NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

CLL442

Trial Indication

Cutaneous Squamous Cell Carcinoma

Protocol Number

CCLL442X2201

Protocol Title

A randomized investigator and patient blind placebo-controlled parallel group first in human and proof of concept study to evaluate the safety tolerability and efficacy of CLL442 in patients with Cutaneous Squamous Cell Carcinoma in situ

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: December 2017
Primary Completion Date: November 2018
Study Completion Date: November 2018

Study Design/Methodology

This study was a non-confirmatory First in human (FIH) and Proof of concept (PoC) study. The study was an investigator-and patient blinded, randomized, placebo-controlled study of topical CLL442 2.5 mg/g in patients with squamous cell carcinoma in situ (SCCis), to assess safety, tolerability and initial efficacy of CLL442. Patients were treated with CLL442 or placebo twice daily for 7 days on lesion free skin (located on the contralateral side of the patient's body of the target lesion). This was followed by a twice-daily application on the target single SCCis lesion until visual clearance of the lesion and for an additional 14 days, or for a total of 84 days, whichever came first.

Centers

8 centers in 3 countries: Australia (3), Belgium (2), United States (3)

Objectives

Primary objectives

- To assess the safety and tolerability of CLL442 in patients with SCCis on both lesion free skin and SCCis lesions.
- To evaluate the initial efficacy of CLL442 on reduction of lesion area in patients with SCCis.

Secondary objectives

- To evaluate systemic pharmacokinetics of CLL442.
- To assess the efficacy of CLL442 on multiple measures of single SCCis lesions.

Test Product, Dose, and Mode of Administration

CLL442 Cutaneous Cream application twice daily

Statistical Methods

A repeated measures analysis of covariance (ANCOVA) was performed for change from baseline in lesion area. The model included effects for baseline, treatment, visit, and treatment by visit interaction. An unstructured variance-covariance structure was used to account for correlation among multiple measurements from the same patient and variance heterogeneity. If the unstructured covariance caused model convergence issues, other simpler covariance structures were considered. Point estimates, the associated two-sided 90% confidence interval as well as the p-values for treatment differences were obtained. The null hypothesis of no treatment difference was tested only at Day 84 (primary interest) at the two-sided 0.10 significance level.

Percent change from baseline in lesion area was analyzed using the same model as stated above except baseline was not included as a covariate. The analysis was conducted on all patient data at the time the trial ended.

For patients in which the actual treatment received did not match the randomized treatment, the treatment actually received was used for the analysis.

The safety analysis set included all patients that received any study drug.

The pharmacokinetic (PK) analysis set included all patients with at least one available valid (i.e., not flagged for exclusion) CLL442 concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The pharmacodynamic (PD) analysis set included all patients with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Written informed consent has been obtained.
- Male and female patients, age ≥ 18 to ≤ 90 years (at the time of the screening visit).

- A primary, clinically diagnosed and histologically confirmed cutaneous squamous cell carcinoma in situ lesion (SCCis), with or without the involvement of the follicular unit, and histologically diagnosed within 30 days of the screening visit. The post-biopsy residual SCCis lesion must be visually evident and at least 3 mm in either length or width.

- The lesion must be located in a place easily accessible for topical application by the patient or their caregiver, excluding the genitals, perianal area, sub-ungual area, eyelids, ear and must be >1 cm away from the eyes and mouth.

Exclusion Criteria

- Evidence of dermatological disease or histological evidence of a confounding skin condition in the treatment area, including but not limited to BCC, worse level/grade of SCC, rosacea, psoriasis, atopic dermatitis, eczema, xeroderma pigmentosa, verrucous lesions or any other tumor in the biopsy specimen. Lesions with atypical histology such as: spindle cell SCC, acantholytic SCC, clear cell SCC, adenosquamous SCC, desmoplastic SCC or lesions that have been present for a short time and have been fast growing.

- Treatment of the target SCCis lesion within 8 weeks of screening visit by any of the following treatments: Liquid nitrogen, Photochemotherapy (PUVA), Long wave ultra violet radiation (UVB light), surgical excision or curettage within 1 cm of target lesion.; Systemic retinoids.; Ionizing radiation or interlesional injections or; Undergone a facial resurfacing procedure, i.e., chemical peel, laser resurfacing, dermabrasion, within the target lesion

- Treatment with the following topical agents within the 4 weeks prior to the screening visit: Levulanic acid, 5-fluorouracil, corticosteroids, retinoids, diclofenac, hyaluronic acid, imiquimod.

- History of recurrence of the target SCCis lesion.

- Systemic use of immunosuppressive drugs within 4 weeks prior to screening visit or during the treatment period - Photodynamic therapy or immunomodulators, cytotoxic drugs, or interferon/interferon inducers within 4 weeks prior to study entry or expected during the study.

- Women of child-bearing potential, unless they are using at least basic methods of contraception during dosing of investigational drug.

- Pregnant or nursing (lactating) women.

Participant Flow Table

Overall Study

	CLL442 2.5 mg/g	Placebo	Total
Arm/Group Description	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).	
Started	30	10	40
Completed	29	10	39
Not Completed	1	NaN	NaN
Subject/Guardian Decision	1		NaN

Baseline Characteristics

	CLL442 2.5 mg/g	Placebo	Total
Arm/Group Description	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).	
Number of Participants [units: participants]	30	10	40
Age, Customized (units: Participants)			

Count of Participants			
Sex: Female, Male (units: Participants) Count of Participants			
Female	17	4	21
Male	13	6	19
Age Continuous (units: years) Mean ± Standard Deviation			
	72.3±9.22	66.1±8.60	

Summary of Efficacy

Primary Outcome Results

Number of Subjects with Adverse Events (AEs), and Serious Adverse Events (SAEs)

(Time Frame: From First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV), up to Day 92 (End of Study (EOS)))

	CLL442 2.5 mg/g	**Placebo**
Arm/Group Description	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).
Number of Participants Analyzed [units: participants]	30	10
Number of Subjects with		

Adverse Events (AEs), and Serious Adverse Events (SAEs) (units: subjects) Count of Participants		
AEs	20	4
SAEs	0	0

Number of Subjects with Local Tolerability Score at Day 7 or Day 84

(Time Frame: Period 1 (P1) Day 1 (D1) to Day 92 (EOS))

	CLL442 2.5 mg/g	**Placebo**
Arm/Group Description	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).
Number of Participants Analyzed [units: participants]	30	10
Number of Subjects with Local Tolerability Score at Day 7 or Day 84 (units: subjects) Count of Participants		
Edema(P1, D1): Mild (n=30,10)	0	0
Edema(P1, D1): Moderate (n=30, 10)	0	0
Edema(P1, D1): Severe (n=30,10)	0	0
Edema(EOS): Mild (n=29,10)	5	0
Edema(EOS): Moderate	1	1

(n=29,10)		
Edema(EOS): Severe (n=29,10)	0	0
Erosion/Ulceration(P1, D1): Mild (n=30,10)	0	0
Erosion/Ulceration(P1, D1): Moderate (n=30,10)	0	0
Erosion/Ulceration(P1, D1): Severe (n=30,10)	0	0
Erosion/Ulceration(EOS): Mild (n=29,10)	2	1
Erosion/Ulceration(EOS): Moderate (n=29,10)	0	0
Erosion/Ulceration(EOS): Severe (n=29,10)	0	0
Erythema(P1, D1): Mild (n=30,10)	4	0
Erythema(P1, D1): Moderate (n=30,10)	0	0
Erythema(P1, D1): Severe (n=30,10)	0	0
Erythema(EOS): Mild (n=29,10)	12	3
Erythema(EOS): Moderate (n=29,10)	5	2
Erythema(EOS): Severe (n=29,10)	0	0
Flaking/Scaling/Dryness(P1, D1): Mild (n=30,10)	5	0
Flaking/Scaling/Dryness(P1, D1): Moderate (n=30,10	0	0
Flaking/Scaling/Dryness(P1,	0	0

D1): Severe (n=30,10)		
Flaking/Scaling/Dryness(EOS): Mild (n=29,10)	11	3
Flaking/Scaling/Dryness(EOS): Moderate (n=29,10)	4	1
Flaking/Scaling/Dryness(EOS): Severe (n=29,10)	0	0
Itching(P1, D1): Mild (n=30,10)	1	0
Itching(P1, D1): Moderate (n=30,10)	0	0
Itching(P1, D1): Severe (n=30,10)	0	0
Itching(EOS): Mild (n=29,10)	1	1
Itching(EOS): Moderate (n=29,10)	0	0
Itching(EOS): Severe (n=29,10)	1	0
Scrabbing/Dryness(P1, D1): Mild (n=30,10)	2	0
Scrabbing/Dryness(P1, D1): Moderate (n=30,10)	0	0
Scrabbing/Dryness(P1, D1): Severe (n=30,10)	0	0
Scrabbing/Dryness(EOS): Mild (n=29,10)	4	2
Scrabbing/Dryness(EOS): Moderate (n=29,10)	4	0
Scrabbing/Dryness(EOS): Severe (n=29,10)	0	0
Vesicles(P1, D1): Mild (n=30,10)	0	0
Vesicles(P1, D1): Moderate	0	0

(n=30,10)		
Vesicles(P1, D1): Severe (n=30,10)	0	0
Vesicles(EOS): Mild (n=29,10)	0	0
Vesicles(EOS): Moderate (n=29,10)	0	0
Vesicles(EOS): Severe (n=29,10)	0	0
Weeping/Exsudates(P1, D1): Mild (n=30,10)	0	0
Weeping/Exsudates(P1, D1): Moderate (n=30,10)	0	0
Weeping/Exsudates(P1, D1): Severe (n=30,10)	0	0
Weeping/Exsudates(EOS): Mild (n=29,10)	2	0
Weeping/Exsudates(EOS): Moderate (n=29,10)	0	0
Weeping/Exsudates(EOS): Severe (n=29,10)	0	0

Visual Analogue Scale (VAS) Score

(Time Frame: P1 Day 1 to Day 92 (EOS))

	CLL442 2.5 mg/g	Placebo
Arm/Group Description	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).
Number of Participants Analyzed [units: participants]	30	10
Visual Analogue Scale (VAS) Score		

(units: score on a scale) Mean ± Standard Deviation		
P1 Day 1 (n=29,10)	1.9 ± 8.90	0.2 ± 0.63
P2 Day 84 (n=29,10)	0.2 ± 1.12	1.9 ± 4.68
EOS (n=29,10)	0.3 ± 1.04	1.0 ± 2.54

Change From Baseline in Lesion Area in Subjects with Squamous Cell Carcinoma in situ (SCCis) at Day 84

(Time Frame: Period 2 Day 1 (Baseline) and Period 2 Day 84)

	CLL442 2.5 mg/g	**Placebo**
Arm/Group Description	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).
Number of Participants Analyzed [units: participants]	29	10
Change From Baseline in Lesion Area in Subjects with Squamous Cell Carcinoma in situ (SCCis) at Day 84 (units: square millimetre (mm^2)) Mean (90% Confidence Interval)		
	-112.62 (-180.57 to 44.68)	-153.80 (-269.51 to 38.09)

Statistical Analysis

Groups	CLL442 2.5 mg/g, Placebo	
P Value	= 0.5984	Change from baseline in lesion area was analyzed using a repeated measures mixed effects model (MMRM) which included effects for baseline lesion area, treatment, visit

and treatment by visit interaction.

Method	Other MMRM
Other Difference in means	41.18
90% Confidence Interval 2-Sided	-93.02 to 175.38

Secondary Outcome Result(s)

Plasma Concentration of CLL442

(Time Frame: Day 1 through Day 84)

Arm/Group Description
Number of Participants Analyzed [units: participants]
Plasma Concentration of CLL442 (units: picograms per millilitre(pg/mL)) Mean ± Standard Deviation

Time Required to Achieve 50% (Partial) Decrease in One Lesion Area

(Time Frame: Up to Day 84)

	CLL442 2.5 mg/g	**Placebo**
Arm/Group Description	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).
Number of Participants Analyzed [units: participants]	29	10

Time Required to Achieve 50% (Partial) Decrease in One Lesion Area (units: days) Median (90% Confidence Interval)		
	57 (55.0 to 92.0)	55.5 (8.0 to *Not evaluable*)

Time Required to Achieve 10% (Partial) Decrease in One Lesion Area

(Time Frame: Up to Day 84)

	CLL442 2.5 mg/g	**Placebo**
Arm/Group Description	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).
Number of Participants Analyzed [units: participants]	29	10
Time Required to Achieve 10% (Partial) Decrease in One Lesion Area (units: days) Median (90% Confidence Interval)		
	28.0 (8.0 to 31.0)	41.5 (8.0 to 57.0)

Time Required to Achieve Complete (100%) SCCis One Lesion Clearance at the End of the Study

(Time Frame: Day 92 (EOS))

	CLL442 2.5 mg/g	Placebo
Arm/Group Description	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).
Number of Participants Analyzed [units: participants]	30	10
Time Required to Achieve Complete (100%) SCCis One Lesion Clearance at the End of the Study (units: days) Median (90% Confidence Interval)	*Not evaluable**	*Not evaluable*

**Statistical Analysis was not applied as there were no responders.*

Percentage of Subjects with Complete Clearance at the End of the Study, Assessed Visually and Histologically

(Time Frame: Day 92 (EOS))

	Placebo	CLL442 2.5 mg/g
Arm/Group Description	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).
Number of Participants Analyzed [units: participants]	10	25
Percentage of Subjects with		

Complete Clearance at the End of the Study, Assessed Visually and Histologically
(units: percentage of subjects)

	20.0	24.0

Summary of Safety

Safety Results

All-Cause Mortality

	Placebo N = 10	CLL442 2.5 mg/g N = 30
Arm/Group Description	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Other Adverse Events by System Organ Class

Time Frame	Adverse events (AEs) were collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until LPLV (up to Day 92 (EOS)).
Source Vocabulary for Table Default	MedDRA 21.1
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	Placebo N = 10	**CLL442 2.5 mg/g N = 30**
Arm/Group Description	CLL442-matching placebo cream was applied topically twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single SCCis lesion for up to 84 days (during P2).	CLL442 cream 2.5 milligrams per gram (mg/g) was applied topically, twice daily for 7 days (during P1) on lesion free skin, followed by twice daily application on the target single Cutaneous Squamous Cell Carcinoma in situ (SCCis) lesion for up to 84 days (during P2).
Total participants affected	4 (40.00%)	20 (66.67%)
Cardiac disorders		
Atrial fibrillation	0 (0.00%)	1 (3.33%)
Sinus bradycardia	0 (0.00%)	1 (3.33%)
Ear and labyrinth disorders		
Vertigo	0 (0.00%)	1 (3.33%)
Gastrointestinal disorders		
Mouth ulceration	1 (10.00%)	1 (3.33%)
Nausea	0 (0.00%)	1 (3.33%)
Oral pain	0 (0.00%)	1 (3.33%)
Paraesthesia oral	0 (0.00%)	1 (3.33%)
Toothache	0 (0.00%)	1 (3.33%)

General disorders and administration site conditions		
Application site erythema	0 (0.00%)	1 (3.33%)
Application site exfoliation	0 (0.00%)	1 (3.33%)
Application site oedema	0 (0.00%)	1 (3.33%)
Application site pain	0 (0.00%)	1 (3.33%)
Application site pruritus	0 (0.00%)	2 (6.67%)
Condition aggravated	0 (0.00%)	1 (3.33%)
Fatigue	1 (10.00%)	0 (0.00%)
Mucosal ulceration	0 (0.00%)	1 (3.33%)
Infections and infestations		
Pharyngitis	0 (0.00%)	1 (3.33%)
Upper respiratory tract infection	0 (0.00%)	6 (20.00%)
Injury, poisoning and procedural complications		
Procedural pain	0 (0.00%)	1 (3.33%)
Investigations		
Amylase increased	0 (0.00%)	1 (3.33%)
Electrocardiogram repolarisation abnormality	0 (0.00%)	1 (3.33%)
Pancreatic enzymes increased	1 (10.00%)	0 (0.00%)

Metabolism and nutrition disorders		
Polydipsia	0 (0.00%)	1 (3.33%)
Musculoskeletal and connective tissue disorders		
Muscle tightness	0 (0.00%)	1 (3.33%)
Myalgia	0 (0.00%)	1 (3.33%)
Neck pain	0 (0.00%)	1 (3.33%)
Pain in extremity	0 (0.00%)	1 (3.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal cell carcinoma	1 (10.00%)	2 (6.67%)
Psychiatric disorders		
Abnormal dreams	0 (0.00%)	1 (3.33%)
Respiratory, thoracic and mediastinal disorders		
Cough	0 (0.00%)	1 (3.33%)
Rhinorrhoea	0 (0.00%)	1 (3.33%)
Skin and subcutaneous tissue disorders		
Actinic keratosis	0 (0.00%)	1 (3.33%)
Pruritus	0 (0.00%)	2 (6.67%)
Rash	0 (0.00%)	1 (3.33%)
Vascular disorders		
Hypertension	0 (0.00%)	2 (6.67%)

Conclusion:

- CLL442 2.5 mg/g, administered topically twice daily was safe and well tolerated in patients with SCCis lesions.
- CLL442 did not meet the primary endpoint of lesion reduction or complete lesion clearance.
- There were no deaths, SAEs or AEs leading to discontinuation in this study.

Date of Clinical Trial Report

8 August 2019