Clinical trial results:
A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, PARALLEL GROUP STUDY TO DETERMINE THE EFFICACY, SAFETY AND TOLERABILITY OF ONCE DAILY ORAL ZPL-3893787-18 (30 MG) ADMINISTERED FOR 12 WEEKS IN ADULT SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS.

Summary

EudraCT number	2015-003812-19
Trial protocol	GB BG
Global end of trial date	22 December 2016

Results information

Result version number	v1 (current)
This version publication date	06 January 2018
First version publication date	06 January 2018

Trial information

Trial identification

Sponsor protocol code	ZPL389/102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02618616
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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	22 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of an oral 30 mg dose of ZPL-3893787-18 when administered once daily, for 12 weeks, to subjects with moderate to severe plaque psoriasis.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 2016
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	Poland: 39
Country: Number of subjects enrolled	United Kingdom: 46
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	129
EEA total number of subjects	118

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)	119

From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Each subject had a screening visit to confirm suitability to enter the study, followed by 7-day run-in period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ZPL-389

Arm description:

ZPL-3893787 30 mg once daily

Arm type	Experimental
Investigational medicinal product name	ZPL-3893787
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Each subject was given 30 mg ZPL-3893787 capsules, to be taken orally OD for 12 weeks.

Arm title	Placebo

Arm description:

Matched placebo once daily

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Each subject was given 30 mg capsules of matching placebo, to be taken orally OD for 12 weeks.

Number of subjects in period 1	ZPL-389	Placebo
Started	87	42
Completed	66	35
Not completed	21	7
Consent withdrawn by subject	8	5
Adverse event, non-fatal	8	-
Pregnancy	-	1
Lost to follow-up	-	1
Lack of efficacy	4	-
Failure to comply with dosing & evaluations	1	-

Baseline characteristics

Reporting groups	
Reporting group title	ZPL-389
Reporting group description: ZPL-3893787 30 mg once daily	

Reporting group title	Placebo
Reporting group description: Matched placebo once daily	

Reporting group values	ZPL-389	Placebo	Total
Number of subjects	87	42	129
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	79	40	119
From 65-84 years	8	2	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	44.5	43.2	
standard deviation	± 13.82	± 12.64	-
Gender categorical Units: Subjects			
Female	33	15	48
Male	54	27	81
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	28.24	27.86	
standard deviation	± 3.491	± 3.575	-

End points

End points reporting groups

Reporting group title	ZPL-389
Reporting group description: ZPL-3893787 30 mg once daily	

Reporting group title	Placebo
Reporting group description: Matched placebo once daily	

Primary: Percent Change From Baseline in Psoriasis Assessment of Severity Index (PASI) at Week 12

End point title	Percent Change From Baseline in Psoriasis Assessment of Severity Index (PASI) at Week 12

End point description:

The PASI is an assessment routinely used for evaluating and grading the severity of psoriatic lesions and their response to therapy. PASI divides the body into 4 regions: the head, trunk, upper extremities (arms) and lower extremities (legs). Each of these areas is assessed separately for erythema, induration and scaling; these symptoms are scored on a 5-point scale from 0-4, where 0 = no symptoms and 4 = very marked. The PASI produces a numeric score that can range from 0 to 72. A higher score indicates more severe disease. A PASI 75 response represents a reduction of at least 75% from baseline in the PASI score.

End point type	Primary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[1]	42[2]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Baseline PASI	18.96 (± 8.019)	19.39 (± 7.898)		
Week 12 percent change from baseline	-28.043 (± 38.4436)	-37.361 (± 32.3581)		

Notes:

[1] - Full analysis set (FAS): All randomised subjects who received at least one dose of study treatment.

[2] - Full analysis set (FAS): All randomised subjects who received at least one dose of study treatment.

Statistical analyses

Statistical analysis title	ANCOVA of PASI at Week 12
Comparison groups	ZPL-389 v Placebo

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8495 [3]
Method	ANCOVA
Parameter estimate	least square difference
Point estimate	8.7
Confidence interval	
level	90 %
sides	1-sided
lower limit	8.4

Notes:

[3] - The 1-sided p-value tests if the ZPL-389 LS mean is < the placebo LS mean.

Secondary: PASI-50 and PASI-75 responders at Week 12

End point title	PASI-50 and PASI-75 responders at Week 12

End point description:

PASI-75 and PASI-50 are defined as a 75% and 50% reduction, respectively, from baseline in PASI score at Week 12.

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[4]	42[5]		
Units: Responders				
number (not applicable)				
PASI-50	21	15		
PASI-75	12	6		

Notes:

[4] - FAS

[5] - FAS

Statistical analyses

Statistical analysis title	Logistic Regression PASI-50
Comparison groups	ZPL-389 v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9058
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.562

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.27
upper limit	1.16

Statistical analysis title	Logistic Regression PASI-75
Comparison groups	ZPL-389 v Placebo
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5422
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.946
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.4
upper limit	2.25

Secondary: Improvement in Investigator Global Assessment (IGA) at Week 12

End point title	Improvement in Investigator Global Assessment (IGA) at Week 12

End point description:

An overall assessment of the severity of psoriasis was made, by the investigator, using the IGA at each visit. IGA scores take values on a 5-point scale from 0-4, where 0 = clear to 4 = severe disease. Responder is defined as a score of clear or almost clear, or a reduction of ≥2 levels. Success is defined as a score of clear or almost clear. Subjects with discontinued and missing data categories at Week 12 were considered non-responders.

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[6]	42[7]		
Units: Participants				
number (not applicable)				
Responder	10	6		
Success	7	3		

Notes:

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the NRS for pruritus (worst itch) at Week 12.

End point title	Change from baseline in the NRS for pruritus (worst itch) at Week 12.

End point description:

The pruritus NRS is an assessment tool used to assess the subject's worst itch as a result of psoriasis in the last 12 hours. The subjects completed the NRS each morning on (or soon after) rising and evening prior to retiring to bed.
The subjects completed the NRS each morning on (or soon after) rising and evening prior to retiring to bed. They were asked the following question: On a scale of 0 (no itching) to 10 (itching as bad as you can imagine), please rate the worst itching that you felt over the last 12 hours.

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[8]	42[9]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
NRS for pruritus (worst itch) at baseline	4.89 (± 2.247)	4.98 (± 2.742)		
Change in baseline at Week 12 (worst itch)	-1.40 (± 2.659)	-1.78 (± 2.810)		

Notes:

[8] - FAS

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC) a week 12

End point title	Patient Global Impression of Change (PGIC) a week 12

End point description:

At the end of treatment (Week 12) or early termination visit, the subject was asked to rate their degree of improvement (or worsening) of their psoriasis compared to before the start of treatment with study drug, using a 7-point scale, standardized PGIC.
Since the start of the study (dosing), my overall status is:
1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[10]	42[11]		
Units: Participant				
number (not applicable)				
Very much improved	12	3		
Much improved	14	9		
Minimally improved	22	11		
No change	15	7		
Minimally worse	5	3		
Much worse	7	6		
Very much worse	8	1		
Missing	4	2		

Notes:

[10] - FAS

[11] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body surface area (BSA) and percentage change from baseline at Week 12

End point title	Change from baseline in body surface area (BSA) and percentage change from baseline at Week 12

End point description:

Assessment of the percentage of a subject's BSA affected by psoriasis was made by best estimates of the investigator at each visit. Hand-size measurement was considered to be the "best estimate" to measure the BSA by the investigators

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[12]	42[13]		
Units: Area score				
arithmetic mean (standard deviation)				
Baseline	25.5 (± 12.60)	27.0 (± 14.19)		
Week 12	22.7 (± 12.35)	22.8 (± 12.77)		
Week 12 change from baseline	-2.8 (± 10.77)	-4.2 (± 9.62)		

Notes:

[12] - FAS

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the daytime and night time NRS for pruritus (worst itch) at Week 12

End point title	Change from baseline in the daytime and night time NRS for pruritus (worst itch) at Week 12

End point description:

The subjects completed the NRS each morning on (or soon after) rising and evening prior to retiring to bed. They were asked the following question: On a scale of 0 (no itching) to 10 (itching as bad as you can imagine), please rate the worst itching that you felt over the last 12 hours.

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[14]	42[15]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
NRS for pruritus (daytime) at baseline	4.32 (± 2.251)	4.52 (± 2.748)		
Change in baseline at Week 12 (daytime)	-1.40 (± 2.765)	-1.42 (± 2.779)		
NRS for pruritus (night time) at baseline	4.19 (± 2.299)	4.34 (± 2.682)		
Change in baseline at Week 12 (night time)	-1.35 (± 2.856)	-1.31 (± 2.860)		

Notes:

[14] - FAS
n at Week 12 = 63
[15] - FAS
n at Week 12 = 33

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the NRS for sleep disturbance at Week 12

End point title	Change from baseline in the NRS for sleep disturbance at Week 12

End point description:

In the morning subjects were asked the following question to determine the level of sleep disturbance due to itching: On a scale of 0 (no sleep disturbance) to 10 (awake all night), please rate how much your sleep was disturbed by itch last night.

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[16]	42[17]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
NRS for pruritus (sleep disturbance) at baseline	2.48 (± 2.172)	2.74 (± 2.559)		
Change in baseline at Week 12 (sleep disturbance)	-0.88 (± 2.417)	-0.93 (± 2.098)		

Notes:

[16] - FAS
n at Week 12 = 63
[17] - FAS
n at Week 12 = 33

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in total, daytime and night time duration of itching at Week 12

End point title	Change from baseline in total, daytime and night time duration of itching at Week 12

End point description:

Subjects were asked the following question to determine their duration of itching: Over the last 12 hours approximately how many hours, if any, did you itch?

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[18]	42[19]		
Units: hours				
arithmetic mean (standard deviation)				
Total duration of itching- Baseline	5.74 (± 4.608)	6.68 (± 5.637)		
Total duration of itching- Change at week 12	-1.15 (± 4.525)	-1.16 (± 5.543)		
Daytime duration of itching-Baseline	3.16 (± 2.682)	3.57 (± 2.994)		
Daytime duration of itching-Change at week 12	-0.60 (± 2.399)	3.63 (± 3.034)		
Night time duration of itching-Baseline	2.58 (± 2.072)	3.11 (± 2.720)		
Night time duration of itching-Change at week 12	-0.55 (± 2.188)	-0.43 (± 2.581)		

Notes:

[18] - FAS
n at Week 12 = 63
[19] - FAS
n at Week 12 = 32

Statistical analyses

No statistical analyses for this end point

Secondary: Verbal Rating Scale (VRS) for pruritus at Week 12

End point title	Verbal Rating Scale (VRS) for pruritus at Week 12

End point description:

Subjects were asked to rate their itch over the last 12 hours using a list of adjectives describing different levels of symptom intensity:
Over the last 12 hours how would you rate your itch? No itch; Mild; Moderate and Severe;
Pruritus was evaluated by the subject, using the eDiary, twice daily for 1 week prior to the start of study treatment (run-in period) and during treatment (baseline to Day 84).

End point type	Secondary

End point timeframe:

From baseline to week 12.

End point values	ZPL-389	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[20]	42[21]		
Units: Scores on a Scale				
number (not applicable)				
Baseline - No itch	2	2		
Baseline - Mild	21	17		
Baseline - Moderate	52	14		
Baseline - Severe	12	9		
Week 12 - No itch	17	11		
Week 12 - Mild	19	10		
Week 12 - Moderate	24	12		
Week 12 - Severe	3	0		
Missing	3	2		
Discontinued	21	7		

Notes:

[20] - FAS

[21] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are 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 Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	ZPL-389

Reporting group description:

ZPL-3893787 30 mg once daily.

Reporting group title	Placebo

Reporting group description:

Matched placebo once daily.

Serious adverse events	ZPL-389	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 87 (5.75%)	0 / 42 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Erythrodermic psoriasis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ZPL-389	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 87 (29.89%)	21 / 42 (50.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 87 (5.75%)	3 / 42 (7.14%)	
occurrences (all)	5	3	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 87 (5.75%)	0 / 42 (0.00%)	
occurrences (all)	5	0	
Psoriasis			
subjects affected / exposed	11 / 87 (12.64%)	1 / 42 (2.38%)	
occurrences (all)	11	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 87 (5.75%)	2 / 42 (4.76%)	
occurrences (all)	5	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported