Clinical trial results:
A randomised, double-blind, placebo-controlled study to investigate the safety, tolerability, pharmacokinetic and pharmacodynamic profiles of CHF6467 after single and repeated ascending doses in subjects with diabetic neuropathic foot ulcers (DFU).

Summary

EudraCT number	2018-001724-19
Trial protocol	BG
Global end of trial date	06 January 2021

Results information

Result version number	v1 (current)
This version publication date	04 February 2022
First version publication date	04 February 2022

Trial information

Trial identification

Sponsor protocol code	CLI-06467AA1-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04077671
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Trasparency, Chiesi Farmaceutici S.p.A., clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Trasparency, Chiesi Farmaceutici S.p.A., clinicaltrials_info@chiesi.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	19 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess:
- the safety and tolerability of single and multiple days topical dosing with CHF6467 in patients with diabetic foot ulcers (DFU);
- the pharmacokinetic (PK) profile of systemically available drug following single and multiple days topical dosing with CHF6467 in patients with DFU;
- the pharmacodynamic (PD) effects of multiple days topical dosing with CHF6467 on the healing of DFU over a 12-week period;
- the potential for immunogenicity through the evaluation of the presence of CHF6467 anti-drug antibodies (ADA).

Protection of trial subjects:

This clinical study was performed in accordance with the principles that have their origin in the declaration of Helsinki, and with local regulations.
The study was carried out in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) notes for guidance on Good Clinical Practice (GCP) (ICH/CPMP/135/95).
Before the start of the study, all patients gave their written informed consent to participate in the study after having been informed of the nature and implications of the study.
The study consisted of two parts:
- Part 1 was a randomised, double-blind, placebo-controlled, single ascending dose, serial Cohort design in patients with neuropathic DFUs.
- Part 2 was a randomised, double-blind, placebo-controlled, multiple ascending dose, off-set parallel group design in patients with neuropathic DFUs.

Background therapy:

CHF6467, human NGF (hNGF) P61S R100E, is a recombinant and “painless” form of hNGF. The mutation on arginine R100 in mature NGF is linked to the rare human genetic disease hereditary sensory autonomic neuropathy type V (HSAN V). In HSAN V subjects, a mutation in the NGFβ gene (exon 3, nucleotide C661T), changing arginine R100 to a tryptophan, determines the complete loss of pain perception without affecting most neurological functions.
In addition to the pain-related R100E mutation, CHF6467 harbours a second “tagging” P61S mutation, which replaces the proline residue at position 61 of hNGF with the serine residue present in murine NGF (mNGF). In vitro and in vivo data have confirmed that CHF6467 maintains neurotrophic and neuroprotective properties identical to NGF in a variety of cell assays, while displaying a significantly reduced pain-inducing activity in vivo. CHF6467 has shown promising efficacy in accelerating the healing of wounds in diabetic mice, without any indication of the induction of pain or hyperalgesia.

Evidence for comparator: -

Actual start date of recruitment	16 October 2018
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	Bulgaria: 94
Worldwide total number of subjects	94
EEA total number of subjects	94

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)	67
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In Part1, a total of 38 subjects were screened: 33 were randomised and divided into 4 Cohorts (A, B, C, D) of 8 subjects each (except for Cohort B which included 9 patients) and 5 failed screening.
In Part 2, a total of 82 subjects were screened: 61 were randomised into one of 2 Cohorts (E, F) with 30 patients in Cohort E and 31 in Cohort F.

Pre-assignment

Screening details:

The screening was performed from 3 to 21 days prior to randomisation (Part 1) and prior to run-in period (Part 2).
The eligibility (inclusion/exclusion criteria) was assessed, medical history, concomitant medications were recorded, and clinical serology, haematology, chemistry, urinalysis, vital sign, ECG, ulcer size measurement were performed.

Period 1

Period 1 title	Treatment Period Part 1 and Part 2 (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?	Yes
Arm title	Part 1: Cohort A (SD1) CHF6467

Arm description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort A consisted of 6 subjects that received the active drug CHF6467 at a dose of 0.3 µg/mm² ulcer area, and 2 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Arm type	Experimental
Investigational medicinal product name	CHF6467
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

CHF6467 was a colourless aqueous solution for topical administration as single doses given in the morning through 1 mL topical graduated syringe using the necessary dilution steps to reach the final concentration which for Cohort A corresponds to: 0.3 µg/mm² (two steps of dilution, final concentration of 0.03 mg/mL).
Doses have been standardised in terms of volume/mm² of ulcer size by serial dilution of CHF6467 at the initial concentration of 1 mg/mL with the corresponding amount of diluent.

Arm title	Part 1: Cohort B (SD2) CHF6467

Arm description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating

dose regimen.
Cohort B consisted of 6 subjects that received the active drug CHF6467 at a dose of 1.0 µg/mm² ulcer area, and 3 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Arm type	Experimental
Investigational medicinal product name	CHF6467
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

CHF6467 was a colourless aqueous solution for topical administration as single doses given in the morning through 1 mL topical graduated syringe using the necessary dilution steps to reach the final concentration which for Cohort B corresponds to: 1.0 µg/mm² (one steps of dilution, final concentration of 0.1 mg/mL).
Doses have been standardised in terms of volume/mm² of ulcer size by serial dilution of CHF6467 at the initial concentration of 1 mg/mL with the corresponding amount of diluent.

Arm title	Part 1: Cohort C (SD3) CHF6467

Arm description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort C consisted of 6 subjects that received the active drug CHF6467 at a dose of 3 µg/mm² ulcer area, and 2 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Arm type	Experimental
Investigational medicinal product name	CHF6467
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

CHF6467 was a colorless aqueous solution for topical administration as single doses given in the morning through 1 mL topical graduated syringe using the necessary dilution steps to reach the final concentration which for Cohort C corresponds to: 3 µg/mm² (one step of dilution, final concentration of 0.3 mg/mL).
Doses have been standardised in terms of volume/mm² of ulcer size by serial dilution of CHF6467 at the initial concentration of 1 mg/mL with the corresponding amount of diluent.

Arm title	Part 1: Cohort D (SD4) CHF6467

Arm description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort D consisted of 6 subjects that received the active drug CHF6467 at a dose of 6 µg/mm² ulcer area, and 2 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Arm type	Experimental

Investigational medicinal product name	CHF6467
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

CHF6467 was a colourless aqueous solution for topical administration as single doses given in the morning through 1 mL topical graduated syringe using the necessary dilution steps to reach the final concentration which for Cohort D corresponds to: 6 µg/mm² (one steps of dilution, final concentration of 0.6 mg/mL).
Doses have been standardised in terms of volume/mm² of ulcer size by serial dilution of CHF6467 at the initial concentration of 1 mg/mL with the corresponding amount of diluent.

Arm title	Part 1: Placebo

Arm description:

Part 1_Includes subjects from Cohorts A, B, C, D who received placebo and are respectively:
Cohort A_2 subjects
Cohort B_3 subjects
Cohort C_2 subjects
Cohort D_2 subjects

Arm type	Placebo
Investigational medicinal product name	CHF6467 - Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

Placebo was a colourless aqueous solution for topical administration as single doses given in the morning through 1 mL topical graduated syringe.

Arm title	Part 2: Cohort E (MD1) CHF6467

Arm description:

Part 2: Multiple ascending doses in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, multiple ascending doses, parallel group design in 2 Cohorts (E, F).
During Part 2, two total dose levels of CHF6467 were administered topically applied as a once daily (q.d.) regimen, for 14 consecutive days according to an escalation scheme.
Cohort E consisted of 17 subjects that received the active drug CHF6467 at a dose of 1 µg/mm²/day for 14 consecutive days q.d., and 10 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Arm type	Experimental
Investigational medicinal product name	CHF6467
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

Multiple doses of CHF6467 - total daily dose 1 µg/mm²/day given q.d. plus SoC.
Topical administration of Active Drug was given under a q.d. dosing regimen in order to achieve a total daily dose of 1 µg/mm² through graduated topical syringe.
Dose was standardised in terms of volume/mm² of ulcer size (10 µL/mm²) by serial dilution (if required) of CHF6467 at the initial concentration of 1 mg/mL with the corresponding amount of vehicle.

Arm title	Part 2: Cohort F (MD2) CHF6467

Arm description:

Part 2: Multiple ascending doses in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, multiple ascending doses, parallel group design in 2 Cohorts (E, F).
During Part 2, two total dose levels of CHF6467 were administered topically applied as a once daily (q.

d.) regimen, for 14 consecutive days according to an escalation scheme.
Cohort F consisted of 18 subjects that received the active drug CHF6467 at a dose of 3 µg/mm²/day for 14 consecutive days q.d., and 10 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Arm type	Experimental
Investigational medicinal product name	CHF6467
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

Multiple doses of CHF6467 - total daily dose 3 µg/mm²/day given q.d. plus SoC.
Topical administration of Active Drug was given under a q.d. dosing regimen in order to achieve a total daily dose of 3 µg/mm² through graduated topical syringe.
Dose was standardised in terms of volume/mm² of ulcer size (10 µL/mm²) by serial dilution (if required) of CHF6467 at the initial concentration of 1 mg/mL with the corresponding amount of vehicle.

Arm title	Part 2: Placebo

Arm description:

Part 2_Includes subjects from Cohorts E, F who received placebo and are respectively:
Cohort E_10 subjects
Cohort F_10 subjects

Arm type	Placebo
Investigational medicinal product name	CHF6467 - Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Topical use

Dosage and administration details:

Placebo was a colourless aqueous solution, topically administered, multiple ascending doses given under a q.d. dosing regimen through a graduated topical 1 mL syringe.

Number of subjects in period 1	Part 1: Cohort A (SD1) CHF6467	Part 1: Cohort B (SD2) CHF6467	Part 1: Cohort C (SD3) CHF6467
Started	6	6	6
Completed	6	6	6
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Part 1: Cohort D (SD4) CHF6467	Part 1: Placebo	Part 2: Cohort E (MD1) CHF6467
Started	6	9	20
Completed	6	8	17
Not completed	0	1	3
Consent withdrawn by subject	-	1	3
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Part 2: Cohort F (MD2) CHF6467	Part 2: Placebo
Started	21	20

Completed	18	17
Not completed	3	3
Consent withdrawn by subject	3	2
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	Part 1: Cohort A (SD1) CHF6467

Reporting group description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort A consisted of 6 subjects that received the active drug CHF6467 at a dose of 0.3 µg/mm² ulcer area, and 2 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 1: Cohort B (SD2) CHF6467

Reporting group description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort B consisted of 6 subjects that received the active drug CHF6467 at a dose of 1.0 µg/mm² ulcer area, and 3 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 1: Cohort C (SD3) CHF6467

Reporting group description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort C consisted of 6 subjects that received the active drug CHF6467 at a dose of 3 µg/mm² ulcer area, and 2 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 1: Cohort D (SD4) CHF6467

Reporting group description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort D consisted of 6 subjects that received the active drug CHF6467 at a dose of 6 µg/mm² ulcer area, and 2 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 1: Placebo

Reporting group description:

Part 1_Includes subjects from Cohorts A, B, C, D who received placebo and are respectively:
Cohort A_2 subjects
Cohort B_3 subjects
Cohort C_2 subjects
Cohort D_2 subjects

Reporting group title	Part 2: Cohort E (MD1) CHF6467

Reporting group description:

Part 2: Multiple ascending doses in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, multiple ascending doses, parallel group design in 2 Cohorts (E, F).
During Part 2, two total dose levels of CHF6467 were administered topically applied as a once daily (q.d.) regimen, for 14 consecutive days according to an escalation scheme.
Cohort E consisted of 17 subjects that received the active drug CHF6467 at a dose of 1 µg/mm²/day for 14 consecutive days q.d., and 10 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 2: Cohort F (MD2) CHF6467

Reporting group description:

Part 2: Multiple ascending doses in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, multiple ascending doses, parallel group design in 2 Cohorts (E, F).
During Part 2, two total dose levels of CHF6467 were administered topically applied as a once daily (q.d.) regimen, for 14 consecutive days according to an escalation scheme.
Cohort F consisted of 18 subjects that received the active drug CHF6467 at a dose of 3 µg/mm²/day for 14 consecutive days q.d., and 10 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 2: Placebo

Reporting group description:

Part 2_Includes subjects from Cohorts E, F who received placebo and are respectively:
Cohort E_10 subjects
Cohort F_10 subjects

Reporting group values	Part 1: Cohort A (SD1) CHF6467	Part 1: Cohort B (SD2) CHF6467	Part 1: Cohort C (SD3) CHF6467
Number of subjects	6	6	6
Age categorical Units: Subjects			
Adults (18-64 years)	4	4	4
From 65-84 years	2	2	2
Age continuous Units: years			
arithmetic mean	58.2	60.2	62.3
standard deviation	± 11.8	± 11.5	± 10.3
Gender categorical Units: Subjects			
Female	1	1	1
Male	5	5	5
Race Units: Subjects			
White	6	6	6
Body Mass Index (BMI) Units: kg/m2			
arithmetic mean	32.39	30.51	28.93
standard deviation	± 3.25	± 5.52	± 2.74

Reporting group values	Part 1: Cohort D (SD4) CHF6467	Part 1: Placebo	Part 2: Cohort E (MD1) CHF6467
Number of subjects	6	9	20
Age categorical Units: Subjects			
Adults (18-64 years)	3	7	15
From 65-84 years	3	2	5

Age continuous			
Units: years			
arithmetic mean	62.5	57.8	58.0
standard deviation	± 9.2	± 8.9	± 9.1
Gender categorical			
Units: Subjects			
Female	1	2	3
Male	5	7	17
Race			
Units: Subjects			
White	6	9	20
Body Mass Index (BMI)			
Units: kg/m2			
arithmetic mean	31.20	31.23	29.957
standard deviation	± 4.26	± 3.57	± 5.319

Reporting group values	Part 2: Cohort F (MD2) CHF6467	Part 2: Placebo	Total
Number of subjects	21	20	94
Age categorical			
Units: Subjects			
Adults (18-64 years)	18	12	67
From 65-84 years	3	8	27
Age continuous			
Units: years			
arithmetic mean	56.7	60.8	
standard deviation	± 8.6	± 8.4	-
Gender categorical			
Units: Subjects			
Female	3	2	14
Male	18	18	80
Race			
Units: Subjects			
White	21	20	94
Body Mass Index (BMI)			
Units: kg/m2			
arithmetic mean	29.338	29.342	
standard deviation	± 5.116	± 3.067	-

End points

End points reporting groups

Reporting group title	Part 1: Cohort A (SD1) CHF6467

Reporting group description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort A consisted of 6 subjects that received the active drug CHF6467 at a dose of 0.3 µg/mm² ulcer area, and 2 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 1: Cohort B (SD2) CHF6467

Reporting group description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort B consisted of 6 subjects that received the active drug CHF6467 at a dose of 1.0 µg/mm² ulcer area, and 3 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 1: Cohort C (SD3) CHF6467

Reporting group description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort C consisted of 6 subjects that received the active drug CHF6467 at a dose of 3 µg/mm² ulcer area, and 2 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 1: Cohort D (SD4) CHF6467

Reporting group description:

Part 1: Single ascending dose in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, single ascending dose, parallel group design in 4 Cohorts (A, B, C, D).
During Part 1, four single dose levels of CHF6467 were administered topically according to an escalating dose regimen.
Cohort D consisted of 6 subjects that received the active drug CHF6467 at a dose of 6 µg/mm² ulcer area, and 2 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 1: Placebo

Reporting group description:

Part 1_Includes subjects from Cohorts A, B, C, D who received placebo and are respectively:
Cohort A_2 subjects
Cohort B_3 subjects
Cohort C_2 subjects
Cohort D_2 subjects

Reporting group title	Part 2: Cohort E (MD1) CHF6467

Reporting group description:

Part 2: Multiple ascending doses in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, multiple ascending doses, parallel group design in 2 Cohorts (E, F).
During Part 2, two total dose levels of CHF6467 were administered topically applied as a once daily (q.d.) regimen, for 14 consecutive days according to an escalation scheme.
Cohort E consisted of 17 subjects that received the active drug CHF6467 at a dose of 1 µg/mm²/day for 14 consecutive days q.d., and 10 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 2: Cohort F (MD2) CHF6467

Reporting group description:

Part 2: Multiple ascending doses in subjects with neuropathic DFUs.
Randomised, double-blind, placebo-controlled, multiple ascending doses, parallel group design in 2 Cohorts (E, F).
During Part 2, two total dose levels of CHF6467 were administered topically applied as a once daily (q.d.) regimen, for 14 consecutive days according to an escalation scheme.
Cohort F consisted of 18 subjects that received the active drug CHF6467 at a dose of 3 µg/mm²/day for 14 consecutive days q.d., and 10 subjects dosed with matching placebo.
The doses to be administered were adapted based on the actual ulcer area.

Reporting group title	Part 2: Placebo

Reporting group description:

Part 2_Includes subjects from Cohorts E, F who received placebo and are respectively:
Cohort E_10 subjects
Cohort F_10 subjects

Subject analysis set title	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomised subjects who received at least one dose of study treatment.

Subject analysis set title	Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomised subjects who received at least one dose of study treatment.

Subject analysis set title	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomised subjects who received at least one dose of study treatment.

Subject analysis set title	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomised subjects who received at least one dose of study treatment.

Subject analysis set title	Part 1: Placebo - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomised subjects who received at least one dose of study treatment.

Subject analysis set title	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomised subjects who received at least one dose of study treatment.

Subject analysis set title	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomised subjects who received at least one dose of study treatment.

Subject analysis set title	Part 2: Placebo - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomised subjects who received at least one dose of study treatment.

Subject analysis set title	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PD population included all subjects from Safety set, also having evaluable PD data (ulcer tissue measurements) in at least one timepoint after the first administration of the study drug and without any major protocol deviation affecting PD evaluation.

Subject analysis set title	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PD population included all subjects from Safety set, also having evaluable PD data (ulcer tissue measurements) in at least one timepoint after the first administration of the study drug and without any major protocol deviation affecting PD evaluation.

Subject analysis set title	Part 2: Placebo - PD set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PD population included all subjects from Safety set, also having evaluable PD data (ulcer tissue measurements) in at least one timepoint after the first administration of the study drug and without any major protocol deviation affecting PD evaluation.

Subject analysis set title	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - PK set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population included all subjects from the safety set excluding subjects without any valid PK measurement and with major protocol deviations affecting PK evaluations.

Subject analysis set title	Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - PK set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population included all subjects from the safety set excluding subjects without any valid PK measurement and with major protocol deviations affecting PK evaluations.

Subject analysis set title	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - PK set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population included all subjects from the safety set excluding subjects without any valid PK measurement and with major protocol deviations affecting PK evaluations.

Subject analysis set title	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - PK set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population included all subjects from the safety set excluding subjects without any valid PK measurement and with major protocol deviations affecting PK evaluations.

Subject analysis set title	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population included all subjects from the safety set excluding subjects without any valid PK measurement and with major protocol deviations affecting PK evaluations.

Subject analysis set title	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK population included all subjects from the safety set excluding subjects without any valid PK measurement and with major protocol deviations affecting PK evaluations.

Primary: 1_Part 1 - Abnormal SBP and DBP Change from baseline - Any post-baseline timepoint

End point title	1_Part 1 - Abnormal SBP and DBP Change from baseline - Any post-baseline timepoint[1]

End point description:

Systolic and diastolic blood pressure was measured after at least 5 min rest in supine position.
Vital signs could be repeated at the discretion of the Investigator for the purposes of safety or to confirm eligibility.
Baseline is defined as pre-dose value on Day 1 of each treatment for Cohorts A, B, C and D.
The number of subjects contributing to the data is indicated (Cohort A, B, C and D).
Then, presented values are representative results of all post-dose time points.
The following change from baseline abnormality categories was defined:
• > 20mmHg for systolic blood pressure;
• > 10mmHg for diastolic blood pressure.

End point type	Primary

End point timeframe:

At any timepoint:
On Day 1 at pre-dose, 15, 30 min, 1, 2, 4, 8, 12 h post-dose, on Day 2 at 24 h post-dose, on Day 3 at 48 h post-dose, on Day 4 at 72 h post-dose, and at follow-up.

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: No statistical evaluation was performed.
The focus of the primary end points was safety.
Evaluation of the safety data was done descriptively

End point values	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - Safety	Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - Safety	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - Safety	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	6	6
Units: subjects				
SBP > 20 mmHg	0	1	0	0
DBP > 10 mmHg	2	0	1	2

End point values	Part 1: Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: subjects				
SBP > 20 mmHg	0			
DBP > 10 mmHg	1			

Statistical analyses

No statistical analyses for this end point

Primary: 2_Part 1 - Abnormal QTcF Change from baseline - Any timepoint

End point title	2_Part 1 - Abnormal QTcF Change from baseline - Any

	timepoint[2]

End point description:

QtcF is QT corrected for the heart rate with the Fridericia formula and derived from triplicate 12-lead ECG parameters extracted from Holter.

End point type	Primary

End point timeframe:

On Day 1 at 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 14 h post-dose.
On Day 2 at 24 h post-dose. On screening using the time-matched points from Day 1.

Notes:

[2] - 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 evaluation was performed.
The focus of the primary end points was safety.
Evaluation of the safety data was done descriptively.

End point values	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - Safety	Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - Safety	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - Safety	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	6	6
Units: subjects				
QTcF <= 30 msec	5	6	6	5
30 <= QTcF change from Baseline <= 60 msec	1	0	0	1
QTcF change from baseline > 60 msec	0	0	0	0

End point values	Part 1: Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: subjects				
QTcF <= 30 msec	9			
30 <= QTcF change from Baseline <= 60 msec	0			
QTcF change from baseline > 60 msec	0			

Statistical analyses

No statistical analyses for this end point

Primary: 3_Part 1 - Heart rate (0-24 h) - Change from Baseline

End point title	3_Part 1 - Heart rate (0-24 h) - Change from Baseline

End point description:

Data were derived from measurements using 12-lead ECG, extracted from 24 h Holter monitoring.
For 12-lead ECG parameter extracted from Holter (HR) the baseline value is defined at each time point as the time-matched triplicate (mean values) at screening. For HR0-24 extracted from Holter the baseline value is the HR0-24 value at screening.
Data are presented as mean and standard deviation.

End point type	Primary

End point timeframe:

24 h 12-lead digital Holter ECG recording: at screening visit, on Day 1 from at least 90 min prior to dosing up to at least 24 h post-dose, on Day 2, and at follow-up.

End point values	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - Safety	Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - Safety	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - Safety	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	6	6
Units: bpm				
arithmetic mean (standard deviation)	-7.8 (± 6.2)	-8.7 (± 7.8)	-8.2 (± 5.1)	-3.7 (± 4.2)

End point values	Part 1: Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: bpm				
arithmetic mean (standard deviation)	-8.4 (± 6.0)			

Statistical analyses

Statistical analysis title	1_CHF6467 SD1 VS Placebo

Statistical analysis description:

HR0-24 extracted from Holter: Mean difference vs. placebo in change from baseline was calculated for HR0-24 for each dose level and 90% CI derived using ANCOVA models with treatment as fixed effect and baseline as covariate.

Comparison groups	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - Safety v Part 1: Placebo - Safety
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.954
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.2
upper limit	4.8

Notes:

[3] - Adjusted mean difference

Statistical analysis title	2_CHF6467 SD2 VS Placebo

Statistical analysis description:

HR0-24 extracted from Holter: Mean difference vs. placebo in change from baseline was calculated for HR0-24 for each dose level and 90% CI derived using ANCOVA models with treatment as fixed effect and baseline as covariate.

Comparison groups	Part 1: Placebo - Safety v Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - Safety
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.736
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6
upper limit	4

Notes:

[4] - Adjusted mean difference

Statistical analysis title	3_CHF6467 SD3 VS Placebo

Statistical analysis description:

HR0-24 extracted from Holter: Mean difference vs. placebo in change from baseline was calculated for HR0-24 for each dose level and 90% CI derived using ANCOVA models with treatment as fixed effect and baseline as covariate.

Comparison groups	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - Safety v Part 1: Placebo - Safety
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.802
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.8
upper limit	4.3

Notes:

[5] - Adjusted mean difference

Statistical analysis title	4_CHF6467 SD4 VS Placebo

Statistical analysis description:

HR0-24 extracted from Holter: Mean difference vs. placebo in change from baseline was calculated for HR0-24 for each dose level and 90% CI derived using ANCOVA models with treatment as fixed effect and baseline as covariate.

Comparison groups	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - Safety v Part 1: Placebo - Safety

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.163
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.8
upper limit	9.2

Notes:

[6] - Adjusted mean difference

Primary: 4_Part 2 - Abnormal SBP and DBP - Any post-baseline timepoint

End point title	4_Part 2 - Abnormal SBP and DBP - Any post-baseline timepoint[7]

End point description:

Systolic and diastolic blood pressure was measured after at least 5 min rest in supine position.
Vital signs could be repeated at the discretion of the Investigator for the purposes of safety or to confirm eligibility.

End point type	Primary

End point timeframe:

On Day 1 and on the day of last administration (Day 14) at pre-dose and 15, 30 min, 1, 2, 4, 8, 12 h post-dose, from Day 2 to Day 13 at pre-dose in the morning, and on Day 15 (24 h post-dose after Day 14 administration), at follow-up.

Notes:

[7] - 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 evaluation was performed.
The focus of the primary end points was safety.
Evaluation of the safety data was done descriptively.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - Safety	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - Safety	Part 2: Placebo - Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	21	20	
Units: subjects				
SBP > 20 mmHg	4	2	1	
DBP > 10 mmHg	10	2	4	

Statistical analyses

No statistical analyses for this end point

Primary: 5_Part 2 - Abnormal QTcF Change from baseline - Any post-dose timepoint

End point title	5_Part 2 - Abnormal QTcF Change from baseline - Any post-dose timepoint[8]

End point description:

QTcF is QT corrected for the heart rate with the Fridericia formula and derived from triplicate 12-lead ECG parameters extracted from Holter.

End point type	Primary

End point timeframe:

On Day 1 at 15, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 h post-dose and at 24 h post-on Day 1 dose (Day 2), on the last administration day (Day 14) at 15, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 24 h 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 evaluation was performed.
The focus of the primary end points was safety.
Evaluation of the safety data was done descriptively.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - Safety	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - Safety	Part 2: Placebo - Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	21	20	
Units: subjects				
QTcF <=30 msec	17	20	19	
30 <= QTcF change from Baseline <= 60 msec	3	1	1	
QTcF change from Baseline > 60 msec	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: 6_Part 2 - Abnormal QTcF Change from baseline - Day 1 Any timepoint

End point title	6_Part 2 - Abnormal QTcF Change from baseline - Day 1 Any timepoint[9]

End point description:

QTcF is QT corrected for the heart rate with the Fridericia formula and derived from triplicate 12-lead ECG parameters extracted from Holter.

End point type	Primary

End point timeframe:

On Day 1 at 15, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 h post-dose and at 24 h post-on Day 1 dose (Day 2), on the last administration day (Day 14) at 15, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 24 h post-dose.

Notes:

[9] - 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 evaluation was performed.
The focus of the primary end points was safety.
Evaluation of the safety data was done descriptively.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - Safety	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - Safety	Part 2: Placebo - Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	21	20	
Units: subjects				
QTcF <=30 msec	18	20	19	
30 <= QTcF change from Baseline <= 60 msec	2	1	1	
QTcF change from baseline > 60 msec	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: 7_Part 2 - Abnormal QTcF Change from Baseline - Day 14 Any timepoint

End point title	7_Part 2 - Abnormal QTcF Change from Baseline - Day 14 Any timepoint[10]

End point description:

QTcF is QT corrected for the heart rate with the Fridericia formula and derived from triplicate 12-lead ECG parameters extracted from Holter.

End point type	Primary

End point timeframe:

On Day 1 at 15, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 h, post-dose and at 24 h post-on Day 1 dose (Day 2), on the last administration day (Day 14) at 15, 30, 45 min, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 24 h post-dose.

Notes:

[10] - 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 evaluation was performed.
The focus of the primary end points was safety.
Evaluation of the safety data was done descriptively.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - Safety	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - Safety	Part 2: Placebo - Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	19	20	20	
Units: subjects				
QTcF <=30 msec	17	20	20	
30 <= QTcF change from Baseline <= 60 msec	2	0	0	
QTcF change from baseline > 60 msec	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: 8_Part 2 - Abnormal Heart rate (0-24 h) Change from baseline - Day 1	
End point title	8_Part 2 - Abnormal Heart rate (0-24 h) Change from baseline - Day 1

End point description:

ECG Mean Heart Rate (beats/min) Change from Baseline to Treatment Day 1, 24 h.
Data are presented as mean and Standard Deviation.

End point type	Primary

End point timeframe:

24 h 12-lead digital Holter ECG recording: at screening visit, on Day 1 and last administration day (Day 14) from at least 90 min prior to dosing up to at least 24 h post-dose. At Day 28 follow-up.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - Safety	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - Safety	Part 2: Placebo - Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	16	16	18	
Units: bpm				
arithmetic mean (standard deviation)	-4.1 (± 6.7)	-7.4 (± 9.2)	-3.7 (± 5.9)	

Statistical analyses

Statistical analysis title	1_CHF6467 MD1 VS Placebo

Statistical analysis description:

HR0-24 extracted from Holter: Mean difference vs. placebo in change from baseline was calculated for HR0-24 for each dose level and 90% CI derived using ANCOVA models with treatment as fixed effect and baseline as covariate.
Estimates was provided for Day 1 and Day 14.

Comparison groups	Part 2: Placebo - Safety v Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - Safety
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.669
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.6
upper limit	4.4

Notes:

[11] - Adjusted mean difference

Statistical analysis title	2_CHF6467 MD2 VS Placebo

Statistical analysis description:

HR0-24 extracted from Holter: Mean difference vs. placebo in change from baseline was calculated for

HR0-24 for each dose level and 90% CI derived using ANCOVA models with treatment as fixed effect and baseline as covariate.
Estimates was provided for Day 1 and Day 14.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - Safety v Part 2: Placebo - Safety
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.308
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.6
upper limit	1.3

Notes:

[12] - Adjusted mean difference

Primary: 9_Part 2 - Abnormal Heart rate (0-24 h) Change from baseline - Day 14

End point title	9_Part 2 - Abnormal Heart rate (0-24 h) Change from baseline - Day 14

End point description:

ECG Mean Heart Rate (beats/min) Change from Baseline to Treatment Day 14, 24 h.
Data are presented as mean and Standard Deviation.

End point type	Primary

End point timeframe:

24 h 12-lead digital Holter ECG recording: at screening visit, on Day 1 and last administration day (Day 14) from at least 90 min prior to dosing up to at least 24 h post-dose. At Day 28 follow-up.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - Safety	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - Safety	Part 2: Placebo - Safety	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	17	17	17	
Units: bpm				
arithmetic mean (standard deviation)	-6.1 (± 9.1)	-8.6 (± 8.1)	-4.8 (± 5.0)	

Statistical analyses

Statistical analysis title	1_CHF6467 MD1 VS Placebo

Statistical analysis description:

HR0-24 extracted from Holter: Mean difference vs. placebo in change from baseline was calculated for HR0-24 for each dose level and 90% CI derived using ANCOVA models with treatment as fixed effect and baseline as covariate.
Estimates was provided for Day 1 and Day 14.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - Safety v

	Part 2: Placebo - Safety
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.722
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.8
upper limit	4.3

Notes:

[13] - Adjusted mean difference

Statistical analysis title	2_CHF6467 MD2 VS Placebo

Statistical analysis description:

HR0-24 extracted from Holter: Mean difference vs. placebo in change from baseline was calculated for HR0-24 for each dose level and 90% CI derived using ANCOVA models with treatment as fixed effect and baseline as covariate.
Estimates was provided for Day 1 and Day 14.

Comparison groups	Part 2: Placebo - Safety v Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - Safety
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.197
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.2
upper limit	0.8

Notes:

[14] - Adjusted mean difference

Secondary: 10_Part 1 - Cmax - PK

End point title	10_Part 1 - Cmax - PK

End point description:

Cmax is the value of the maximum plasma concentration of CHF6467.
Dose proportionality (assessed considering the absolute individual dose) of CHF6467 for Cmax was evaluated using the power model, including the log-transformed PK parameters as dependent variables and the log-transformed CHF6467 dose as fixed effect.
The slope for log-transformed dose (ß) was estimated with its 90% CI to examine dose proportionality.
Data are presented as mean and standard deviation.
Statistical analysis was not reported but was performed.
The results are described below:
The 90% CI of the slope of Cmax did not include 1, indicating that CHF6467 Cmax did not increase dose-proportionally but less than dose-proportionally between 1 µg/mm2 and 6 µg/mm2.

End point type	Secondary

End point timeframe:

The Cmax of CHF6467 was studied in serum up to 72 h post-dose after four single ascending topical doses (CHF6467 SD1 0.3 µg/mm2; CHF6467 SD2 1 µg/mm2; CHF6467 SD3 3 µg/mm2; CHF6467 SD4 6 µg/mm2) in subjects with DFU.

End point values	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - PK set	Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - PK set	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - PK set	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - PK set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2[15]	4[16]	5[17]	5[18]
Units: pg/mL				
arithmetic mean (standard deviation)	1.27 (± 0.948)	8.58 (± 5.46)	4.58 (± 3.61)	9.67 (± 9.22)

Notes:

[15] - PK population

[16] - PK population

[17] - PK population

[18] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 11_Part 1 - AUC 0-t - PK

End point title	11_Part 1 - AUC 0-t - PK

End point description:

AUC 0-t is the area under the plasma concentration-time curve from 0 to the last quantifiable concentration, computed using the linear trapezoidal rule.
Dose proportionality (assessed considering the absolute individual dose) of CHF6467 for AUC 0-t was evaluated using the power model, including the log-transformed pharmacokinetic parameters as dependent variables and the log transformed CHF6467 dose as fixed effect. The slope for log-transformed dose (ß) was estimated with its 90% CI to examine dose proportionality.
Data are presented as mean and standard deviation.

Statistical analysis was not reported but was performed.
The results are described below:
The 90% CI of the slope of AUC 0-t included 1, suggesting that CHF6467 AUC 0-t increased dose proportionally. However, it can be noted that the point estimate (PE) was not close to 1 and that the mean AUC 0-t values were comparable for both 1 µg/mm² and 6 µg/mm² doses and the intersubject variability was high.

End point type	Secondary

End point timeframe:

The AUC 0-t of CHF6467 was studied in serum up to 72 h post-dose after four single ascending topical doses (CHF6467 SD1 0.3 µg/mm²; CHF6467 SD2 1 µg/mm²; CHF6467 SD3 3 µg/mm²; CHF6467 SD4 6 µg/mm²) in subjects with DFU.

End point values	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - PK set	Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - PK set	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - PK set	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - PK set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[19]	4[20]	4[21]	5[22]
Units: pg.h/mL				
arithmetic mean (standard deviation)	6.25 (± 0)	43.4 (± 28.5)	53.8 (± 74.7)	43.1 (± 36.9)

Notes:

[19] - PK population
CHF6467 SD1 SD= Not Calculated

[20] - PK population

[21] - PK population

[22] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 12_Part 1 - Tmax - PK

End point title	12_Part 1 - Tmax - PK

End point description:

Tmax is the time of the maximum plasma concentration of CHF6467, obtained directly from the experimental data without interpolation.
Data are presented as median (minimum-maximum).

End point type	Secondary

End point timeframe:

The Tmax of CHF6467 was studied in serum up to 72 h post-dose after four single ascending topical doses (CHF6467 SD1 0.3 µg/mm2; CHF6467 SD2 1 µg/mm2; CHF6467 SD3 3 µg/mm2; CHF6467 SD4 6 µg/mm2) in subjects with DFU.

End point values	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - PK set	Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - PK set	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - PK set	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - PK set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2[23]	4[24]	5[25]	5[26]
Units: hours				
median (full range (min-max))	3.40 (0.75 to 6.05)	2.50 (2.0 to 3.0)	2.0 (0.75 to 6.0)	2.0 (0.50 to 2.0)

Notes:

[23] - PK population

[24] - PK population

[25] - PK population

[26] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 13_Part 2 - Cmax - Day 1 - PK

End point title	13_Part 2 - Cmax - Day 1 - PK

End point description:

Cmax is the value of the maximum plasma concentration of CHF6467.
The dose proportionality (assessed as absolute individual dose) of CHF6467 for Cmax was evaluated using the power model, including the log-transformed PK parameters as dependent variables and the log-transformed dose as fixed effect. The analysis was performed separately on Day 1 and on the last administration day. The slope for log-transformed dose (ß) was estimated with its 90% CI to examine dose proportionality.
Data are presented as mean and standard deviation.

End point type	Secondary

End point timeframe:

After repeated q.d. CHF6467 topical doses for 14 days in subjects with DFU, the Cmax of CHF6467 was studied in serum up to 24 h post-dose after the first dose and 336 h post-dose (i.e., 14 days after the last CHF6467 application) after the last dose.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[27]	10[28]		
Units: pg/mL				
arithmetic mean (standard deviation)	2.37 (± 1.54)	3.77 (± 3.64)		

Notes:

[27] - PK population

[28] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 14_Part 2 - Cmax - Day 14 - PK

End point title	14_Part 2 - Cmax - Day 14 - PK

End point description:

Cmax is the value of the maximum plasma concentration of CHF6467.
The dose proportionality (assessed as absolute individual dose) of CHF6467 for Cmax was evaluated using the power model, including the log-transformed PK parameters as dependent variables and the log-transformed dose as fixed effect. The analysis was performed separately on Day 1 and on the last administration day. The slope for log-transformed dose (ß) was estimated with its 90% CI to examine dose proportionality.
Data are presented as mean and standard deviation.

End point type	Secondary

End point timeframe:

After repeated q.d. CHF6467 topical doses for 14 days in subjects with DFU, the Cmax of CHF6467 was studied in serum up to 24 h post-dose after the first dose and 336 h post-dose (i.e., 14 days after the last CHF6467 application) after the last dose.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[29]	9[30]		
Units: pg/mL				
arithmetic mean (standard deviation)	1.93 (± 1.24)	5.90 (± 7.39)		

Notes:

[29] - PK population

[30] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 15_Part 2 - AUC 0-t - Day 1 - PK

End point title	15_Part 2 - AUC 0-t - Day 1 - PK

End point description:

AUC 0-t is the area under the plasma concentration-time curve from 0 to the last quantifiable concentration, computed using the linear trapezoidal rule.
Data are presented as mean and standard deviation.

End point type	Secondary

End point timeframe:

After repeated q.d. CHF6467 topical doses for 14 days in subjects with DFU, the AUC 0-t of CHF6467 was studied in serum up to 24 h post-dose after the first dose and 336 h post-dose (i.e., 14 days after the last CHF6467 application) after the last dose.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[31]	10[32]		
Units: pg.h/mL				
arithmetic mean (standard deviation)	7.77 (± 8.31)	27.7 (± 48.9)		

Notes:

[31] - PK population

[32] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 16_Part 2 - AUC 0-t - Day 14 - PK

End point title	16_Part 2 - AUC 0-t - Day 14 - PK

End point description:

AUC 0-t is the area under the plasma concentration-time curve from 0 to the last quantifiable concentration, computed using the linear trapezoidal rule.
Data are presented as mean and standard deviation.

End point type	Secondary

End point timeframe:

After repeated q.d. CHF6467 topical doses for 14 days in subjects with DFU, the AUC 0-t of CHF6467 was studied in serum up to 24 h post-dose after the first dose and 336 h post-dose (i.e., 14 days after the last CHF6467 application) after the last dose.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[33]	9[34]		
Units: pg.h/mL				
arithmetic mean (standard deviation)	26.5 (± 65.6)	131 (± 201)		

Notes:

[33] - PK population

[34] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 17_Part 2 - AUC 0-12 - Day 1 - PK

End point title	17_Part 2 - AUC 0-12 - Day 1 - PK

End point description:

AUC 0-12 is the area under the plasma concentration-time curve from 0 to 12 hours post-dose of CHF6467.
Data are presented as mean and standard deviation.

End point type	Secondary

End point timeframe:

After repeated q.d. CHF6467 topical doses for 14 days in subjects with DFU, the PK of CHF6467 was studied in serum up to 12 h post-dose after the first dose and 336 h post-dose (i.e., 14 days after the last CHF6467 application) after the last dose.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2[35]	2[36]		
Units: pg.h/mL				
arithmetic mean (standard deviation)	22.4 (± 1.15)	67.1 (± 44.0)		

Notes:

[35] - PK population

[36] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 18_Part 2 - AUC 0-12 - Day 14 - PK

End point title	18_Part 2 - AUC 0-12 - Day 14 - PK

End point description:

AUC 0-12 is the area under the plasma concentration-time curve from 0 to 12 hours post-dose of CHF6467.
Data are presented as mean and standard deviation.

End point type	Secondary

End point timeframe:

After repeated q.d. CHF6467 topical doses for 14 days in subjects with DFU, the PK of CHF6467 was studied in serum up to 12 h post-dose after the first dose and 336 h post-dose (i.e., 14 days after the last CHF6467 application) after the last dose.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[37]	6[38]		
Units: pg.h/mL				
arithmetic mean (standard deviation)	27.2 (± 0)	54.7 (± 62.8)		

Notes:

[37] - PK population
SD=Not Calculated
[38] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 19_Part 2 - Ulcer Area (cm²) Actual Values - Baseline - PD

End point title	19_Part 2 - Ulcer Area (cm²) Actual Values - Baseline - PD

End point description:

Ulcer tissue measurements was performed following the standard of care procedure at the time points indicated in the Timeframe. Area (in cm²), volume (in cm³), average depth (in mm), maximum depth (in mm), perimeter (in cm), tissue type 1 to 7 presence (yes/no), and tissue type 1 to 7 percentage, if present and measured.
Tissue types:
- Type 1: Granulating tissue/Granulation
- Type 2: Hypergranulating tissue/Hypergranulation
- Type 3: Epithelizing tissue/epithelial
- Type 4: Healed tissue/healthy
- Type 5: Scab/Eschar
- Type 6: Necrotic tissue/Slough
- Type 7: Other/not classified
Data are presented as mean and standard deviation.

End point type	Secondary

End point timeframe:

Timing of the ulcer measurements
- During treatment period: daily assessments (from Day 1 to Day 15)
- During the follow-up period: weekly assessments (Day 21, Day 28, Day 35, Day 42, Day 49, Day 56, Day 63, Day 70, Day 77, Day 84).

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set	Part 2: Placebo - PD set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[39]	20[40]	20[41]	
Units: cm2				
arithmetic mean (standard deviation)	4.190 (± 0.770)	3.620 (± 0.841)	3.745 (± 0.737)	

Notes:

[39] - PD population

[40] - PD population

[41] - PD population

Statistical analyses

Statistical analysis title	1_CHF6467 MD1 VS Placebo

Statistical analysis description:

The model for repeated measures (MMRM) is linear mixed model including treatment, visit, and treatment by visit interaction as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed and the Kenward-Roger adjustment was used for the degrees of freedom.

Comparison groups	Part 2: Placebo - PD set v Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	= 0.691
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.54

Notes:

[42] - MMRM model

Statistical analysis title	2_CHF6467 MD2 VS Placebo

Statistical analysis description:

The model for repeated measures (MMRM) is linear mixed model including treatment, visit, and treatment by visit interaction as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed and the Kenward-Roger adjustment was used for the degrees of freedom.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Placebo - PD set

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.761
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	0.75

Notes:

[43] - MMRM Model

Statistical analysis title	3_CHF6467 MD1 VS CHF6467 MD2

Statistical analysis description:

The model for repeated measures (MMRM) is linear mixed model including treatment, visit, and treatment by visit interaction as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix was assumed and the Kenward-Roger adjustment was used for the degrees of freedom.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	= 0.495
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	0.45

Notes:

[44] - MMRM Model

Secondary: 20_Part 2 - Ulcer Area (cm²) Change from baseline - Day 14 - PD

End point title	20_Part 2 - Ulcer Area (cm²) Change from baseline - Day 14 - PD

End point description:

Ulcer tissue measurements was performed following the standard of care procedure at the time points indicated in the Timeframe. Area (in cm²), volume (in cm³), average depth (in mm), maximum depth (in mm), perimeter (in cm), tissue type 1 to 7 presence (yes/no), and tissue type 1 to 7 percentage, if present and measured.
Tissue types:
- Type 1: Granulating tissue/Granulation
- Type 2: Hypergranulating tissue/Hypergranulation
- Type 3: Epithelizing tissue/epithelial
- Type 4: Healed tissue/healthy
- Type 5: Scab/Eschar
- Type 6: Necrotic tissue/Slough
- Type 7: Other/not classified

Data are presented as mean and standard deviation.

End point type	Secondary

End point timeframe:

Timing of the ulcer measurements
- During treatment period: daily assessments (from Day 1 to Day 15)
- During the follow-up period: weekly assessments (Day 21, Day 28, Day 35, Day 42, Day 49, Day 56, Day 63, Day 70, Day 77, Day 84).

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set	Part 2: Placebo - PD set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	19[45]	20[46]	20[47]	
Units: cm2				
arithmetic mean (standard deviation)	-1.626 (± 0.892)	-1.395 (± 0.630)	-1.630 (± 0.761)	

Notes:

[45] - PD population

[46] - PD population

[47] - PD population

Statistical analyses

Statistical analysis title	1_CHF6467 MD1 VS Placebo

Statistical analysis description:

P-values and estimates are based on an MMRM model on Change From Baseline including Treatment, Visit, Baseline, Treatment by Visit interaction and Treatment by Baseline interaction as effects.
An unstructured covariance matrix is assumed and Kenward-Roger adjustment was used for the degrees of freedom.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set v Part 2: Placebo - PD set
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[48]
P-value	= 0.761
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	0.56

Notes:

[48] - Adjusted mean difference

Statistical analysis title	2_CHF6467 MD2 VS Placebo

Statistical analysis description:

P-values and estimates are based on an MMRM model on Change From Baseline including Treatment, Visit, Baseline, Treatment by Visit interaction and Treatment by Baseline interaction as effects.

An unstructured covariance matrix is assumed and Kenward-Roger adjustment was used for the degrees of freedom.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Placebo - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	= 0.428
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.89

Notes:

[49] - Adjusted mean difference

Statistical analysis title	3_CHF6467 MD1 VS CHF6467 MD2

Statistical analysis description:

P-values and estimates are based on an MMRM model on Change From Baseline including Treatment, Visit, Baseline, Treatment by Visit interaction and Treatment by Baseline interaction as effects.
An unstructured covariance matrix is assumed and Kenward-Roger adjustment was used for the degrees of freedom.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[50]
P-value	= 0.292
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	0.31

Notes:

[50] - Adjusted mean difference

Secondary: 21_Part 2 - Ulcer Area (cm²) Change from baseline - Day 84 - PD

End point title	21_Part 2 - Ulcer Area (cm²) Change from baseline - Day 84 - PD

End point description:

Ulcer tissue measurements were performed following the standard of care procedure at the time points indicated in the Timeframe. Area (in cm²), volume (in cm³), average depth (in mm), maximum depth (in mm), perimeter (in cm), tissue type 1 to 7 presence (yes/no), and tissue type 1 to 7 percentage, if present and measured.
Tissue types:
- Type 1: Granulating tissue/Granulation
- Type 2: Hypergranulating tissue/Hypergranulation
- Type 3: Epithelizing tissue/epithelial

- Type 4: Healed tissue/healthy
- Type 5: Scab/Eschar
- Type 6: Necrotic tissue/Slough
- Type 7: Other/not classified

Data are presented as mean and standard deviation.

End point type	Secondary

End point timeframe:

Timing of the ulcer measurements
- During treatment period: daily assessments (from Day 1 to Day 15)
- During the follow-up period: weekly assessments (Day 21, Day 28, Day 35, Day 42, Day 49, Day 56, Day 63, Day 70, Day 77, Day 84).

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set	Part 2: Placebo - PD set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	17	18	17	
Units: cm2				
arithmetic mean (standard deviation)	-3.224 (± 1.513)	-2.844 (± 0.720)	-2.835 (± 1.229)	

Statistical analyses

Statistical analysis title	1_CHF6467 MD1 VS Placebo

Statistical analysis description:

P-values and estimates are based on an MMRM model on Change From Baseline including Treatment, Visit, Baseline, Treatment by Visit interaction and Treatment by Baseline interaction as effects.
An unstructured covariance matrix is assumed and Kenward-Roger adjustment was used for the degrees of freedom.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set v Part 2: Placebo - PD set
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.541
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	0.55

Notes:

[51] - Adjusted mean difference

Statistical analysis title	2_CHF6467 MD2 VS Placebo

Statistical analysis description:

P-values and estimates are based on an MMRM model on Change From Baseline including Treatment, Visit, Baseline, Treatment by Visit interaction and Treatment by Baseline interaction as effects.
An unstructured covariance matrix is assumed and Kenward-Roger adjustment was used for the degrees of freedom.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Placebo - PD set
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[52]
P-value	= 0.605
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	0.57

Notes:

[52] - Adjusted mean difference

Statistical analysis title	3_CHF6467 MD1 VS CHF6467 MD2

Statistical analysis description:

P-values and estimates are based on an MMRM model on Change From Baseline including Treatment, Visit, Baseline, Treatment by Visit interaction and Treatment by Baseline interaction as effects.
An unstructured covariance matrix is assumed and Kenward-Roger adjustment was used for the degrees of freedom.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set v Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.913
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	0.76

Notes:

[53] - Adjusted mean difference

Secondary: 22_Part 2 - Time to Healing (days) >= 50%

End point title	22_Part 2 - Time to Healing (days) >= 50%

End point description:

Time to healing (days) is the date of healing (depending on the degree of healing as listed above).
Four different degrees of healing were computed at a given day as follow:
A) Healed_50 (Y/N) = ≥50% ulcer area reduction (also considered as the % of healed tissue);
B) Healed_66 (Y/N) = ≥66% ulcer area reduction (also considered as the % of healed tissue);
C) Healed_75 (Y/N) = ≥75% ulcer area reduction (also considered as the % of healed tissue);
D) Healed_100_CH (Y/N) = 100% ulcer area reduction (no more ulcer) also considered as the 100% of

healed tissue (Tissue type 4) (complete healing).

The subjects who contributed to the following statistical analyses of time to healing were all subjects in the PD set (both healed and non-healed subjects).

End point type	Secondary

End point timeframe:

Day 14, 21, 28, 56, and 84

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set	Part 2: Placebo - PD set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[54]	20[55]	20[56]	
Units: days				
arithmetic mean (standard deviation)	21.2 (± 19.6)	23.1 (± 20.1)	16.8 (± 10.2)	

Notes:

[54] - PD population
number of patients/number of patients with data:
20/13
[55] - PD population
number of patients/number of patients with data:
20/17
[56] - PD population
number of patients/number of patients with data:
20/16

Statistical analyses

Statistical analysis title	1_CHF6467 MD1 VS Placebo

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD1 vs Placebo.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set v Part 2: Placebo - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.148
Method	Logrank
Parameter estimate	median time to healing

Statistical analysis title	2_CHF6467 MD2 VS Placebo

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD2 vs Placebo.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Placebo - PD set

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.886
Method	Logrank
Parameter estimate	median time to healing (Days)

Statistical analysis title	3_CHF6467 MD1 VS CHF6467 MD2

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD1 vs CHF6467 MD2.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set v Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.205
Method	Logrank
Parameter estimate	median time to healing

Secondary: 23_Part 2 - Time to Healing (days) >= 66%

End point title	23_Part 2 - Time to Healing (days) >= 66%

End point description:

Time to healing (days) is the date of healing (depending on the degree of healing as listed above).
Four different degrees of healing were computed at a given day as follow:
A) Healed_50 (Y/N) = ≥50% ulcer area reduction (also considered as the % of healed tissue);
B) Healed_66 (Y/N) = ≥66% ulcer area reduction (also considered as the % of healed tissue);
C) Healed_75 (Y/N) = ≥75% ulcer area reduction (also considered as the % of healed tissue);
D) Healed_100_CH (Y/N) = 100% ulcer area reduction (no more ulcer) also considered as the 100% of healed tissue (Tissue type 4) (complete healing).

The subjects who contributed to the following statistical analyses of time to healing were all subjects in the PD set (both healed and non-healed subjects).

End point type	Secondary

End point timeframe:

Day 14, 21, 28, 56, and 84

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set	Part 2: Placebo - PD set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[57]	20[58]	20[59]	
Units: days				
arithmetic mean (standard deviation)	32.2 (± 15.0)	30.2 (± 16.6)	29.5 (± 19.9)	

Notes:
[57] - PD population
number of patients/number of patients with data:
20/12
[58] - PD population
number of patients/number of patients with data:
20/15
[59] - PD population
number of patients/number of patients with data:
20/15

Statistical analyses

Statistical analysis title	1_CHF6467 MD1 VS Placebo

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD1 vs Placebo.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set v Part 2: Placebo - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.152
Method	Logrank
Parameter estimate	median time to healing

Statistical analysis title	2_CHF6467 MD2 VS Placebo

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD2 vs Placebo.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Placebo - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.797
Method	Logrank
Parameter estimate	median time to healing

Statistical analysis title	3_CHF6467 MD1 VS CHF6467 MD2

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD1 vs CHF6467 MD2.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set v Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.245
Method	Logrank
Parameter estimate	median time to healing

Secondary: 24_Part 2 - Time to Healing (days) >= 75%

End point title	24_Part 2 - Time to Healing (days) >= 75%

End point description:

Time to healing (days) is the date of healing (depending on the degree of healing as listed above).
Four different degrees of healing were computed at a given day as follow:
A) Healed_50 (Y/N) = ≥50% ulcer area reduction (also considered as the % of healed tissue);
B) Healed_66 (Y/N) = ≥66% ulcer area reduction (also considered as the % of healed tissue);
C) Healed_75 (Y/N) = ≥75% ulcer area reduction (also considered as the % of healed tissue);
D) Healed_100_CH (Y/N) = 100% ulcer area reduction (no more ulcer) also considered as the 100% of healed tissue (Tissue type 4) (complete healing).

The subjects who contributed to the following statistical analyses of time to healing were all subjects in the PD set (both healed and non-healed subjects).

End point type	Secondary

End point timeframe:

Day 14, 21, 28, 56, and 84.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set	Part 2: Placebo - PD set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[60]	20[61]	20[62]	
Units: days				
arithmetic mean (standard deviation)	40.8 (± 18.8)	42.0 (± 19.8)	40.8 (± 20.1)	

Notes:

[60] - PD population
number of patients/number of patients with data:
20/12
[61] - PD population
number of patients/number of patients with data:
20/13
[62] - PD population
number of patients/number of patients with data:
20/13

Statistical analyses

Statistical analysis title	1_CHF6467 MD1 VS Placebo

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD1 vs Placebo.

Comparison groups	Part 2: Placebo - PD set v Part 2: Cohort E - MD1 - CHF6467 -

	1 µg/mm²/day - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.672
Method	Logrank
Parameter estimate	median time to healing

Statistical analysis title	2_CHF6467 MD2 VS Placebo

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD2 vs Placebo.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Placebo - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.916
Method	Logrank
Parameter estimate	median time to healing

Statistical analysis title	3_CHF6467 MD1 VS CHF6467 MD2

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD1 vs CHF6467 MD2.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set v Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.752
Method	Logrank
Parameter estimate	median time to healing

Secondary: 25_Part 2 - Time to Healing (days) 100%

End point title	25_Part 2 - Time to Healing (days) 100%

End point description:

Time to healing (days) is the date of healing (depending on the degree of healing as listed above).
Four different degrees of healing were computed at a given day as follow:
A) Healed_50 (Y/N) = ≥50% ulcer area reduction (also considered as the % of healed tissue);
B) Healed_66 (Y/N) = ≥66% ulcer area reduction (also considered as the % of healed tissue);
C) Healed_75 (Y/N) = ≥75% ulcer area reduction (also considered as the % of healed tissue);
D) Healed_100_CH (Y/N) = 100% ulcer area reduction (no more ulcer) also considered as the 100% of healed tissue (Tissue type 4) (complete healing).

The subjects who contributed to the following statistical analyses of time to healing were all subjects in the PD set (both healed and non-healed subjects).

End point type	Secondary

End point timeframe:

Day 14, 21, 28, 56, and 84.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set	Part 2: Placebo - PD set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[63]	20[64]	20[65]	
Units: days				
arithmetic mean (standard deviation)	43.4 (± 12.5)	59.5 (± 14.8)	47.4 (± 18.7)	

Notes:

[63] - PD population
number of patients/number of patients with data:
20/5
[64] - PD population
number of patients/number of patients with data:
20/2
[65] - PD population
number of patients/number of patients with data:
20/5

Statistical analyses

Statistical analysis title	1_CHF6467 MD1 VS Placebo

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD1 vs Placebo.

Comparison groups	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set v Part 2: Placebo - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.983
Method	Logrank
Parameter estimate	median time to healing

Statistical analysis title	2_CHF6467 MD2 VS Placebo

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD2 vs Placebo.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Placebo - PD set

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.226
Method	Logrank
Parameter estimate	median time to healing

Statistical analysis title	3_CHF6467 MD1 VS CHF6467 MD2

Statistical analysis description:

Comparison between treatments was performed using the following contrasts (P vs MD1, P vs MD2, MD1 vs MD2).
Curves were compared by the two-sided Log-Rank test.
Values present the Log-Rank test results for the comparison of CHF6467 MD1 vs CHF6467 MD2.

Comparison groups	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PD set v Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PD set
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.216
Method	Logrank
Parameter estimate	median time to healing

Secondary: 26_ Part 1 - CHF6467 Anti-Drug Antibodies Presence - Day 1 and Day 24	
End point title	26_ Part 1 - CHF6467 Anti-Drug Antibodies Presence - Day 1 and Day 24

End point description:

The potential for immunogenicity was determined by assessing the presence of CHF6467 Anti-Drug Antibodies (ADA).

No subjects were reported with the presence of CHF6467 ADAs in Part 1.

End point type	Secondary

End point timeframe:

The Blood samples were collected for the determination of CHF6467 anti-drug antibodies (ADA) presence and titer when appropriate at Day 1, pre-dose and Day 24.

End point values	Part 1: Cohort A - SD1 - CHF6467 - 0.3 µg/mm² - PK set	Part 1: Cohort B - SD2 - CHF6467 - 1 µg/mm² - PK set	Part 1: Cohort C - SD3 - CHF6467 - 3 µg/mm² - PK set	Part 1: Cohort D - SD4 - CHF6467 - 6 µg/mm² - PK set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[66]	6[67]	6[68]	6[69]
Units: subjects				
(Day 1) No	6	6	6	6
(Day 24) No	6	6	6	6

Notes:

[66] - PK population

[67] - PK population

[68] - PK population

[69] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 27_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Treatment Day 1

End point title	27_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Treatment Day 1

End point description:

The potential for immunogenicity was determined by assessing the presence of CHF6467 Anti-Drug Antibodies (ADA).

No subjects were reported with the presence of CHF6467 ADAs in Part 2 on Day 1.

End point type	Secondary

End point timeframe:

The Blood samples were collected for the determination of CHF6467 anti-drug antibodies (ADA) presence and titer when appropriate at day 1, pre-dose, Day 15, and follow-up Day 24, Day 52, and Day 80.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[70]	21[71]		
Units: subjects				
No	20	21		
Yes	0	0		

Notes:

[70] - PK population

[71] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 28_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Treatment Day 15

End point title	28_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Treatment Day 15

End point description:

The potential for immunogenicity was determined by assessing the presence of CHF6467 Anti-Drug Antibodies (ADA).

One subject had a positive ADA screening test on Day 15 after application of placebo (titer of 1), which was likely a false positive result.

End point type	Secondary

End point timeframe:

The Blood samples were collected for the determination of CHF6467 anti-drug antibodies (ADA) presence and titer when appropriate at Day 1, pre-dose, Day 15, and follow-up Day 24, Day 52, and Day 80.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[72]	20[73]		
Units: subjects				
No	19	20		
Yes	0	0		

Notes:

[72] - PK population

[73] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 29_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Follow Up Day 24

End point title	29_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Follow Up Day 24

End point description:

The potential for immunogenicity was determined by assessing the presence of CHF6467 Anti-Drug Antibodies (ADA).

One subject had a positive ADA screening test on follow-up Day 24 (titer of 10) after application of CHF6467 MD2.

End point type	Secondary

End point timeframe:

The Blood samples were collected for the determination of CHF6467 anti-drug antibodies (ADA) presence and titer when appropriate at Day 1, pre-dose, Day 15, and follow-up Day 24, Day 52, and Day 80.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[74]	19[75]		
Units: subjects				
No	19	18		
Yes	0	1		

Notes:

[74] - PK population

[75] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 30_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Follow Up Day 52

End point title	30_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Follow Up Day 52

End point description:

The potential for immunogenicity was determined by assessing the presence of CHF6467 Anti-Drug Antibodies (ADA).

One subject had a positive ADA screening test on follow-up Day 52 (titer of 5) after application of CHF6467 MD2.

End point type	Secondary

End point timeframe:

The Blood samples were collected for the determination of CHF6467 anti-drug antibodies (ADA) presence and titer when appropriate at Day 1, pre-dose, Day 15, and follow-up Day 24, Day 52, and Day 80.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18[76]	18[77]		
Units: subjects				
No	18	17		
Yes	0	1		

Notes:

[76] - PK population

[77] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: 31_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Follow Up Day 80

End point title	31_Part 2 - CHF6467 Anti-Drug Antibodies Presence - Follow Up Day 80

End point description:

The potential for immunogenicity was determined by assessing the presence of CHF6467 Anti-Drug Antibodies (ADA).

One subject had a positive ADA screening test on follow-up Day 80 (titer of 1) after application of CHF6467 MD2.

End point type	Secondary

End point timeframe:

The Blood samples were collected for the determination of CHF6467 anti-drug antibodies (ADA) presence and titer when appropriate at Day 1, pre-dose, Day 15, and follow-up Day 24, Day 52, and Day 80.

End point values	Part 2: Cohort E - MD1 - CHF6467 - 1 µg/mm²/day - PK set	Part 2: Cohort F - MD2 - CHF6467 - 3 µg/mm²/day - PK set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17[78]	18[79]		
Units: subjects				
No	17	17		
Yes	0	1		

Notes:

[78] - PK population

[79] - PK population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported from the Informed Consent signature until the subject's study participation ends (study completion or discontinuation).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Part 1: Cohort A (SD1) CHF6467

Reporting group description:

Part 1 of the study: Subjects who received a single dose of CHF6467 (total dose 0.3 µg/mm²)

Reporting group title	Part 1: Cohort B (SD2) CHF6467

Reporting group description:

Part 1 of the study: Subjects who received a single dose of CHF6467 (total dose 1 µg/mm²).

Reporting group title	Part 1: Cohort C (SD3) CHF6467

Reporting group description:

Part 1 of the study: Subjects who received a single dose of CHF6467 (total dose 3 µg/mm²).

Reporting group title	Part 1: Cohort D (SD4) CHF6467

Reporting group description:

Part 1 of the study: Subjects who received a single dose of CHF6467 (total dose 6 µg/mm²).

Reporting group title	Part 1: Placebo

Reporting group description:

Part 1 of the study: Subjects who received a single dose of Placebo.

Reporting group title	Part 2: Cohort E (MD1) CHF6467

Reporting group description:

Part 2 of the study: Subjects who received a multiple doses of CHF6467 for 14 consecutive days (total daily dose 1 µg/mm²/day).

Reporting group title	Part 2: Cohort F (MD2) CHF6467

Reporting group description:

Part 2 of the study: Subjects who received a multiple doses of CHF6467 for 14 consecutive days (total daily dose 3 µg/mm²/day).

Reporting group title	Part 2: Placebo

Reporting group description:

Part 2 of the study: Subjects who received a multiple doses of Placebo for 14 consecutive days.

Serious adverse events	Part 1: Cohort A (SD1) CHF6467	Part 1: Cohort B (SD2) CHF6467	Part 1: Cohort C (SD3) CHF6467
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Part 1: Cohort D (SD4) CHF6467	Part 1: Placebo	Part 2: Cohort E (MD1) CHF6467

Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Part 2: Cohort F (MD2) CHF6467	Part 2: Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (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: 0 %

Non-serious adverse events	Part 1: Cohort A (SD1) CHF6467	Part 1: Cohort B (SD2) CHF6467	Part 1: Cohort C (SD3) CHF6467
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	0 / 6 (0.00%)
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatine increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastric pH decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Atrial tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Supraventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Hyperchlorhydria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diabetic foot infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Erysipelas			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Coronavirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part 1: Cohort D (SD4) CHF6467	Part 1: Placebo	Part 2: Cohort E (MD1) CHF6467
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	2 / 9 (22.22%)	9 / 20 (45.00%)

Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Blood creatine increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastric pH decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Atrial tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Supraventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Ventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 6 (50.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	3	0	1

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Hyperchlorhydria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 9 (11.11%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Diabetic foot infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Infection			

subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Erysipelas			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Coronavirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 2: Cohort F (MD2) CHF6467	Part 2: Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 21 (38.10%)	13 / 20 (65.00%)	
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Blood creatine increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Gastric pH decreased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	

Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 0	0 / 20 (0.00%) 0	
Atrial tachycardia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	0 / 20 (0.00%) 0	
Supraventricular tachycardia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 20 (5.00%) 1	
Ventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 20 (5.00%) 1	
Ventricular tachycardia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	0 / 20 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	3 / 20 (15.00%) 4	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 20 (0.00%) 0	
Gastrointestinal disorders Hyperchlorhydria subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 20 (5.00%) 1	
Vomiting subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 20 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 20 (5.00%) 1	
Toothache subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	0 / 20 (0.00%) 0	

Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	1 / 21 (4.76%)	3 / 20 (15.00%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 21 (9.52%)	4 / 20 (20.00%)	
occurrences (all)	2	4	
Diabetic foot infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Erysipelas			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Coronavirus infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2019	A substantial protocol amendment (CTP version 3.0, dated 21 March 2019) was created to list and clarify all changes implemented in the protocol from version 1.0, dated 9 July 2018 to version 3.0, dated 21 March 2019. Below listed the main changes: - An additional secondary objective was added; - In the study population of Part 2, Texas grade 2A (deeper ulcers) was added to allow the recruitment of DFU subjects with ulcer located at metatarsal level where the nature of the ulcer could involve the exposure of tendon, bone, or joint capsule as per the Texas grade 2A description. Moreover, the definition of the depth (e.g., inclusion criterion 6) was clarified; - Exclusion criterion 2 (points a and g) was clarified; - Exclusion criterion 3 was rephrased; - In the study design of Part 2, the dose regimen was made flexible and the run-in period description was updated according to the changes in inclusion criterion 6; - Throughout Part 2, a new section on microbiology assessments was added; - The statistical analysis section was adapted; - The early withdrawal assessments were listed and clarified; - A new section was created to regulate the possibility of re-screening subjects at discretion of the Principal Investigator.
20 December 2019	A substantial protocol amendment (CTP version 4.0, dated 8 November 2019) was created to record the following changes: - Change of site location; - The time window for the study drug administration has been enlarged; - IMP dose options for the Cohort F have been clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported