Clinical trial results:
A dual-center prospective phase I/II trial to establish safety, tolerability and to obtain first data on efficacy of losartan in children with recessive dystrophic epidermolysis bullosa (RDEB)

Summary

EudraCT number	2015-003670-32
Trial protocol	DE AT
Global end of trial date	12 February 2021

Results information

Result version number	v1 (current)
This version publication date	03 September 2022
First version publication date	03 September 2022

Trial information

Trial identification

Sponsor protocol code	REFLECT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00009269

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
Public contact	Prof. Dr. Dimitra Kiritsi, Medical Center - University of Freiburg, ++49 761270-67100, dimitra.kiritsi@uniklinik-freiburg.de
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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	01 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2021
Global end of trial reached?	Yes
Global end of trial date	12 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Establish tolerability and saftey of losartan in children with moderate to serve RDEB

Protection of trial subjects:

Risk-based monitoring was done according to ICH-GCP E6 and SOPs to verify that patients' rights and wellbeing are protected, reported trial data are accurate, complete and verifiable from source documents and that the trial is conducted in compliance with the currently approved protocol/amendment, with ICH-GCP and with the applicable regulatory requirements to ensure safety and integrity of clinical trial data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 July 2017
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	Germany: 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)	24
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment
Recruitment details: -

Pre-assignment
Screening details: -

Pre-assignment period milestones	
Number of subjects started	29
Number of subjects completed	29

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

Blinding implementation details:

Not applicable: prospective, open, single-arm phase I/II clinical trial

Arms	
Arm title	Losartan

Arm description:

Study medication: Losartan potassium, 2.5 mg/ml, extemporaneous oral liquid suspension.

Arm type	Experimental
Investigational medicinal product name	Losartan HEXAL
Investigational medicinal product code	Losartan potassium
Other name	
Pharmaceutical forms	Film-coated tablet, Oral liquid, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Dosage form: Film-coated tablets
Strength: 50 mg
Maximum daily dose: 1.4 mg/kg

Number of subjects in period 1	Losartan
Started	29
Completed	29

Baseline characteristics

Reporting groups

Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	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)	24	24	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	6.44		
standard deviation	± 3.81	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	16	16	

Subject analysis sets

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

All analyses (safety and efficacy) were performed in the safety population (SAF) which included all patients who fulfilled the inclusion and exclusion criteria, and for whom treatment was started, i.e. 29 patients.

Reporting group values	SAF		
Number of subjects	29		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	24		

Adolescents (12-17 years)	5		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	 ±		
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Losartan

Reporting group description:

Study medication: Losartan potassium, 2.5 mg/ml, extemporaneous oral liquid suspension.

Subject analysis set title	SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

All analyses (safety and efficacy) were performed in the safety population (SAF) which included all patients who fulfilled the inclusion and exclusion criteria, and for whom treatment was started, i.e. 29 patients.

Primary: Occurrence of a serious safety concern

End point title	Occurrence of a serious safety concern[1]

End point description:

The primary endpoint was defined as the occurrence of a serious safety concern, specified as one of the following side effects of losartan:
• clinically relevant severe hypotension
• immediate hypersensitivity reactions to the drug
• clinical relevant severe hypo- und hyperkalaemia

End point type	Primary

End point timeframe:

During study

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: Single arm trial.

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Birmingham Epidermolysis Bullosa Severity Score

End point title	Birmingham Epidermolysis Bullosa Severity Score

End point description:

Birmingham Epidermolysis Bullosa Severity Score (BEBS) (0=best, 100=worst)

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	Losartan			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Severity Score				
arithmetic mean (confidence interval 95%)	-3.00 (-5.79 to -0.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) Total activity score

End point title	Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) Total activity score

End point description:

Change in the total activity score (0=best, 276=worst) of the Epidermolysis Bullosa Disease Activity and Scarring Index

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	Losartan			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Scarring Index				
arithmetic mean (confidence interval 95%)	-7.36 (-16.13 to 1.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) – Total damage score

End point title	Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) – Total damage score

End point description:

EBDASI total damage score (ranging from 0=best to 230=worst)

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: Total damage score				
arithmetic mean (confidence interval 95%)	-10.50 (-20.81 to -0.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) – Overall total score

End point title	Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) – Overall total score

End point description:

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: Overall total score				
arithmetic mean (confidence interval 95%)	-17.86 (-31.11 to -4.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hand function assessment score of Colville and Terrill

End point title	Hand function assessment score of Colville and Terrill

End point description:

Hand function assessment score of Colville and Terrill, ranging from 0=best to 3=worst. Improvement of at least 1 level.

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: Number of patients	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Mayo Dysphagia Questionnaire-day 30 (MDQ-30)

End point title	Mayo Dysphagia Questionnaire-day 30 (MDQ-30)

End point description:

The Mayo Dysphagia Questionnaire-day 30 (MDQ-30) was used to assess oesophageal involvement. Dysphagia score: 0=best, 100=worst

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: Dysphagia score				
arithmetic mean (confidence interval 95%)	3.04 (-7.20 to 13.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Itch Assessment Scale

End point title	Itch Assessment Scale

End point description:

Itch assessment scale for the pediatric burn patients, ranging from 0=best to 4=worst. Improvement of at least one level.

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: Number of patients	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Wong-Baker FACES Scale for Pain

End point title	Wong-Baker FACES Scale for Pain

End point description:

Wong-Baker FACES Scale for Pain (ranging from 0=best to 10=worst). Improvement of at least 1 level.

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: Number of patients	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life in EB (QOLEB)

End point title	Quality of Life in EB (QOLEB)

End point description:

The change in the total score (0=best, 51=worst) of the Quality of Life in EB (QOLEB) during the study.

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: QoL				
arithmetic mean (confidence interval 95%)	0.54 (-2.40 to 3.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Children’s Dermatology Life Quality Index (CDLQI) - Total scale

End point title	Children’s Dermatology Life Quality Index (CDLQI) - Total scale

End point description:

Change in the total scale (0=best, 30=worst) of the Children’s Dermatology Life Quality Index (CDLQI) during the study

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: CDLQI				
arithmetic mean (confidence interval 95%)	-2.64 (-4.35 to -0.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Morphometric Scoring Instrument of Pseudosyndactyly Progression

End point title	Morphometric Scoring Instrument of Pseudosyndactyly Progression

End point description:

Maximal distance of thumb and index finger – Mean of left and right

End point type	Secondary

End point timeframe:

Difference between baseline and month 9

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: Maximal distance				
arithmetic mean (confidence interval 95%)	6.92 (3.48 to 10.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse event

End point title	Adverse event

End point description:

Number of patient with at least one adverse event

End point type	Secondary

End point timeframe:

During the whole study period

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Number of patients	25			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse event of severe intensity

End point title	Adverse event of severe intensity

End point description:

Number of patients with at least one AE of severe intensity

End point type	Secondary

End point timeframe:

During study

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Number of patients	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse event possibly related to study medication

End point title	Adverse event possibly related to study medication
End point description:	
Number of patients with at least one AE possibly related to study medication	
End point type	Secondary
End point timeframe:	
During study	

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Number of patients	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Severe adverse event possibly related to study medication

End point title	Severe adverse event possibly related to study medication
End point description:	
Number of patients with at least one severe adverse event possibly related to study medication	
End point type	Secondary
End point timeframe:	
During study	

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Serious adverse event

End point title	Serious adverse event

End point description:

Number of patients with at least one serious adverse event

End point type	Secondary

End point timeframe:

During study

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Number of patients	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Serious adverse event possibly related to study medication

End point title	Serious adverse event possibly related to study medication

End point description:

Number of patients with at least one SAE possibly related to study medication

End point type	Secondary

End point timeframe:

During study

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Serious adverse event leading to death

End point title	Serious adverse event leading to death

End point description:

Number of patients with at least one SAE leading to death

End point type	Secondary

End point timeframe:

During study

End point values	SAF			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Complete study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Losartan
Reporting group description:	
Losartan	

Serious adverse events	Losartan		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 29 (13.79%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			

subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudomonal sepsis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin bacterial infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection bacterial			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device failure			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Losartan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 29 (79.31%)		
Investigations			
Body temperature increased			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Pain threshold decreased			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Eye injury subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1 1 / 29 (3.45%) 1		
Surgical and medical procedures Artificial crown procedure subjects affected / exposed occurrences (all) Parasitic infection prophylaxis subjects affected / exposed occurrences (all)	 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 3 / 29 (10.34%) 6		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Impaired healing subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Temperature intolerance subjects affected / exposed occurrences (all)	 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 2 / 29 (6.90%) 2 2 / 29 (6.90%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 1 / 29 (3.45%) 1		
Eye disorders			

Eye pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	4		
Odynophagia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Tooth disorder			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Epistaxis			

subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Skin and subcutaneous tissue disorders Blister subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Vitiligo subjects affected / exposed occurrences (all)	 1 / 29 (3.45%) 1 3 / 29 (10.34%) 3 1 / 29 (3.45%) 1		
Musculoskeletal and connective tissue disorders Groin pain subjects affected / exposed occurrences (all)	 1 / 29 (3.45%) 1		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Croup infectious subjects affected / exposed occurrences (all) Gastrointestinal viral infection subjects affected / exposed occurrences (all) Hand-foot-and-mouth disease subjects affected / exposed occurrences (all) Medical device site infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral herpes	 2 / 29 (6.90%) 2 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 1 / 29 (3.45%) 2 5 / 29 (17.24%) 6		

subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Oral infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Pseudomonas infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Tinea infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2019	Administrative changes, update of the responsibility list: • change of coordinating investigator • departure of one of the project manager from the CTU Formal specification of the inclusion criterion 3: OLD: Male or female patients from 2 to 16 years (age of >25 months); NEW: Male or female patients from 2 to 16 years (starting from the 25th month of life).
18 February 2020	Administrative changes, update of the responsibility list: • change of coordinating investigator Synopsis and chapter 3.4 Trial timetable: • Updates regarding timelines

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported