Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group Study Followed by a Dose-Blind Period and Open-Label Follow-Up to Evaluate the Efficacy and Safety of Certolizumab Pegol in Subjects with Moderate to Severe Chronic Plaque Psoriasis

Summary

EudraCT number	2014-003486-14
Trial protocol	DK AT
Global end of trial date	12 September 2018

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	PS0002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02326272
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Biopharma, SPRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, B-1070
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.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	02 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of Certolizumab Pegol (CZP) administered subcutaneous (sc) at the doses of CZP 400 mg every two weeks (Q2W) and CZP 200 mg Q2W after a loading dose of CZP 400 mg at Weeks 0, 2, and 4 in the treatment of moderate to severe chronic plaque psoriasis (PSO).

Protection of trial subjects:

During the conduct of the study all participants were closely monitored.

Background therapy:

Background therapy/concomitant medication was permitted as defined in the study protocol.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	15 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Canada: 60
Country: Number of subjects enrolled	Poland: 63
Country: Number of subjects enrolled	United States: 97
Worldwide total number of subjects	227
EEA total number of subjects	70

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)	206
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in December 2014 and concluded in September 2018 from multiple sites in Europe and North America. 227 participants were included in the Randomized Set (RS) shown in the Participant Flow.

Pre-assignment

Screening details:

The study included a 5 Week Screening Period, a Double-blind Initial Treatment Period up to Week 16, a Dose-blind Maintenance Treatment Period up to Week 48, an Open-label Treatment Period up to Week 144 and a Post Study Safety Follow-up Period up to Week 152.
Participant Flow refers to the Randomized Set, Open Label Set and Maintenance Set.

Period 1

Period 1 title	Initial Period (Week 0 to Week 16)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Q2W

Arm description:

Placebo sc injection Q2W.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16, who did not achieve a PASI75 response at Week 16 received CZP 400 mg at Weeks 16, 18 and 20 (loading doses) followed by CZP 200 mg Q2W starting at Week 22.
•PASI75 responders at Week 16 continued to receive Placebo.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the Open-label Extension (OLE) Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections Q2W, administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	CZP 200 mg Q2W

Arm description:

CZP 400 mg at Weeks 0, 2, 4, followed by CZP 200 mg Q2W from Week 6 to Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 200 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W.
Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to

CZP 200 mg Q2W.
Depending on PASI50 or PASI75 responses at Week 60 or a later time point, participants may have switched to CZP 400 mg Q2W or withdrew from the study.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	CZP 400 mg Q2W

Arm description:

CZP 400 mg Q2W through Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 400 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Participants who achieved a PASI75 response during the OLE Period may have switched to CZP 200 mg Q2W.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Number of subjects in period 1	Placebo Q2W	CZP 200 mg Q2W	CZP 400 mg Q2W
Started	49	91	87
Completed Week 16	45	84	83
Finished Wk16 entered Maintenance Period	45	84	81
Completed	45	84	81
Not completed	4	7	6
Consent withdrawn by subject	3	2	1
Adverse event, non-fatal	-	3	1
Lost to follow-up after completing wk16	-	-	1
Missed two doses	-	-	1
Lost to follow-up	1	2	-
Consent withdrawn after completing wk16	-	-	1

Moved from the study area	-	-	1

Period 2

Period 2 title	Maintenance Period (Week 16 to Week 48)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Carer, Assessor, Investigator

Blinding implementation details:

Participants who entered the escape arms of the study received open-label CZP 400 mg every two weeks.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Placebo Q2W

Arm description:

This arm consisted of participants initially randomized in the Placebo arm, who achieved a PASI75 response at Week 16 and continued to receive Placebo in the Maintenance Period (Week 16 to Week 48).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections Q2W, administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	Placebo/CZP 200 mg Q2W

Arm description:

This arm consisted of participants initially randomized in the Placebo arm, who achieved a PASI50 response at Week 16 but not a PASI75 response and received CZP 400 mg at Weeks 16, 18, and 20 (loading doses) followed by CZP 200 mg Q2W (starting at Week 22).

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections Q2W, administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia

Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	CZP 200 mg Q2W/CZP 200 mg Q2W

Arm description:

This arm consisted of participants initially randomized in the CZP 200 mg Q2W arm, who achieved a PASI50 response at Week 16 and continued to receive CZP 200 mg Q2W.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	CZP 400 mg Q2W/CZP 400 mg Q2W

Arm description:

This arm consisted of participants initially randomized in the CZP 400 mg Q2W arm, who achieved a PASI50 response at Week 16 and continued to receive CZP 400 mg Q2W.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	Placebo/Escape CZP 400 mg Q2W

Arm description:

This arm consisted of participants initially randomized in the Placebo arm, who did not achieve a PASI50 response at Week 16 escaped from the blinded treatment and received unblinded CZP 400 mg Q2W, for 16 weeks. participants who did not achieve PASI50 after 16 weeks of unblinded treatment were withdrawn from the study.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections Q2W, administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites:

lateral abdominal wall and upper outer thigh.

Arm title	CZP 200 mg Q2W/Escape CZP 400 mg Q2W

Arm description:

This arm consisted of participants initially randomized in the CZP 200 mg Q2W arm, who did not achieve a PASI50 response at Week 16 escaped from the blinded treatment and received CZP unblinded 400 mg Q2W, for 16 weeks. Participants who did not achieve PASI50 after 16 weeks of unblinded treatment were withdrawn from the study.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	CZP 400 mg Q2W/Escape CZP 400 mg Q2W

Arm description:

This arm consisted of participants initially randomized in the CZP 400 mg Q2W arm, who did not achieve a PASI50 response at Week 16 escaped from the blinded treatment and received unblinded CZP 400 mg Q2W, for 16 weeks. Participants who did not achieve PASI50 after 16 weeks of unblinded treatment were withdrawn from the study.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Number of subjects in period 2	Placebo/Placebo Q2W	Placebo/CZP 200 mg Q2W	CZP 200 mg Q2W/CZP 200 mg Q2W
Started	6	5	76
Completed Week 48	5	3	64
Finished Wk48 entered Open-label Period	5	3	63
Completed	5	3	63
Not completed	1	2	13
Adverse event after completing wk48	-	-	1
Consent withdrawn by subject	1	-	3
Subject moved out of state	-	-	-
Adverse event, non-fatal	-	2	3

Did not achieve PASI50 after wk48	-	-	-
Pregnancy	-	-	-
Non-compliance	-	-	-
Lost to follow-up	-	-	2
Lack of efficacy	-	-	2
Did not achieve PASI50	-	-	2

Number of subjects in period 2	CZP 400 mg Q2W/CZP 400 mg Q2W	Placebo/Escape CZP 400 mg Q2W	CZP 200 mg Q2W/Escape CZP 400 mg Q2W
Started	69	34	8
Completed Week 48	61	27	3
Finished Wk48 entered Open-label Period	60	27	3
Completed	60	27	3
Not completed	9	7	5
Adverse event after completing wk48	-	-	-
Consent withdrawn by subject	1	1	-
Subject moved out of state	-	1	-
Adverse event, non-fatal	4	2	1
Did not achieve PASI50 after wk48	1	-	-
Pregnancy	1	-	-
Non-compliance	-	-	1
Lost to follow-up	-	2	-
Lack of efficacy	1	-	1
Did not achieve PASI50	1	1	2

Number of subjects in period 2	CZP 400 mg Q2W/Escape CZP 400 mg Q2W
Started	12
Completed Week 48	10
Finished Wk48 entered Open-label Period	10
Completed	10
Not completed	2
Adverse event after completing wk48	-
Consent withdrawn by subject	1
Subject moved out of state	-
Adverse event, non-fatal	-
Did not achieve PASI50 after wk48	-
Pregnancy	-
Non-compliance	-
Lost to follow-up	-

Lack of efficacy	1
Did not achieve PASI50	-

Period 3

Period 3 title	Open-label Period (Week 48 to Week 144)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/CZP 200 mg Q2W OLE

Arm description:

This arm consisted of participants who received dose-blind Placebo during the Maintenance Period, who achieved a PASI50 response at Week 48 and entered the OLE Period receiving CZP 200 mg Q2W.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Investigational medicinal product name	Placebo
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections Q2W, administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	CZP 200 mg Q2W/CZP 200 mg Q2W OLE

Arm description:

This arm consisted of participants who received CZP 200mg Q2W in the Maintenance Period, who achieved a PASI50 response at Week 48 and entered OLE.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	CZP 400 mg Q2W/CZP 200 mg Q2W OLE

Arm description:

This arm consisted of participants who received blinded CZP 400mg Q2W in the Maintenance Period, who achieved a PASI50 response at Week 48, and entered OLE on the CZP 200mg Q2W dose.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	CZP 400 mg Q2W/CZP 400 mg Q2W OLE

Arm description:

This arm consisted of participants who received blinded CZP 400mg Q2W in the Maintenance Period and entered OLE on the CZP 400mg Q2W dose.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Arm title	Escape CZP 400 mg Q2W/CZP 400 mg Q2W OLE

Arm description:

This arm consisted of participants who received open-label CZP 400mg Q2W in the Maintenance Period and entered OLE.

Arm type	Experimental
Investigational medicinal product name	Certolizumab pegol
Investigational medicinal product code	CZP
Other name	Cimzia
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections: 200 mg Q2W or 400 mg Q2W were administered at separate injection sites: lateral abdominal wall and upper outer thigh.

Number of subjects in period 3	Placebo/CZP 200 mg Q2W OLE	CZP 200 mg Q2W/CZP 200 mg Q2W OLE	CZP 400 mg Q2W/CZP 200 mg Q2W OLE
Started	5	66	59
Completed	2	51	48
Not completed	3	15	11
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	-	4	-
Adverse event, non-fatal	1	8	3

Loss of efficacy	-	1	-
Pregnancy	-	-	1
Lost to follow-up	1	-	2
Lack of efficacy	1	-	1
Protocol deviation	-	1	-
Did not achieve PASI50	-	1	3

Number of subjects in period 3	CZP 400 mg Q2W/CZP 400 mg Q2W OLE	Escape CZP 400 mg Q2W/CZP 400 mg Q2W OLE
Started	1	40
Completed	1	31
Not completed	0	9
Adverse event, serious fatal	-	-
Consent withdrawn by subject	-	2
Adverse event, non-fatal	-	1
Loss of efficacy	-	-
Pregnancy	-	-
Lost to follow-up	-	3
Lack of efficacy	-	-
Protocol deviation	-	-
Did not achieve PASI50	-	3

Baseline characteristics

Reporting groups

Reporting group title	Placebo Q2W

Reporting group description:

Placebo sc injection Q2W.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16, who did not achieve a PASI75 response at Week 16 received CZP 400 mg at Weeks 16, 18 and 20 (loading doses) followed by CZP 200 mg Q2W starting at Week 22.
•PASI75 responders at Week 16 continued to receive Placebo.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the Open-label Extension (OLE) Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.

Reporting group title	CZP 200 mg Q2W

Reporting group description:

CZP 400 mg at Weeks 0, 2, 4, followed by CZP 200 mg Q2W from Week 6 to Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 200 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W.
Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Depending on PASI50 or PASI75 responses at Week 60 or a later time point, participants may have switched to CZP 400 mg Q2W or withdrew from the study.

Reporting group title	CZP 400 mg Q2W

Reporting group description:

CZP 400 mg Q2W through Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 400 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Participants who achieved a PASI75 response during the OLE Period may have switched to CZP 200 mg Q2W.

Reporting group values	Placebo Q2W	CZP 200 mg Q2W	CZP 400 mg Q2W
Number of subjects	49	91	87
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	46	84	76
>=65 years	3	7	11
Age continuous Units: years			
arithmetic mean	43.3	46.7	46.4
standard deviation	± 14.5	± 13.3	± 13.5

Gender categorical Units: Subjects			
Male	26	58	43
Female	23	33	44

Reporting group values	Total		
Number of subjects	227		
Age categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	206		
>=65 years	21		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Male	127		
Female	100		

Subject analysis sets

Subject analysis set title	Placebo Q2W (RS)
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo sc injection Q2W.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16, who did not achieve a PASI75 response at Week 16 received CZP 400 mg at Weeks 16, 18 and 20 (loading doses) followed by CZP 200 mg Q2W starting at Week 22.
•PASI75 responders at Week 16 continued to receive Placebo.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Participants formed the Randomized Set (RS).

Subject analysis set title	CZP 200 mg Q2W (RS)
Subject analysis set type	Full analysis

Subject analysis set description:

CZP 400 mg at Weeks 0, 2, 4, followed by CZP 200 mg Q2W from Week 6 to Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 200 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W.
Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Depending on PASI50 or PASI75 responses at Week 60 or a later time point, participants may have switched to CZP 400 mg Q2W or withdrew from the study.
Participants formed the RS.

Subject analysis set title	CZP 400 mg Q2W (RS)
Subject analysis set type	Full analysis

Subject analysis set description:

CZP 400 mg Q2W through Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 400 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Participants who achieved a PASI75 response during the OLE Period may have switched to CZP 200 mg Q2W.
Participants formed the RS.

Subject analysis set title	CZP 200 mg Q2W (TCS)
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm consisted of all participants who received CZP 200 mg at any time during the study.

Subject analysis set title	CZP 400 mg Q2W (TCS)
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm consisted of all participants who received CZP 400 mg at any time during the study.

Reporting group values	Placebo Q2W (RS)	CZP 200 mg Q2W (RS)	CZP 400 mg Q2W (RS)
Number of subjects	49	91	87
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	46	84	76
>=65 years	3	7	11
Age continuous Units: years			
arithmetic mean	43.3	46.7	46.4
standard deviation	± 14.5	± 13.3	± 13.5
Gender categorical Units: Subjects			
Male	26	58	43
Female	23	33	44

Reporting group values	CZP 200 mg Q2W (TCS)	CZP 400 mg Q2W (TCS)	
Number of subjects	170	149	
Age categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	155	132	
>=65 years	15	17	
Age continuous Units: years			
arithmetic mean	45.7	46.3	
standard deviation	± 13.6	± 13.7	
Gender categorical Units: Subjects			
Male	100	76	
Female	70	73	

End points

End points reporting groups

Reporting group title	Placebo Q2W

Reporting group description:

Placebo sc injection Q2W.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16, who did not achieve a PASI75 response at Week 16 received CZP 400 mg at Weeks 16, 18 and 20 (loading doses) followed by CZP 200 mg Q2W starting at Week 22.
•PASI75 responders at Week 16 continued to receive Placebo.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the Open-label Extension (OLE) Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.

Reporting group title	CZP 200 mg Q2W

Reporting group description:

CZP 400 mg at Weeks 0, 2, 4, followed by CZP 200 mg Q2W from Week 6 to Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 200 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W.
Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Depending on PASI50 or PASI75 responses at Week 60 or a later time point, participants may have switched to CZP 400 mg Q2W or withdrew from the study.

Reporting group title	CZP 400 mg Q2W

Reporting group description:

CZP 400 mg Q2W through Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 400 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Participants who achieved a PASI75 response during the OLE Period may have switched to CZP 200 mg Q2W.

Reporting group title	Placebo/Placebo Q2W

Reporting group description:

This arm consisted of participants initially randomized in the Placebo arm, who achieved a PASI75 response at Week 16 and continued to receive Placebo in the Maintenance Period (Week 16 to Week 48).

Reporting group title	Placebo/CZP 200 mg Q2W

Reporting group description:

This arm consisted of participants initially randomized in the Placebo arm, who achieved a PASI50 response at Week 16 but not a PASI75 response and received CZP 400 mg at Weeks 16, 18, and 20 (loading doses) followed by CZP 200 mg Q2W (starting at Week 22).

Reporting group title	CZP 200 mg Q2W/CZP 200 mg Q2W

Reporting group description:

This arm consisted of participants initially randomized in the CZP 200 mg Q2W arm, who achieved a PASI50 response at Week 16 and continued to receive CZP 200 mg Q2W.

Reporting group title	CZP 400 mg Q2W/CZP 400 mg Q2W

Reporting group description:

This arm consisted of participants initially randomized in the CZP 400 mg Q2W arm, who achieved a PASI50 response at Week 16 and continued to receive CZP 400 mg Q2W.

Reporting group title	Placebo/Escape CZP 400 mg Q2W

Reporting group description:

This arm consisted of participants initially randomized in the Placebo arm, who did not achieve a PASI50 response at Week 16 escaped from the blinded treatment and received unblinded CZP 400 mg Q2W, for 16 weeks. participants who did not achieve PASI50 after 16 weeks of unblinded treatment were withdrawn from the study.

Reporting group title	CZP 200 mg Q2W/Escape CZP 400 mg Q2W

Reporting group description:

This arm consisted of participants initially randomized in the CZP 200 mg Q2W arm, who did not achieve a PASI50 response at Week 16 escaped from the blinded treatment and received CZP unblinded 400 mg Q2W, for 16 weeks. Participants who did not achieve PASI50 after 16 weeks of unblinded treatment were withdrawn from the study.

Reporting group title	CZP 400 mg Q2W/Escape CZP 400 mg Q2W

Reporting group description:

This arm consisted of participants initially randomized in the CZP 400 mg Q2W arm, who did not achieve a PASI50 response at Week 16 escaped from the blinded treatment and received unblinded CZP 400 mg Q2W, for 16 weeks. Participants who did not achieve PASI50 after 16 weeks of unblinded treatment were withdrawn from the study.

Reporting group title	Placebo/CZP 200 mg Q2W OLE

Reporting group description:

This arm consisted of participants who received dose-blind Placebo during the Maintenance Period, who achieved a PASI50 response at Week 48 and entered the OLE Period receiving CZP 200 mg Q2W.

Reporting group title	CZP 200 mg Q2W/CZP 200 mg Q2W OLE

Reporting group description:

This arm consisted of participants who received CZP 200mg Q2W in the Maintenance Period, who achieved a PASI50 response at Week 48 and entered OLE.

Reporting group title	CZP 400 mg Q2W/CZP 200 mg Q2W OLE

Reporting group description:

This arm consisted of participants who received blinded CZP 400mg Q2W in the Maintenance Period, who achieved a PASI50 response at Week 48, and entered OLE on the CZP 200mg Q2W dose.

Reporting group title	CZP 400 mg Q2W/CZP 400 mg Q2W OLE

Reporting group description:

This arm consisted of participants who received blinded CZP 400mg Q2W in the Maintenance Period and entered OLE on the CZP 400mg Q2W dose.

Reporting group title	Escape CZP 400 mg Q2W/CZP 400 mg Q2W OLE

Reporting group description:

This arm consisted of participants who received open-label CZP 400mg Q2W in the Maintenance Period and entered OLE.

Subject analysis set title	Placebo Q2W (RS)
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo sc injection Q2W.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16, who did not achieve a PASI75 response at Week 16 received CZP 400 mg at Weeks 16, 18 and 20 (loading doses) followed by CZP 200 mg Q2W starting at Week 22.
•PASI75 responders at Week 16 continued to receive Placebo.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Participants formed the Randomized Set (RS).

Subject analysis set title	CZP 200 mg Q2W (RS)
Subject analysis set type	Full analysis

Subject analysis set description:

CZP 400 mg at Weeks 0, 2, 4, followed by CZP 200 mg Q2W from Week 6 to Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 200 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W.
Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Depending on PASI50 or PASI75 responses at Week 60 or a later time point, participants may have switched to CZP 400 mg Q2W or withdrew from the study.
Participants formed the RS.

Subject analysis set title	CZP 400 mg Q2W (RS)
Subject analysis set type	Full analysis

Subject analysis set description:

CZP 400 mg Q2W through Week 14.
Treatment received from Week 16 - 48 was based on initial treatment and response to treatment:
•PASI50 responders at Week 16 continued to receive CZP 400 mg Q2W.
•PASI50 non-responders at Week 16 were removed from blinded study medication and escaped to unblinded CZP 400 mg Q2W. Participants who received unblinded CZP 400 mg Q2W for 16 weeks and did not achieve a PASI50 response were withdrawn from the study.
•PASI50 non-responders at Week 32 or a later time point were withdrawn from the study.
Participants who completed the Maintenance Period (with PASI50 response at Week 48) entered the OLE Period on CZP 200 mg Q2W. Week 48 completers in the escape arm continued to receive CZP 400 mg Q2W or may have switched to CZP 200 mg Q2W.
Participants who achieved a PASI75 response during the OLE Period may have switched to CZP 200 mg Q2W.
Participants formed the RS.

Subject analysis set title	CZP 200 mg Q2W (TCS)
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm consisted of all participants who received CZP 200 mg at any time during the study.

Subject analysis set title	CZP 400 mg Q2W (TCS)
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm consisted of all participants who received CZP 400 mg at any time during the study.

Primary: Proportion of participants who achieve a Psoriasis Activity and Severity Index (PASI75) response at Week 16

End point title	Proportion of participants who achieve a Psoriasis Activity and Severity Index (PASI75) response at Week 16

End point description:

The PASI75 response assessments are based on at least 75% improvement in the PASI score from Baseline. This is a scoring system that averages the redness, thickness, and scaliness of the psoriatic lesions (on a 0-4 scale) and weights the resulting score by the area of skin involved. Body divided into 4 areas: head, arms, trunk to groin, and legs to top of buttocks. Assignment of an average score for the redness, thickness, and scaling for each of the 4 body areas with a score of 0 (clear) to 4 (very marked). Determining the percentage of skin covered with PSO for each of the body areas and converting to a 0 to 6 scale. Final PASI= average redness, thickness, and scaliness of the psoriatic skin lesions, multiplied by the involved psoriasis area score of the respective section, and weighted by the percentage of the person’s affected skin for the respective section. The minimum possible PASI score is 0=no disease, the maximum score is 72=maximal disease.

End point type	Primary

End point timeframe:

Week 16

End point values	Placebo Q2W (RS)	CZP 200 mg Q2W (RS)	CZP 400 mg Q2W (RS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	91	87	
Units: percentage of participants				
number (not applicable)	11.6	81.4	82.6	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 200 mg Q2W (RS)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	33.405
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	9.965
upper limit	111.983

Notes:

[1] - The p-value for the primary analysis was evaluated at a 2-sided significance level of 0.025 for each CZP dose versus (vs) placebo (PBO).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 200 mg Q2W (RS)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Estimated difference in responder rate
Point estimate	69.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	57.12
upper limit	82.36

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.	
Comparison groups	Placebo Q2W (RS) v CZP 400 mg Q2W (RS)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	36.212
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	10.686
upper limit	122.713

Notes:

[2] - The p-value for the primary analysis was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.	
Comparison groups	Placebo Q2W (RS) v CZP 400 mg Q2W (RS)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Estimated difference in responder rate
Point estimate	71
Confidence interval	
level	95 %
sides	2-sided
lower limit	58.47
upper limit	83.43

Primary: Proportion of participants who achieve a Physician's Global Assessment (PGA) Clear or Almost Clear (with at least 2-category improvement) response at Week 16

End point title	Proportion of participants who achieve a Physician's Global Assessment (PGA) Clear or Almost Clear (with at least 2-category improvement) response at Week 16

End point description:

The Investigator assessed the overall severity of Psoriasis (PSO) using the following 5-point scale: 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe.

End point type	Primary

End point timeframe:

Week 16

End point values	Placebo Q2W (RS)	CZP 200 mg Q2W (RS)	CZP 400 mg Q2W (RS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	91	87	
Units: percentage of participants				
number (not applicable)	2.0	66.8	71.6	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 200 mg Q2W (RS)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	106.225
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	9.572
upper limit	1178.843

Notes:

[3] - The p-value for the primary analysis was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 200 mg Q2W (RS)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Estimated difference in responder rate
Point estimate	64.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	52.16
upper limit	77.46

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 400 mg Q2W (RS)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	133.163
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	11.904
upper limit	1489.578

Notes:

[4] - The p-value for the primary analysis was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 400 mg Q2W (RS)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Estimated difference in responder rate
Point estimate	69.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	57.48
upper limit	81.77

Secondary: Proportion of participants who achieve a Psoriasis Activity and Severity Index (PASI90) response at Week 16

End point title	Proportion of participants who achieve a Psoriasis Activity and Severity Index (PASI90) response at Week 16

End point description:

The PASI90 response assessments are based on at least 90% improvement in the PASI score from Baseline. This is a scoring system that averages the redness, thickness, and scaliness of the psoriatic lesions (on a 0-4 scale) and weights the resulting score by the area of skin involved. Body divided into 4 areas: head, arms, trunk to groin, and legs to top of buttocks. Assignment of an average score for the redness, thickness, and scaling for each of the 4 body areas with a score of 0 (clear) to 4 (very marked). Determining the percentage of skin covered with PSO for each of the body areas and converting to a 0 to 6 scale. Final PASI= average redness, thickness, and scaliness of the psoriatic skin lesions, multiplied by the involved psoriasis area score of the respective section, and weighted by the percentage of the person's affected skin for the respective section. The minimum possible PASI score is 0=no disease, the maximum score is 72=maximal disease.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W (RS)	CZP 200 mg Q2W (RS)	CZP 400 mg Q2W (RS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	91	87	
Units: percentage of participants				
number (not applicable)	4.5	52.6	55.4	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 200 mg Q2W (RS)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	24.283
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	4.386
upper limit	134.432

Notes:

[5] - The p-value for this analysis as used in the fixed sequence testing procedure was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 200 mg Q2W (RS)

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Estimated difference in responder rate
Point estimate	48.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.04
upper limit	61.26

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 400 mg Q2W (RS)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	27.204
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	4.895
upper limit	151.198

Notes:

[6] - The p-value for this analysis as used in the fixed sequence testing procedure was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 400 mg Q2W (RS)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Estimated difference in responder rate
Point estimate	51
Confidence interval	
level	95 %
sides	2-sided
lower limit	37.75
upper limit	64.19

Secondary: Proportion of participants who achieve a Physician's Global Assessment (PGA) Clear or Almost Clear (with at least 2-category improvement) response at Week 48

End point title	Proportion of participants who achieve a Physician's Global Assessment (PGA) Clear or Almost Clear (with at least 2-category improvement) response at Week 48

End point description:

The Investigator assessed the overall severity of Psoriasis (PSO) using the following 5-point scale: 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe.

End point type	Secondary

End point timeframe:

Week 48

End point values	CZP 200 mg Q2W (RS)	CZP 400 mg Q2W (RS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: percentage of participants				
number (confidence interval 95%)	72.6 (61.22 to 83.92)	66.6 (54.35 to 78.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants who achieve a Psoriasis Activity and Severity Index (PASI75) response at Week 48

End point title	Proportion of participants who achieve a Psoriasis Activity and Severity Index (PASI75) response at Week 48

End point description:

The PASI75 response assessments are based on at least 75% improvement in the PASI score from Baseline. This is a scoring system that averages the redness, thickness, and scaliness of the psoriatic lesions (on a 0-4 scale) and weights the resulting score by the area of skin involved. Body divided into 4 areas: head, arms, trunk to groin, and legs to top of buttocks. Assignment of an average score for the redness, thickness, and scaling for each of the 4 body areas with a score of 0 (clear) to 4 (very marked). Determining the percentage of skin covered with PSO for each of the body areas and converting to a 0 to 6 scale. Final PASI= average redness, thickness, and scaliness of the psoriatic skin lesions, multiplied by the involved psoriasis area score of the respective section, and weighted by the percentage of the person’s affected skin for the respective section. The minimum possible PASI score is 0=no disease, the maximum score is 72=maximal disease.

End point type	Secondary

End point timeframe:

Week 48

End point values	CZP 200 mg Q2W (RS)	CZP 400 mg Q2W (RS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: percentage of participants				
number (confidence interval 95%)	78.7 (68.93 to 88.45)	81.3 (71.90 to 90.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Dermatology Life Quality Index (DLQI) at Week 16

End point title	Change from Baseline in Dermatology Life Quality Index (DLQI) at Week 16

End point description:

The DLQI is a subject-reported questionnaire designed for use in adult subjects with PSO. The DLQI is a skin disease-specific questionnaire aimed at the evaluation of how symptoms and treatment affect patients' health related quality of life (HRQoL). This instrument asks subjects about symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. It has been shown to be valid and reproducible in PSO patients. The DLQI score ranges from 0 to 30 with higher scores indicating lower HRQoL. A higher than or equal to (>=) 4-point change in the DLQI score (DLQI response) has been reported to be meaningful for the patient (within-patient minimal important difference Basra et al, 2015) a DLQI absolute score of lower than or equal to (=<) 1 indicates DLQI remission (i.e., no or small impact of the disease on HRQoL).

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo Q2W (RS)	CZP 200 mg Q2W (RS)	CZP 400 mg Q2W (RS)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	90	87	
Units: Scores on a scale				
least squares mean (standard error)	-3.8 (± 0.84)	-10.4 (± 0.62)	-10.0 (± 0.64)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 200 mg Q2W (RS)

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	Adjusted Mean Treatment Differences
Point estimate	-6.62
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-8.88
upper limit	-4.36

Notes:

[7] - The P-value was obtained for each treatment group comparison tested at a significance level of 0.025 in the fixed sequence testing procedure.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The statistical analysis of the co-primary efficacy variables and key secondary efficacy variables accounted for multiplicity by using a fixed sequence testing procedure.

Comparison groups	Placebo Q2W (RS) v CZP 400 mg Q2W (RS)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	ANCOVA
Parameter estimate	Adjusted Mean Treatment Differences
Point estimate	-6.19
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-8.46
upper limit	-3.93

Notes:

[8] - The P-value was obtained for each treatment group comparison tested at a significance level of 0.025 in the fixed sequence testing procedure.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from Baseline (Week 0) until the Post Study Safety Follow-up Visit (Week 152).

Adverse event reporting additional description:

As per design, participants randomized to PBO either switched to CZP 200mg Q2W or escaped to CZP 400mg Q2W at Week 16, leading to a significantly lower exposure in PBO arm than in CZP arm. Considering the limitations of such comparison, AEs reported while the participants were on PBO are not included in this summary.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	CZP 200 mg Q2W (TCS)

Reporting group description:

This arm consisted of all participants who received CZP 200 mg at any time during the study.

Reporting group title	CZP 400 mg Q2W (TCS)

Reporting group description:

This arm consisted of all participants who received CZP 400 mg at any time during the study.

Serious adverse events	CZP 200 mg Q2W (TCS)	CZP 400 mg Q2W (TCS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 170 (14.12%)	12 / 149 (8.05%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	1 / 170 (0.59%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Distributive shock			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy with contraceptive device			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bite			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			

subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile swelling			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital haemorrhage			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal swelling			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Laryngeal cyst			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar cyst			

subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood count abnormal			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest X-ray abnormal			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			

subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 170 (1.18%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Eye disorders			
Tolosa-Hunt syndrome			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhagic necrotic pancreatitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Colitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngo-oesophageal diverticulum			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	2 / 170 (1.18%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic arthropathy			
subjects affected / exposed	2 / 170 (1.18%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			

subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholin's abscess			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian abscess			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic sinusitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 170 (0.59%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 170 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CZP 200 mg Q2W (TCS)	CZP 400 mg Q2W (TCS)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 170 (44.71%)	75 / 149 (50.34%)	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	8 / 170 (4.71%)	5 / 149 (3.36%)	
occurrences (all)	8	5	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 170 (4.12%)	9 / 149 (6.04%)	
occurrences (all)	8	9	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 170 (5.29%)	6 / 149 (4.03%)	
occurrences (all)	10	6	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 170 (1.76%)	8 / 149 (5.37%)	
occurrences (all)	3	8	
Psoriasis			
subjects affected / exposed	9 / 170 (5.29%)	12 / 149 (8.05%)	
occurrences (all)	10	19	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	6 / 170 (3.53%)	8 / 149 (5.37%)	
occurrences (all)	6	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	33 / 170 (19.41%)	35 / 149 (23.49%)	
occurrences (all)	55	45	
Upper respiratory tract infection			
subjects affected / exposed	19 / 170 (11.18%)	18 / 149 (12.08%)	
occurrences (all)	20	21	
Sinusitis			
subjects affected / exposed	13 / 170 (7.65%)	4 / 149 (2.68%)	
occurrences (all)	15	4	
Pharyngitis			
subjects affected / exposed	10 / 170 (5.88%)	4 / 149 (2.68%)	
occurrences (all)	12	4	
Urinary tract infection			
subjects affected / exposed	11 / 170 (6.47%)	10 / 149 (6.71%)	
occurrences (all)	15	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2015	The Global Protocol Amendment included the following changes: - CIMPASI-2 (name of the PS0002 protocol) was added. - Updated study contact information and serious adverse event (SAE) reporting contact information. - Added the secondary efficacy variable: at least 90% reduction from Baseline in PASI (PASI90). - Removed the other efficacy variables: absolute PASI score and absolute Body Surface Area (BSA) affected by PSO. - Corrected: the Subject Questionnaire for Tuberculosis (TB) was removed as a safety variable. - Clarified the responsibilities of the unblinded and blinded study personnel. - Provided additional details regarding breaking the treatment blind in an emergency situation - Revised Exclusion Criteria #21 to add secukinumab and require a 24-week washout period. - Allowed flexibility of self-administration of Certolizumab Pegol (CZP) during the Open label Treatment Period. - Corrected: subject treatment assignment was stratified by site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29660421