Clinical trial results:
Early prospective therapy trial to delay renal failure in children with Alport syndrome.

Summary

EudraCT number	2010-024300-10
Trial protocol	DE
Global end of trial date	25 March 2019

Results information

Result version number	v1 (current)
This version publication date	27 May 2020
First version publication date	27 May 2020
Summary attachment (see zip file)	ALPORT_Summary report_V01_20200319 (Abschlussbericht_ALPORT_V01_20200319_final.pdf)

Trial information

Trial identification

Sponsor protocol code	00814

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01485978
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsmedizin der Georg-August-Universität Göttingen
Sponsor organisation address	Robert-Koch-Straße 40, Göttingen, Germany, 37075
Public contact	Study centre-UMG, University Medical Center Goettingen (UMG), +49 55139171347, sz-umg.sponsor-qm@med.uni-goettingen.de
Scientific contact	Abt. Nephrologie und Rheumatologie, University Medical Center Goettingen, +49 5513966331, gross.oliver@med.uni-goettingen.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	19 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2019
Global end of trial reached?	Yes
Global end of trial date	25 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to determine the safety and efficacy of the ACEi ramipril in delaying disease progression in patients with early stages of Alport Syndrome, in a setting of multi-centre, randomised, placebo-controlled, patient- and investigator-blind trial.

Protection of trial subjects:

Medications affecting blood pressure and immune-suppressants were avoided in the randomized arm of this study. Non-steroidal anti-inflammatory drugs (NSAID) were allowed to be administered for no more than 1 week e.g., for the treatment of an acute injury. For randomised patients treated in a double blind fashion, emergency codes were available to the investigator. A code, which revealed the treatment group for a specific study patient, was opened during the study only if the choice of treatment depends on the study subject's therapy assignment or if the patient progresses to the next disease level.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 66
Worldwide total number of subjects	66
EEA total number of subjects	66

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)	46
Adolescents (12-17 years)	20

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

Subject disposition

Recruitment

Recruitment details:

Recruitment period: 3.5 years
First patient in: 07.05.2012
Last patient in: 30.09.2015

Pre-assignment

Screening details:

not apllicable.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramipril (randomized)

Arm description:

For patients randomised to receive ramipril, the dose of ramipril will be up-titrated over a period of 12 months from 1 to 6 mg/m2 or until the individual maximum tolerated dose (MTD) is reached.

Arm type	Experimental
Investigational medicinal product name	Ramipril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage of ramipril in patients <18 years will be calculated using the Mosteller formula for the calculation of the body surface area (m2). For paediatric patients, the maximum daily dose of ramipril will be 6 mg/m2. For adults, the maximum daily dose of ramipril will be 10 mg. The same number of tablets will be administered for placebo treatment.

Investigational medicinal product name	Ramipril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage of ramipril in patients <18 years will be calculated using the Mosteller formula for the calculation of the body surface area (m2). For paediatric patients, the maximum daily dose of ramipril will be 6 mg/m2. For adults, the maximum daily dose of ramipril will be 10 mg. The same number of tablets will be administered for placebo treatment.

Arm title	Placebo (randomized)

Arm description:

For patients randomised to receive ramipril, the dose of ramipril will be up-titrated over a period of 12 months from 1 to 6 mg/m2 or until the individual maximum tolerated dose (MTD) is reached. Patients randomised to receive placebo will take the same number of tablets. The individual MTD should be held throughout the study. Placebo tablets are identical in appearance to the study medication but do not contain the active ingredient.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage of ramipril in patients <18 years will be calculated using the Mosteller formula for the calculation of the body surface area (m2). For paediatric patients, the maximum daily dose of ramipril will be 6 mg/m2. For adults, the maximum daily dose of ramipril will be 10 mg. For all patients, there will be an initial up-titration phase for ramipril. The same number of tablets will be administered for placebo treatment.

Arm title	Ramipril (open label)

Arm description:

Patients may be treated open label with ramipril, including previously treated as well as un-treated patients who, or whose parents/legal guardian refuse randomisation after eligibility is confirmed. All patients will undergo study-specific procedures according to the study schedule without regard to treatment/ randomisation.

Arm type	Experimental
Investigational medicinal product name	Ramipril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dosage of ramipril in patients <18 years will be calculated using the Mosteller formula for the calculation of the body surface area (m2). For paediatric patients, the maximum daily dose of ramipril will be 6 mg/m2. For adults, the maximum daily dose of ramipril will be 10 mg. For all patients, there will be an initial up-titration phase for ramipril.

Number of subjects in period 1	Ramipril (randomized)	Placebo (randomized)	Ramipril (open label)
Started	12	10	44
Completed	12	10	44

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	66	66	
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)	46	46	
Adolescents (12-17 years)	20	20	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	2	2	
Male	64	64	

End points

End points reporting groups

Reporting group title	Ramipril (randomized)
Reporting group description:	
For patients randomised to receive ramipril, the dose of ramipril will be up-titrated over a period of 12 months from 1 to 6 mg/m2 or until the individual maximum tolerated dose (MTD) is reached.	
Reporting group title	Placebo (randomized)
Reporting group description:	
For patients randomised to receive ramipril, the dose of ramipril will be up-titrated over a period of 12 months from 1 to 6 mg/m2 or until the individual maximum tolerated dose (MTD) is reached. Patients randomised to receive placebo will take the same number of tablets. The individual MTD should be held throughout the study. Placebo tablets are identical in appearance to the study medication but do not contain the active ingredient.	
Reporting group title	Ramipril (open label)
Reporting group description:	
Patients may be treated open label with ramipril, including previously treated as well as un-treated patients who, or whose parents/legal guardian refuse randomisation after eligibility is confirmed. All patients will undergo study-specific procedures according to the study schedule without regard to treatment/ randomisation.	

Primary: Safety - adverse events before disease progression

End point title	Safety - adverse events before disease progression
End point description:	
End point type	Primary
End point timeframe:	
Time before disease progression varies from 0.41 to 5.1 years.	

End point values	Ramipril (randomized)	Placebo (randomized)	Ramipril (open label)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	9	42	
Units: Adverse events before disease progressio	289	176	0	

Statistical analyses

Statistical analysis title	Safety - adverse events before disease progression
Comparison groups	Ramipril (randomized) v Placebo (randomized)

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.53

Primary: Efficacy - disease progression

End point title	Efficacy - disease progression

End point description:

End point type	Primary

End point timeframe:

Observation period until final examination after 6 years.

End point values	Ramipril (randomized)	Placebo (randomized)	Ramipril (open label)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	9	42	
Units: Disease progression	3	5	17	

Statistical analyses

Statistical analysis title	Efficacy - time before disease progression
Comparison groups	Ramipril (randomized) v Placebo (randomized)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Weibull regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	2.2

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
Adverse events were recorded during the full study period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	ICD-10
Dictionary version	2019

Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Information about Adverse events can be found under End point section

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2012	Amendement due to changes in the summary of product characterisitcs of the investigetional product.
20 March 2013	Update of Protocol (new version 3.0 dated 18.02.2013) due to changes in storage conditions of investigational product.
15 July 2014	Update of protocol (new version 4.0 dated 06.06.2014) due to adjustment of randomization ratio and changes in the maunfacturing process of the investigational product (verum).
14 July 2015	Update of protocol (new version 5.0 dated 12.06.2015) due to extension of shelf-life of the placebo and extension of recruitment period.
20 April 2017	Update of Protocol (new version 6.0 dated 30.03.2017) due to changes in destruction of medication, permitted concomitant medication and AE-documentation. Furthermore the unblinding process is described in more detail.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported