with paediatric nephrologists, for the treatment of CKD stage 5 (on dialysis) and hyperphosphataemia

Pre-assignment

Screening details:

The study comprised of a screening period (1 to 4 weeks) and a wash-out period (1 to 4 weeks). A total of 23 subjects were screened. 13 subjects were withdrawn before randomisation (screen failed)

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MCI-196 3g

Arm description:

Colestilan administered orally at a BSAeq fixed dose of 3g/day (i.e., 1.73 g/m2/day), for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.

Arm type	Experimental
Investigational medicinal product name	Colestilan
Investigational medicinal product code	MCI-196
Other name	
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

1 g tablets, and granules of approx 20 mg packaged in 2g or 3g sachets

Arm title	MCI-196 9g

Arm description:

Colestilan administered orally at a BSAeq fixed dose of 9g/day (i.e., 5.20 g/m2/day) for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.

Arm type	Experimental
Investigational medicinal product name	Colestilan
Investigational medicinal product code	MCI-196
Other name	
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

1 g tablets, and granules of approx 20 mg packaged in 2g or 3g sachets

Arm title	MCI-196 6g

Arm description:

Colestilan administered orally at a BSAeq fixed dose of 6g/day (i.e., 3.47 g/m2/day) for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.

Arm type	Experimental

Investigational medicinal product name	Colestilan
Investigational medicinal product code	MCI-196
Other name	
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

1 g tablets, and granules of approx 20 mg packaged in 2g or 3g sachets

Arm title	CBPB

Arm description:

CBPB administered orally at the standard prescribed dose (equivalent to dose prior to enrolment into this study) as instructed by the Investigator.

Arm type	Active comparator
Investigational medicinal product name	CBPB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per physician's guidance.

Number of subjects in period 1	MCI-196 3g	MCI-196 9g	MCI-196 6g
Started	3	2	3
Completed	1	1	1
Not completed	2	1	2
Consent withdrawn by subject	1	-	1
Physician decision	1	-	-
Hyperphosphataemia	-	1	1

Number of subjects in period 1	CBPB
Started	2
Completed	1
Not completed	1
Consent withdrawn by subject	-
Physician decision	1
Hyperphosphataemia	-

Baseline characteristics

Reporting groups	
Reporting group title	MCI-196 3g
Reporting group description:	
Colestilan administered orally at a BSAeq fixed dose of 3g/day (i.e., 1.73 g/m2/day), for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.	
Reporting group title	MCI-196 9g
Reporting group description:	
Colestilan administered orally at a BSAeq fixed dose of 9g/day (i.e., 5.20 g/m2/day) for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.	
Reporting group title	MCI-196 6g
Reporting group description:	
Colestilan administered orally at a BSAeq fixed dose of 6g/day (i.e., 3.47 g/m2/day) for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.	
Reporting group title	CBPB
Reporting group description:	
CBPB administered orally at the standard prescribed dose (equivalent to dose prior to enrolment into this study) as instructed by the Investigator.	

Reporting group values	MCI-196 3g	MCI-196 9g	MCI-196 6g
Number of subjects	3	2	3
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	3	2	3
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	15.3	16.5	13.3
standard deviation	± 1.5	± 0.7	± 1.2
Gender categorical Units: Subjects			
Female	1	2	1
Male	2	0	2

Reporting group values	CBPB	Total	
Number of subjects	2	10	

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)	2	10	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	16		
standard deviation	± 1.4	-	
Gender categorical Units: Subjects			
Female	1	5	
Male	1	5	

End points

End points reporting groups

Reporting group title	MCI-196 3g

Reporting group description:

Colestilan administered orally at a BSAeq fixed dose of 3g/day (i.e., 1.73 g/m2/day), for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.

Reporting group title	MCI-196 9g

Reporting group description:

Colestilan administered orally at a BSAeq fixed dose of 9g/day (i.e., 5.20 g/m2/day) for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.

Reporting group title	MCI-196 6g

Reporting group description:

Colestilan administered orally at a BSAeq fixed dose of 6g/day (i.e., 3.47 g/m2/day) for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.

Reporting group title	CBPB

Reporting group description:

CBPB administered orally at the standard prescribed dose (equivalent to dose prior to enrolment into this study) as instructed by the Investigator.

Primary: Mean change in serum P

End point title	Mean change in serum P[1]

End point description:

The mean absolute change in serum phosphorus levels from baseline to week 17 or last observation carried forward (LOCF) for all subjects whilst on monotherapy with either fixed-dose of colestilan or the standard therapy of CBPB.

End point type	Primary

End point timeframe:

baseline to Week 17 (or LOCF)

Notes:

[1] - 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: This study was prematurely terminated. The available data were very limited and highly variable. No consistent reductions (>0.5 mmol/L) from baseline in phosphorus levels were observed for any subject after dosing with standard CBPB or MCI-196.

End point values	MCI-196 3g	MCI-196 9g	MCI-196 6g	CBPB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: mmol/L				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[2] - This study was prematurely terminated. No statistical analyses were completed.

[3] - This study was prematurely terminated. No statistical analyses were completed.

[4] - This study was prematurely terminated. No statistical analyses were completed.

[5] - This study was prematurely terminated. No statistical analyses were completed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs that occured from the time written informed consent/assent was obtained to the End Of Study or discontinuation visit were recorded in the source documents and reported in the CRF

Adverse event reporting additional description:

AEs were classified as 'treatment emergent' (i.e., TEAEs or serious TEAEs) if they occurred following administration of IMP. All events reported in this database are treatment emergent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	MCI-196 3g

Reporting group description:

Colestilan administered orally at a BSAeq fixed dose of 3g/day (i.e., 1.73 g/m2/day), for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.

Reporting group title	MCI-196 6g

Reporting group description:

Colestilan administered orally at a BSAeq fixed dose of 6g/day (i.e., 3.47 g/m2/day) for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.

Reporting group title	MCI-196 9g

Reporting group description:

Colestilan administered orally at a BSAeq fixed dose of 9g/day (i.e., 5.20 g/m2/day) for 17 weeks. The dose was spread throughout the day with food and taken relative to P intake, as recommended by the Investigator.

Reporting group title	CBPB

Reporting group description:

CBPB administered orally at the standard prescribed dose (equivalent to dose prior to enrolment into this study) as instructed by the Investigator.

Serious adverse events	MCI-196 3g	MCI-196 6g	MCI-196 9g
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 2 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Arteriovenous Fistula Thrombosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Arteriovenous Fistula Operation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	CBPB		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Arteriovenous Fistula Thrombosis			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Arteriovenous Fistula Operation			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	MCI-196 3g	MCI-196 6g	MCI-196 9g
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	2 / 2 (100.00%)
Injury, poisoning and procedural complications			
Arteriovenous Fistula Occlusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Arteriovenous Fistula Site Complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Arteriovenous Fistula Thrombosis			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Haemodialysis-Induced Symptom			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Joint Injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Arteriovenous Fistula Operation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Balance Disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 2 (100.00%)
occurrences (all)	0	0	2
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 2 (100.00%)
occurrences (all)	0	0	2
Abdominal Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	CBPB		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)		
Injury, poisoning and procedural complications			
Arteriovenous Fistula Occlusion			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Arteriovenous Fistula Site Complication			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Arteriovenous Fistula Thrombosis			

subjects affected / exposed occurrences (all) Haemodialysis-Induced Symptom subjects affected / exposed occurrences (all) Joint Injury subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 0 / 2 (0.00%) 0		
Surgical and medical procedures Arteriovenous Fistula Operation subjects affected / exposed occurrences (all)	 0 / 2 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Balance Disorder subjects affected / exposed occurrences (all)	 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all)	 0 / 2 (0.00%) 0 0 / 2 (0.00%) 1		
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	 0 / 2 (0.00%) 0		
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Abdominal Pain			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	0 / 2 (0.00%)		
occurrences (all)	0		

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? Yes

Date	Interruption	Restart date
14 January 2015	Study Early Termination	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were significant challenges to recruitment in all age groups and in this patient population. The study was terminated early due to the withdrawal of the MAA.

Notes: