Clinical trial results:
Clinical evaluation of two different dosage groups of Tacrosolv over 8 days with once daily administration in a placebo controlled cross-over design to evaluate safety and efficacy in patients suffering from grass pollen-induced allergic rhinoconjunctivitis in the Vienna Challenge Chamber.

Summary

EudraCT number	2019-002847-62
Trial protocol	AT
Global end of trial date	05 May 2021

Results information

Result version number	v1 (current)
This version publication date	22 October 2022
First version publication date	22 October 2022

Trial information

Trial identification

Sponsor protocol code	TCS_19_02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Marinomed Biotech AG
Sponsor organisation address	Hovengasse 25, Korneuburg, Austria, 2100
Public contact	Project Manager, Marinomed Biotech AG, +43 1250774460, svenja.sladek@marinomed.com
Scientific contact	CSO, Marinomed Biotech AG, +43 1250774460, eva.prieschl-grassauer@marinomed.com

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	29 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2021
Global end of trial reached?	Yes
Global end of trial date	05 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to demonstrate the safety and efficacy of two doses of Tacrosolv (1 drop per eye per day - low dose treatment; 2 drops per eye per day - high dose treatment) in a cross-over design on day 8 of treatment.

Protection of trial subjects:

This study was performed in compliance with the ICH E6 Guideline for Good Clinical Practice, the principles that have their origin in the Declaration of Helsinki and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 January 2020
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	Austria: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	64
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Dates of recruitment:

Beginning: 04th August 2020

End of recruitment: 13th of Jannuary 2021

Territory: Austria

Pre-assignment

Screening details:

Subjects exhibit a moderate to severe response within the first 2 hours of the challenge (4 hours in total)
Total ocular symptom score (TOSS) of at least 4 (out of 12)
at least one single ocular symptom scored ≥2 (“moderate”) at least twice during the first two hours

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo 1

Arm description:

32 subjects were randomised into the cross-over treatment Placebo1 and Tacrosolv high dose. One subject had a protocol deviation. 31 subjects completed the trial.

Arm type	placebo high dose
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Conjunctival use

Dosage and administration details:

two eye drops per eye

Arm title	Tacrosolv low-dose day 8

Arm description:

32 subjects were randomised into the cross-over treatment Tacrosolv low-dose and Placebo 2. One subject had a protocol deviation. 31 subjects completed the trial.

Arm type	Tacrosolv low-dose
Investigational medicinal product name	Tacrosolv
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Conjunctival use

Dosage and administration details:

one eye drop per eye

Arm title	Placebo 2

Arm description:

32 subjects were randomised into the cross-over treatment Placebo 2 and Tacrosolv low dose. One subject had a protocol deviation. 31 subjects completed the trial

Arm type	Placebo high dose
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Conjunctival use

Dosage and administration details:

two eye drops per eye

Arm title	Tacrosolv high-dose day 8

Arm description:

32 were randomised into the cross-over treatment Tacrsolv high dose and Placebo 1. One subject had a protocol deviation. 31 subjects completed the trial

Arm type	Tacrosolv high dose
Investigational medicinal product name	Tacrosolv
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Conjunctival use

Dosage and administration details:

two eye drops per eye

Number of subjects in period 1	Placebo 1	Tacrosolv low-dose day 8	Placebo 2
Started	32	32	32
Completed	32	32	32

Number of subjects in period 1	Tacrosolv high-dose day 8
Started	32
Completed	32

Baseline characteristics

Reporting groups	
Reporting group title	Placebo 1
Reporting group description:	
32 subjects were randomised into the cross-over treatment Placebo1 and Tacrosolv high dose. One subject had a protocol deviation. 31 subjects completed the trial.	
Reporting group title	Tacrosolv low-dose day 8
Reporting group description:	
32 subjects were randomised into the cross-over treatment Tacrosolv low-dose and Placebo 2. One subject had a protocol deviation. 31 subjects completed the trial.	
Reporting group title	Placebo 2
Reporting group description:	
32 subjects were randomised into the cross-over treatment Placebo 2 and Tacrosolv low dose. One subject had a protocol deviation. 31 subjects completed the trial	
Reporting group title	Tacrosolv high-dose day 8
Reporting group description:	
32 were randomised into the cross-over treatment Tacrsolv high dose and Placebo 1. One subject had a protocol deviation. 31 subjects completed the trial	

Reporting group values	Placebo 1	Tacrosolv low-dose day 8	Placebo 2
Number of subjects	32	32	32
Age categorical Units: Subjects			
Adults (18-64 years)	32	32	32
Gender categorical Units: Subjects			
Female	19	19	19
Male	13	13	13

Reporting group values	Tacrosolv high-dose day 8	Total	
Number of subjects	32	64	
Age categorical Units: Subjects			
Adults (18-64 years)	32	64	
Gender categorical Units: Subjects			
Female	19	38	
Male	13	26	

End points

End points reporting groups

Reporting group title	Placebo 1
Reporting group description:	
32 subjects were randomised into the cross-over treatment Placebo1 and Tacrosolv high dose. One subject had a protocol deviation. 31 subjects completed the trial.	
Reporting group title	Tacrosolv low-dose day 8
Reporting group description:	
32 subjects were randomised into the cross-over treatment Tacrosolv low-dose and Placebo 2. One subject had a protocol deviation. 31 subjects completed the trial.	
Reporting group title	Placebo 2
Reporting group description:	
32 subjects were randomised into the cross-over treatment Placebo 2 and Tacrosolv low dose. One subject had a protocol deviation. 31 subjects completed the trial	
Reporting group title	Tacrosolv high-dose day 8
Reporting group description:	
32 were randomised into the cross-over treatment Tacrsolv high dose and Placebo 1. One subject had a protocol deviation. 31 subjects completed the trial	

Primary: Total Ocular Symptom Score

End point title	Total Ocular Symptom Score

End point description:

The primary efficacy endpoint was the mean 'Total Ocular Symptom Score' (TOSS), calculated as the mean of TOSS measured every 15 minutes during the grass pollen allergen exposure challenge from time-point 0 to 4 hours on day 8.
TOSS is defined as the sum of the four individual ocular symptoms:

- ocular redness (red eye)
- ocular itching (itchy eyes)
- watery eye
- gritty feeling

End point type	Primary

End point timeframe:

The mean of TOSS measured every 15 minutes during the grass pollen allergen exposure challenge from time-point 0 to 4 hours on day 8.

End point values	Placebo 1	Tacrosolv low-dose day 8	Placebo 2	Tacrosolv high-dose day 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	31	31	31
Units: points				
arithmetic mean (standard deviation)	3.22 (± 1.9)	3.56 (± 2.52)	3.80 (± 2.37)	3.63 (± 2.59)

Statistical analyses

Statistical analysis title	Mean difference placebo 1 - Tacrosolv 1

Statistical analysis description:

A 95% confidence interval will be calculated for the mean difference between the active treatment and placebo from a two-sided paired t-test. We assume superiority of Tacrosolv versus Placebo. Superiority could be stated if the upper limit of the confidence interval does not exceed 0.

Comparison groups	Placebo 2 v Tacrosolv low-dose day 8
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.355
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	0.4

Statistical analysis title	mean difference placebo 2 - Tacrosolv 2
Comparison groups	Tacrosolv high-dose day 8 v Placebo 1
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.566
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.81

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs/SAEs will be recorded from the beginning of the study (signing consent form) up to the follow-up visit (end of trial).

Adverse event reporting additional description:

Each subject will be monitored by the Investigator or study personnel for adverse events occurring throughout the study. During the treatment period, the Investigator or designee will inquire about AEs by asking the subject about changes in AEs or Concomitant medications.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Tacrosolv

Reporting group description:

As it was a cross-over trial subjects received both treatment and placebo during the trial.

Reporting group title	Placebo

Reporting group description:

As it was a cross-over design subjects received placebo and treatment during the trial.

Serious adverse events	Tacrosolv	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Tacrosolv	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 64 (85.94%)	20 / 64 (31.25%)	
Injury, poisoning and procedural complications			
Barotrauma			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Disturbance in attention			

subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	4 / 64 (6.25%)	1 / 64 (1.56%)	
occurrences (all)	4	1	
Migraine			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 64 (3.13%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	6 / 64 (9.38%)	0 / 64 (0.00%)	
occurrences (all)	6	0	
Asthenopia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Blepharitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	14 / 64 (21.88%)	1 / 64 (1.56%)	
occurrences (all)	14	1	
Eye irritation			
subjects affected / exposed	30 / 64 (46.88%)	6 / 64 (9.38%)	
occurrences (all)	30	6	
Eye pruritus			
subjects affected / exposed	9 / 64 (14.06%)	5 / 64 (7.81%)	
occurrences (all)	9	5	
Eyelid irritation			
subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Eye swelling			

subjects affected / exposed	5 / 64 (7.81%)	1 / 64 (1.56%)	
occurrences (all)	5	1	
Foreign body sensation in eyes			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Eyelids pruritus			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	14 / 64 (21.88%)	1 / 64 (1.56%)	
occurrences (all)	14	1	
Ocular discomfort			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	9 / 64 (14.06%)	3 / 64 (4.69%)	
occurrences (all)	9	3	
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	9 / 64 (14.06%)	1 / 64 (1.56%)	
occurrences (all)	9	1	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Pneumonia			

subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 64 (0.00%) 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? No

Limitations and caveats

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

- Small study group
- Short observation period
- Eye irritation due to Tacrolimus

Notes: