Clinical trial results:
A two-year multi-center Phase 3 study to investigate the efficacy and safety of secukinumab in adult patients with active, moderate to severe thyroid eye disease (ORBIT), with a randomized, parallel-group, double-blind, placebo-controlled, 16-week treatment period, and a follow-up/retreatment period

Summary

EudraCT number	2020-001611-24
Trial protocol	DE
Global end of trial date	16 May 2023

Results information

Result version number	v1
This version publication date	30 May 2024
First version publication date	30 May 2024

Trial information

Trial identification

Sponsor protocol code	CAIN457ADE16

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04737330
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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	16 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2023
Global end of trial reached?	Yes
Global end of trial date	16 May 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that secukinumab was superior to placebo with regard to the overall responder rate after 16 weeks of treatment.

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	29 November 2021
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	Germany: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	24
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 5 centers in Germany.

Pre-assignment

Screening details:

Eligible participants were randomized in a 1:1 ratio to one of the following double-blinded treatment arms: Secukinumab 300 mg (arm 1) and Placebo (arm 2).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Secukinumab 300 mg

Arm description:

Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12

Arm type	Active comparator
Investigational medicinal product name	Secukinumab
Investigational medicinal product code	
Other name	AIN457
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12

Arm title	Placebo

Arm description:

Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12

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

Dosage and administration details:

Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12

Number of subjects in period 1	Secukinumab 300 mg	Placebo
Started	14	14
Completed	12	12
Not completed	2	2
Study terminated by sponsor	1	2
Lost to follow-up	1	-

Period 2	
Period 2 title	Follow-up period (Week 16 to Week 108)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Secukinumab 300 mg

Arm description:

Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12

Arm type	Active comparator
Investigational medicinal product name	Secukinumab
Investigational medicinal product code	
Other name	AIN457
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12

Arm title	Placebo

Arm description:

Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12

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

Dosage and administration details:

Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12

Number of subjects in period 2	Secukinumab 300 mg	Placebo
Started	12	12
Completed	8	9
Not completed	4	3
Not satisfied	1	-
Study terminated by sponsor	3	1
Therapy national guidelines	-	1
No benefit IMP	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Secukinumab 300 mg
Reporting group description:	
Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	
Reporting group title	Placebo
Reporting group description:	
Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	

Reporting group values	Secukinumab 300 mg	Placebo	Total
Number of subjects	14	14	28
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)	12	12	24
From 65-84 years	2	2	4
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	53.6	57.7	
standard deviation	± 11.85	± 10.64	-
Sex: Female, Male Units: Participants			
Female	9	12	21
Male	5	2	7
Smoking History Units: Subjects			
Current	3	4	7
Former	8	6	14
Never	3	4	7
Race/Ethnicity, Customized Units: Subjects			
White	14	14	28

End points

End points reporting groups

Reporting group title	Secukinumab 300 mg
Reporting group description:	
Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	
Reporting group title	Placebo
Reporting group description:	
Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	
Reporting group title	Secukinumab 300 mg
Reporting group description:	
Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	
Reporting group title	Placebo
Reporting group description:	
Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	

Primary: Plan A - Proportion of participants achieving overall response

End point title	Plan A - Proportion of participants achieving overall response[1]
End point description:	
The proportion of participants achieving overall response was defined as follows: >= 2 points reduction in clinical activity score (CAS) AND >= 2 mm reduction in proptosis from Baseline in the study eye, provided there was no corresponding deterioration in CAS or proptosis (>= 2 point or 2 mm increase, respectively) in the fellow eye after 16 weeks of treatment. Due to premature study discontinuation, purely descriptive analyses were performed for the primary endpoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 16	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to premature study discontinuation, purely descriptive analyses were performed for the primary endpoint.

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Participants				
Yes	0	3		
No	12	8		
Missing	2	3		

Statistical analyses

No statistical analyses for this end point

Primary: Plan B - Proportion of participants achieving response in reduction of

proptosis

End point title	Plan B - Proportion of participants achieving response in reduction of proptosis[2]

End point description:

The proportion of participants achieving response in reduction of proptosis at Week 16 was defined as follows: reduction of >= 2 mm from Baseline in the study eye without deterioration (>= 2 mm increase) of proptosis in the fellow eye. Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the primary endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 16

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated)" for the primary endpoint

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Participants				

Notes:

[3] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

[4] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

Statistical analyses

No statistical analyses for this end point

Secondary: Plan A - Proportion of participants achieving response in reduction of clinical activity score (CAS)

End point title	Plan A - Proportion of participants achieving response in reduction of clinical activity score (CAS)

End point description:

The proportion of participants achieving response in reduction of clinical activity score (CAS) at Week 16 was defined as follows: reduction of >= 2 points from Baseline in the study eye without deterioration (>= 2 points increase) of CAS in the fellow eye. Due to premature study discontinuation, purely descriptive analyses were performed for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Participants				
Yes	0	3		
No	12	8		
Missing	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Plan A - Proportion of participants achieving response in reduction of proptosis

End point title	Plan A - Proportion of participants achieving response in reduction of proptosis

End point description:

The proportion of participants achieving response in reduction of proptosis at Week 16 was defined as follows: reduction of >= 2 mm from Baseline in the study eye without deterioration (>= 2 mm increase) of proptosis in the fellow eye. Due to premature study discontinuation, purely descriptive analyses were performed for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Participants				
Yes	0	0		
No	12	11		
Missing	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Plan A - Proportion of participants achieving response in diplopia

End point title	Plan A - Proportion of participants achieving response in diplopia

End point description:

The proportion of participants achieving response in diplopia at Week 16 was defined as follows: Baseline diplopia > 0 and a reduction of >= 1 grade with no corresponding deterioration (>= 1 grade worsening) in the fellow eye at Week 16. Due to premature study discontinuation, purely descriptive analyses were performed for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Participants				
Yes	1	1		
No	11	11		
Missing	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Plan A - Mean change from Baseline to Week 16 in clinical activity score (CAS) in the study eye

End point title	Plan A - Mean change from Baseline to Week 16 in clinical activity score (CAS) in the study eye

End point description:

Thyroid Eye Disease (TED) activity was assessed using the CAS at the frequency indicated in the study schedule based on the following signs and symptoms in accordance with the European Group on Graves' Orbitopathy (EUGOGO) guideline:
• Symptoms
~ Spontaneous retrobulbar pain
~ Pain on attempted upward or downward gaze
• Signs
~ Redness of eyelids
~ Redness of conjunctiva
~ Swelling of caruncle or plica
~ Swelling of eyelids
~ Swelling of conjunctiva (chemosis)

For each item present, 1 point is given. The sum of these points is the CAS score, i.e., minimum score of 0 and maximum score of 7.
• Inactive TED: CAS < 3.
• Active TED: CAS >= 3.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Change from BL at Week 2	-0.21 (± 0.58)	-0.29 (± 0.47)		
Change from BL at Week 4	-0.14 (± 1.10)	-0.29 (± 0.73)		
Change from BL at Week 8	0.00 (± 1.00)	-0.21 (± 0.58)		

Change from BL at Week 12	-0.67 (± 1.15)	-0.57 (± 0.94)		
Change from BL at Week 16	0.00 (± 0.95)	-0.73 (± 1.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plan A - Mean change from Baseline to Week 16 in proptosis in the study eye

End point title	Plan A - Mean change from Baseline to Week 16 in proptosis in the study eye

End point description:

Proptosis measurements were performed at the frequency indicated in the study schedule. The same Hertel instrument, and the same outer intercanthal distance, were to be used for each measurement. Due to premature study discontinuation, purely descriptive analyses were performed for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Change from BL at Week 2	0.18 (± 0.72)	-0.07 (± 0.73)		
Change from BL at Week 4	0.18 (± 0.72)	0.00 (± 1.18)		
Change from BL at Week 8	0.42 (± 1.00)	0.43 (± 1.28)		
Change from BL at Week 12	0.67 (± 0.98)	0.29 (± 1.33)		
Change from BL at Week 16	0.83 (± 1.03)	0.64 (± 1.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plan A - Proportion of participants with improvement in EUGOGO disease severity

End point title	Plan A - Proportion of participants with improvement in EUGOGO disease severity

End point description:

Thyroid Eye Disease (TED) activity was assessed using the CAS at the frequency indicated in the study schedule based on the following signs and symptoms in accordance with the European Group on Graves' Orbitopathy (EUGOGO) guideline. Improvement in EUGOGO disease severity was categorized: Mild, Moderate to severe and Sight threatening.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Participants				
Baseline|Mild	0	0		
Week 2|Mild	0	0		
Week 4|Mild	1	1		
Week 8|Mild	0	1		
Week 12|Mild	1	1		
Week 16|Mild	1	1		
Baseline|Moderate to severe	14	14		
Week 2|Moderate to severe	14	14		
Week 4|Moderate to severe	13	12		
Week 8|Moderate to severe	13	13		
Week 12|Moderate to severe	11	13		
Week 16|Moderate to severe	11	10		
Baseline|Sight threatening	0	0		
Week 2|Sight threatening	0	0		
Week 4|Sight threatening	0	0		
Week 8|Sight threatening	0	0		
Week 12|Sight threatening	0	0		
Week 16|Sight threatening	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plan A - Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 1: Visual functioning) over time

End point title	Plan A - Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 1: Visual functioning) over time

End point description:

The Graves' ophthalmopathy quality of life questionnaire (GO-QOL) contains 8 questions on visual functioning and 8 questions on appearance; answers on each subscale are transformed to scores ranging from 0 (worst) to 100 (best). Due to premature study discontinuation, purely descriptive analyses were performed for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Baseline	64.1 (± 23.04)	66.6 (± 24.38)		
Week 2	62.9 (± 27.71)	66.4 (± 20.51)		
Week 4	56.7 (± 28.11)	66.7 (± 23.82)		
Week 8	51.0 (± 27.93)	59.1 (± 24.75)		
Week 12	54.7 (± 29.45)	60.8 (± 28.71)		
Week 16	52.1 (± 29.36)	61.9 (± 30.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plan A - Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 2: Psychosocial functioning) over time

End point title	Plan A - Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 2: Psychosocial functioning) over time

End point description:

The Graves' ophthalmopathy quality of life questionnaire (GO-QOL) contains 8 questions on visual functioning and 8 questions on appearance; answers on each subscale are transformed to scores ranging from 0 (worst) to 100 (best). Due to premature study discontinuation, purely descriptive analyses were performed for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Baseline	65.6 (± 22.43)	60.3 (± 20.60)		
Week 2	68.3 (± 16.16)	62.5 (± 29.42)		
Week 4	69.2 (± 21.01)	56.7 (± 30.37)		
Week 8	65.4 (± 20.51)	52.2 (± 30.87)		
Week 12	63.5 (± 26.09)	53.1 (± 34.47)		
Week 16	66.2 (± 26.84)	56.8 (± 30.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plan B - Proportion of participants achieving response in reduction of clinical activity score (CAS)

End point title	Plan B - Proportion of participants achieving response in reduction of clinical activity score (CAS)

End point description:

The proportion of participants achieving response in reduction of CAS at Week 16 was defined as follows: reduction of >= 2 points from Baseline in the study eye without deterioration (>= 2 points increase) of CAS in the fellow eye. Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: Participants				

Notes:

[5] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

[6] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

Statistical analyses

No statistical analyses for this end point

Secondary: Plan A - Number of participants with Adverse Events

End point title	Plan A - Number of participants with Adverse Events

End point description:

The distribution of adverse events during Plan A study treatment period was done via the analysis of frequencies for Adverse Event (AEs) and Serious Adverse Event (SAEs), through the monitoring of relevant clinical and laboratory safety parameters.

End point type	Secondary

End point timeframe:

From first dose of study treatment until Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Participants				
Any adverse event (AE)	9	6		
Study treatment related AE	3	1		
AE leading to study treatment discontinuation	0	0		
Serious adverse event (SAE)	0	1		
Study treatment related SAE	0	0		

SAE leading to study treatment discontinuation	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plan B - Proportion of participants achieving overall response

End point title	Plan B - Proportion of participants achieving overall response

End point description:

The proportion of participants achieving overall response was defined as follows: >= 2 points reduction in CAS AND >= 2 mm reduction in proptosis from Baseline in the study eye, provided there was no corresponding deterioration in CAS or proptosis (>= 2 point or 2 mm increase, respectively) in the fellow eye after 16 weeks of treatment. Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Participants				

Notes:

[7] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

[8] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

Statistical analyses

No statistical analyses for this end point

Secondary: Plan B - Mean change from Baseline to Week 16 in proptosis in the study eye.

End point title	Plan B - Mean change from Baseline to Week 16 in proptosis in the study eye.

End point description:

Proptosis is the protrusion of the eyeball. Exophthalmos means the same, and this term is usually used when describing proptosis due to Grave's disease. Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Participants				

Notes:

[9] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

[10] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

Statistical analyses

No statistical analyses for this end point

Secondary: Plan B - Mean change from Baseline to Week 16 in clinical activity score (CAS) in the study eye.

End point title	Plan B - Mean change from Baseline to Week 16 in clinical activity score (CAS) in the study eye.

End point description:

Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: Participants				

Notes:

[11] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

[12] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

Statistical analyses

No statistical analyses for this end point

Secondary: Plan B - Proportion of participants achieving response in diplopia

End point title	Plan B - Proportion of participants achieving response in diplopia

End point description:

The proportion of participants achieving response in diplopia at Week 16 was defined as follows: Baseline diplopia > 0 and a reduction of >= 1 grade with no corresponding deterioration (>= 1 grade worsening) in the fellow eye at Week 16. Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: Participants				

Notes:

[13] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

[14] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

Statistical analyses

No statistical analyses for this end point

Secondary: Plan B - Number of participants with Adverse Events

End point title	Plan B - Number of participants with Adverse Events

End point description:

Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.

End point type	Secondary

End point timeframe:

From first dose of study treatment until Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: Participants				

Notes:

[15] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

[16] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

Statistical analyses

No statistical analyses for this end point

Secondary: Plan B - Mean change from Baseline to Week 16 in the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 2: Psychosocial functioning)

End point title	Plan B - Mean change from Baseline to Week 16 in the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 2: Psychosocial functioning)

End point description:

The Graves' ophthalmopathy quality of life questionnaire (GO-QOL) contains 8 questions on visual functioning and 8 questions on appearance; answers on each subscale are transformed to scores ranging from 0 (worst) to 100 (best). Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: Unit on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[17] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

[18] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

Statistical analyses

No statistical analyses for this end point

Secondary: Plan B - Mean change from Baseline to Week 16 in the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 1: Visual functioning)

End point title	Plan B - Mean change from Baseline to Week 16 in the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 1: Visual functioning)

End point description:

The Graves' ophthalmopathy quality of life questionnaire (GO-QOL) contains 8 questions on visual functioning and 8 questions on appearance; answers on each subscale are transformed to scores ranging from 0 (worst) to 100 (best). Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16

End point values	Secukinumab 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[19]	0[20]		
Units: Unit on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[19] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

[20] - Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs are presented for the double-blind treatment period (16 weeks) and for the follow-up/open-label re-treatment period, including AEs in FUP for all patients who received at least one dose of Secukinumab during the entire study up (maximum of 108 weeks).

Adverse event reporting additional description:

The safety analysis were done on the safety population, which included all randomized subjects who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Secukinumab 300 mg (Double-blind)

Reporting group description:

Secukinumab 300 mg (Double-blind): Double-blind treatment period (from first dose of study treatment until Week 16)

Reporting group title	Any Secukinumab 300 mg (entire study)

Reporting group description:

All events reported from the beginning of the study up until the end of follow-up/open-label retreatment period (from first dose of study treatment up to Week 108)

Reporting group title	Placebo (Double-blind)

Reporting group description:

Secukinumab matching placebo (Double-blind): Double-blind treatment period (from first dose of study treatment until Week 16)

Serious adverse events	Secukinumab 300 mg (Double-blind)	Any Secukinumab 300 mg (entire study)	Placebo (Double-blind)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	1 / 14 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Eye disorders			
Endocrine ophthalmopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Graves' disease			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Secukinumab 300 mg (Double-blind)	Any Secukinumab 300 mg (entire study)	Placebo (Double-blind)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	23 / 26 (88.46%)	12 / 14 (85.71%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	3 / 26 (11.54%)	2 / 14 (14.29%)
occurrences (all)	1	4	2
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	2	4	1
Injection site swelling			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Injection site pruritus			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Injection site pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	4	4	0
Injection site haematoma			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Injection site erythema			

subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	2 / 14 (14.29%)	2 / 26 (7.69%)	0 / 14 (0.00%)
occurrences (all)	2	4	0
Swelling			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Anxiety			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Investigations			
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Haematocrit decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Red blood cell count decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Thyroxine free decreased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Tri-iodothyronine increased			

subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)	5 / 26 (19.23%)	2 / 14 (14.29%)
occurrences (all)	9	20	7
Horner's syndrome			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	2	3	0
Neutropenia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Eye disorders			
Chalazion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
Conjunctival hyperaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Conjunctival oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Diplopia			

subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
Swelling of eyelid			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
Pupillary reflex impaired			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Ocular discomfort			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Metamorphopsia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Erythema of eyelid			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Eye swelling			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Eye pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Visual field defect			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	3	6	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	1	1

Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 26 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Endocrine disorders			
Thyroid dermatopathy			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Arthralgia			
subjects affected / exposed	2 / 14 (14.29%)	2 / 26 (7.69%)	0 / 14 (0.00%)
occurrences (all)	2	4	0
Infections and infestations			
Oral herpes			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Oral candidiasis			

subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
COVID-19			
subjects affected / exposed	4 / 14 (28.57%)	10 / 26 (38.46%)	6 / 14 (42.86%)
occurrences (all)	4	14	6
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Borrelia infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 26 (3.85%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	2 / 26 (7.69%)	3 / 14 (21.43%)
occurrences (all)	0	2	3
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 14 (7.14%)	1 / 26 (3.85%)	0 / 14 (0.00%)
occurrences (all)	1	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2021	Amended Protocol Version 01: The main purpose of this amendment is to add additional ophthalmological assessments to the study protocol. Exclusion criterion #13 was specified by the addition of a wash-out period for the prior use of oral corticosteroids. For patients who prematurely discontinue the study or study treatment, the follow-up assessment 12 weeks after last administration of study treatment was amended to an End of Study (EOS) visit which includes safety and efficacy assessments and will be recorded in the eCRF in order to increase data consistency and to comply with current Novartis standards. Furthermore, minor clarifications and corrections of certain aspects and procedures as well as changes to correct formatting errors and administrative inconsistencies were made where applicable. At the time of the amendment, no patients had been screened for inclusion.
15 March 2022	Amended Protocol Version 02: The main purpose of this amendment is to provide clarification of wording for inclusion criterion 6 and for the requirement of patients to be fasting prior to laboratory assessments. Furthermore, information was added that live vaccinations should not be given until 12 weeks after last study treatment administration to comply with current Novartis standards.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported