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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Secukinumab/AIN457

Trial Indication(s)

Thyroid eye disease (TED)

Protocol Number

CAIN457ADE16

Protocol Title

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

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

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Study Start/End Dates

Study Start Date: November 29, 2021 (Actual)
Primary Completion Date: May 16, 2023 (Actual)
Study Completion Date: May 16, 2023 (Actual)

Reason for Termination (If applicable)

Analysis of blinded patient data showed a very low probability of the study meeting the primary efficacy endpoints. No safety concerns were identified

Study Design/Methodology

This was a randomized, placebo-controlled, double-blind, parallel-group, interventional, multicenter study in adult patients with moderate to severe TED. This study consisted of the following 3 periods (screening, treatment, follow-up/open-label retreatment).

The investigational treatment was secukinumab 300 mg, supplied as 2 x 150 mg prefilled syringes (PFS). Control treatment was placebo, also be supplied as 2 x PFS.

It was planned to randomize approximately 70 patients. Due to early termination, 33 patients were screened, 28 patients were randomized by the time of study discontinuation.

Centers

Germany (5)

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Objectives:

Primary objective	Endpoint for primary objective
• To demonstrate that secukinumab is superior to placebo with regard to the overall responder rate after 16 weeks of treatment.	• Proportion of patients achieving overall response defined as follows: ≥ 2 points reduction in CAS AND ≥ 2 mm reduction in proptosis from Baseline in the study eye, provided there is no corresponding deterioration in CAS or proptosis (≥ 2 point or 2 mm increase, respectively) in the fellow eye after 16 weeks of treatment.
Secondary objectives	**Endpoints for secondary objectives**
• To demonstrate that secukinumab is superior to placebo with regard to the CAS responder rate after 16 weeks of treatment.	• Proportion of patients achieving response in reduction of CAS at Week 16 defined as follows: reduction of ≥ 2 points from Baseline in the study eye without deterioration (≥ 2 points increase) of CAS in the fellow eye.
• To demonstrate that secukinumab is superior to placebo with regard to the proptosis responder rate after 16 weeks of treatment.	• Proportion of patients achieving response in reduction of proptosis at Week 16 defined as follows: reduction of ≥ 2 mm from Baseline in the study eye without deterioration (≥ 2 mm increase) of proptosis in the fellow eye.
• To demonstrate that secukinumab is superior to placebo with regard to reduction in diplopia after 16 weeks of treatment.	• Proportion of patients achieving response in diplopia at Week 16 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.
• To demonstrate that secukinumab is superior to placebo with regard to reduction in CAS after 16 weeks of treatment.	• Mean change from Baseline to Week 16 in CAS in the study eye.
• To demonstrate that secukinumab is superior to placebo with regard to reduction in proptosis after 16 weeks of treatment.	• Mean change from Baseline to Week 16 in proptosis in the study eye.
• To demonstrate that secukinumab is superior to placebo with regard to improvement in disease severity after 16 weeks of treatment.	• Proportion of patients with improvement in EUGOGO disease severity between Baseline and Week 16.

• To demonstrate that secukinumab is superior to placebo with regard to improvement in GO-QoL after 16 weeks of treatment.	• Mean change from Baseline to Week 16 in GO-QoL score.
• To evaluate the safety of secukinumab compared to placebo.	• Frequency of AEs, TEAEs, AEs resulting in treatment discontinuation, SAEs.
AE = adverse event, CAS = clinical activity score, EUGOGO = European Group on Graves' Orbitopathy, GO-QoL = Graves' orbitopathy quality of life, SAE = serious adverse event, TEAE = treatment emergent adverse event	

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational treatment was secukinumab 300 mg, reference treatment was placebo, both supplied as 2x pre-filled syringes (PFS).

Study treatment	Dose form	Route and frequency of administration
Baseline to Week 16 (Double-blind)		
Secukinumab 300 mg	2 × 150 mg PFS	subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8 and Week 12.
Placebo	2 x 0 mg PFS	subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8 and Week 12.
Week 16 to end of study (EOS) (open-label)		
Secukinumab 300 mg	2 x 150 mg PFS	Non-responders at Week 16: subcutaneous (s.c.) injection at Week 16, Week 17, Week 18, Week 19, Week 20, Week 24 and Week 28. Responders at Week 16 who relapse thereafter: subcutaneous (s.c.) injection at time of relapse, then 1, 2, 3, 4, 8 and 12 weeks from time of relapse.

Statistical Methods

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) expressed different preferences regarding the primary and secondary objectives and endpoints and their ordering. Therefore, this study intended to have 2 different analysis strategies and corresponding primary, secondary objective, and endpoint definitions:

- Plan A was intended for submission in Europe (EU) and other applicable countries
- Plan B was intended for submission in the United States (US) and other applicable countries.

As the study was early terminated, only Plan A analysis was conducted.

The Full analysis set (FAS) consisted of all patients to whom study treatment (secukinumab or placebo) had been assigned. The Safety analysis set (SAF) consisted of all patients who received at least one dose of study treatment during the treatment period. Patients were analyzed according to the study treatment received.

Due to premature study discontinuation, purely descriptive analyses were performed for the primary endpoint. Analysis on primary endpoints were done based on FAS. Superiority testing was omitted. The primary endpoint was the proportion of patients achieving overall response.

The secondary objectives were analyzed in a purely descriptive manner: summary statistics by visit and change from baseline. No testing strategy was applied.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

• Patient had to be able to understand and communicate with the investigator and comply with the requirements of the study and had to give a written, signed and dated informed consent before any study assessment was performed.

• Male or non-pregnant, non-lactating female patients ≥ 18 years of age.

• Clinical diagnosis of active, moderate to severe TED (not sight-threatening) in the study eye at Baseline associated with 2 or more of the following:

-- Lid retraction >= 2 mm

-- Moderate or severe soft tissue involvement

-- Exophthalmos >= 3 mm above normal

-- Inconstant or constant diplopia

• Onset of TED symptoms fewer than 12 months prior to Baseline.

• CAS >= 4 (on a 7-point scale, with a score of >= 3 indicating active TED) in the more severely affected (study) eye at Screening and Baseline. Note: Proptosis is the primary qualifier for selection of the study eye. In case both eyes showed a similar degree of proptosis, other inflammatory signs and symptoms (CAS) were taken into account by the investigator for the selection of the study

eye.

• Peripheral euthyroidism or mild hypo-/hyperthyroidism defined as free T3 (fT3) and free T4 (fT4) < 30% above/below normal limits at Screening. Every effort was to be made to correct the mild hypo-/hyperthyroidism promptly and to maintain the euthyroid state until the end of this study.

• Orbital MRI assessment available confirming the diagnosis of TED for patients initially presenting with hypo- or euthyroidism (without treatment for hyperthyroidism) before or at the time of TED diagnosis (to rule out other potential causes of orbital signs and symptoms.

Key Exclusion Criteria:

• Improvement in CAS of >= 2 points and/or improvement in proptosis of >= 2 mm in the study eye between Screening and Baseline.

• Signs of sight-threatening TED defined by optic neuropathy or severe corneal injury.

• Patients, in the opinion of the investigator, requiring immediate or urgent medical treatment with glucocorticoids for TED.

• Patients requiring immediate surgical ophthalmological intervention or planning corrective surgery/irradiation during the course of the study.

• Decreased best corrected visual acuity (BCVA) as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect or color defect within the last 6 months.

• Any other ophthalmic and/or orbital disease or condition that might interfere with the assessment of TED.

• Previous orbital radiotherapy.

• Previous ophthalmological/orbital surgery for TED (e.g., orbital decompression).

• Previous use of biological agents for the treatment of TED.

• Previous use of systemic, non-biologic, immunomodulatory agents for the treatment of TED (e.g., mycophenolate or cyclosporine).

• Previous exposure to secukinumab or other biologic drugs directly targeting IL-17A or the IL 17 receptor (e.g., ixekizumab, brodalumab).

• Previous treatment with rituximab, tocilizumab or teprotumumab.

• Previous use of systemic corticosteroids for the treatment of TED, except for oral corticosteroids with a cumulative dose equivalent to < 1 g oral prednisone/prednisolone if the corticosteroid was discontinued at least 4 weeks prior to Baseline.

• Previous treatment with any cell-depleting therapies including but not limited to anti-cluster of differentiation 20 (CD20) or investigational agents (e.g., CAMPATH, anti CD4, anti-CD5, anti-CD3, anti-CD19).

• Use of other investigational drugs within 5 half-lives of enrollment or within 30 days, whichever is longer.

• Previous or ongoing use of prohibited treatments (see Appendix 16.1.1-Protocol Section 6.2.2). Respective washout periods detailed in this section needed to be adhered to.

• History of hypersensitivity to any of the study drug constituents.

Other protocol defined Inclusion/Exclusion may apply.

Participant Flow Table

Treatment period (Baseline to Week 16)

	Secukinumab 300 mg	Placebo	Total
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	
Started	14	14	28
Completed	12	12	24
Not Completed	2	2	4
Lost to Follow-up	1	0	1
Study terminated by sponsor	1	2	3

Follow-up period (Week 16 to Week 108)

	Secukinumab 300 mg	Placebo	Total
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	
Started	12	12	24
Completed	8	9	17
Not Completed	4	3	7
Not satisfied	1	0	1
Study terminated by sponsor	3	1	4
No benefit IMP	0	1	1
Therapy national guidelines	0	1	1

Baseline Characteristics

	Secukinumab 300 mg	Placebo	Total
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	
Number of Participants [units: participants]	14	14	28
Baseline Analysis Population Description			
Age Continuous (units: Years)			

Analysis Population Type: Participants
Mean ± Standard Deviation

	53.6±11.85	57.7±10.64	55.6±11.25
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	9	12	21
Male	5	2	7
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
White	14	14	28
Study Specific Characteristic **Smoking History** (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Current	3	4	7
Former	8	6	14
Never	3	4	7

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Primary Outcome Result(s)

Plan A - Percentage of participants achieving overall response

Description	The percentage 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.
Time Frame	Baseline, Week 16
Analysis Population Description	Full Analysis Set (FAS)

	Secukinumab 300 mg	**Placebo**
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	14	14
Plan A - Percentage of participants achieving overall response (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Yes	0 (%)	0 (%)
No	12 (85.71%)	11 (78.57%)
Missing	2 (14.29%)	3 (21.43%)

Plan B - Percentage of participants achieving response in reduction of proptosis

Description	The percentage 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.

Time Frame	Baseline, Week 16
Analysis Population Description	Full Analysis Set (FAS). Due to premature study discontinuation, only Plan A was conducted (no data collected for Plan B, as Plan B was not initiated).

	Secukinumab 300 mg	Placebo
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	0	0
Plan B - Percentage of participants achieving response in reduction of proptosis (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	(NaN%)	(NaN%)

Secondary Outcome Result(s)

Plan A - Percentage of participants achieving response in reduction of clinical activity score (CAS)

Description	The percentage 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.
Time Frame	Baseline, Week 16
Analysis Population Description	Full Analysis Set (FAS)

	Secukinumab 300 mg	**Placebo**
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	14	14
Plan A - Percentage of participants achieving response in reduction of clinical activity score (CAS) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Yes	0 (%)	3 (21.43%)
No	12 (85.71%)	8 (57.14%)
Missing	2 (14.29%)	3 (21.43%)

Plan A - Percentage of participants achieving response in reduction of proptosis

Description	The percentage 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.

Time Frame	Baseline, Week 16
Analysis Population Description	Full Analysis Set (FAS)

	Secukinumab 300 mg	Placebo
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	14	14
Plan A - Percentage of participants achieving response in reduction of proptosis (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Yes	0 (%)	0 (%)
No	12 (85.71%)	11 (78.57%)
Missing	2 (14.29%)	3 (21.43%)

Plan A - Percentage of participants achieving response in diplopia

Description	The percentage 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.
Time Frame	Baseline, Week 16
Analysis Population Description	Full Analysis Set (FAS)

	Secukinumab 300 mg	Placebo
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	14	14
Plan A - Percentage of participants achieving response in diplopia (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Yes	1 (7.14%)	1 (7.14%)
No	11 (78.57%)	11 (78.57%)
Missing	2 (14.29%)	2 (14.29%)

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

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.
Time Frame	Baseline, Week 2, Week 4, Week 8, Week 12, Week 16
Analysis Population Description	Full Analysis Set (FAS). Only participants with a value at both Baseline and post-baseline visit included.

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

Number of Participants Analyzed [units: participants]	14	14
Plan A - Mean change from Baseline to Week 16 in clinical activity score (CAS) in the study eye (units: Unit on a scale)	**Mean ± Standard Deviation**	**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

Plan A - Mean change from Baseline to Week 16 in millimeters (mm) of proptosis in the study eye

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. The mean of measurements (change from baseline in millimeters (mm) of proptosis, calculated as: (Post-Baseline value - Baseline value) / Baseline value * 100)) for each group were presented. Due to premature study discontinuation, purely descriptive analyses were performed for the secondary endpoint.
Time Frame	Baseline, Week 2, Week 4, Week 8, Week 12, Week 16
Analysis Population Description	Full Analysis Set (FAS). Only participants with a value at both Baseline and post-baseline visit included.

	Secukinumab 300 mg	**Placebo**
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	14	14
Plan A - Mean change from Baseline to Week 16 in millimeters (mm) of proptosis in the study eye (units: millimeters (mm))	**Mean ± Standard Deviation**	**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

Plan A - Percentage of participants with improvement in EUGOGO disease severity

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.
Time Frame	Baseline, Week 2, Week 4, Week 8, Week 12, Week 16
Analysis Population Description	Full Analysis Set (FAS). Only participants with a value at both Baseline and post-baseline visit included.

	Secukinumab 300 mg	**Placebo**
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	14	14
Plan A - Percentage of participants with improvement in EUGOGO disease severity (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Baseline : Mild	0 (%)	0 (%)
Baseline : Moderate to severe	14 (100%)	14 (100%)
Baseline : Sight threatening	0 (%)	0 (%)

Week 2 : Mild	0 (%)	0 (%)
Week 2 : Moderate to severe	14 (100%)	14 (100%)
Week 2 : Sight threatening	0 (%)	0 (%)
Week 4 : Mild	1 (7.14%)	1 (7.69%)
Week 4 : Moderate to severe	13 (92.86%)	12 (92.31%)
Week 4 : Sight threatening	0 (%)	0 (%)
Week 8 : Mild	0 (%)	1 (7.14%)
Week 8 : Moderate to severe	13 (100%)	13 (92.86%)
Week 8 : Sight threatening	0 (%)	0 (%)
Week 12 : Mild	1 (8.33%)	1 (7.14%)
Week 12 : Moderate to severe	11 (91.67%)	13 (92.86%)
Week 12 : Sight threatening	0 (%)	0 (%)
Week 16 : Mild	1 (8.33%)	1 (9.09%)
Week 16 : Moderate to severe	11 (91.67%)	10 (90.91%)
Week 16 : Sight threatening	0 (%)	0 (%)

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

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.
Time Frame	Baseline, Week 2, Week 4, Week 8, Week 12, Week 16
Analysis Population Description	Full Analysis Set (FAS). Only participants with a value at both Baseline and post-baseline visit included.

	Secukinumab 300 mg	**Placebo**
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	14	14
Plan A - Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 1: Visual functioning) over time (units: Unit on a scale)	**Mean ± Standard Deviation**	**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

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

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.
Time Frame	Baseline, Week 2, Week 4, Week 8, Week 12, Week 16
Analysis Population Description	Full Analysis Set (FAS). Only participants with a value at both Baseline and post-baseline visit included.

	Secukinumab 300 mg	**Placebo**
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	14	14
Plan A - Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 2: Psychosocial functioning) over time (units: Unit on a scale)	**Mean ± Standard Deviation**	**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

Plan A - Number of participants with Adverse Events

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.

Time Frame	From first dose of study treatment until Week 16
Analysis Population Description	Safety Analysis Set (SAF)

	Secukinumab 300 mg	Placebo
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	14	14
Plan A - Number of participants with Adverse Events (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Any adverse event (AE)	9 (64.29%)	6 (42.86%)
Study treatment related AE	3 (21.43%)	1 (7.14%)
AE leading to study treatment discontinuation	0 (%)	0 (%)
Serious adverse event (SAE)	0 (%)	1 (7.14%)
Study treatment related SAE	0 (%)	0 (%)
SAE leading to study treatment discontinuation	0 (%)	0 (%)

Plan B - Percentage of participants achieving response in reduction of clinical activity score (CAS)

Description	The percentage 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.
Time Frame	Baseline, Week 16

Analysis Population Description	Full Analysis Set (FAS). Due to premature study discontinuation, only Plan A was conducted (no data collected for Plan B, as Plan B was not initiated).

	Secukinumab 300 mg	Placebo
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	0	0
Plan B - Percentage of participants achieving response in reduction of clinical activity score (CAS) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	(NaN%)	(NaN%)

Plan B - Percentage of participants achieving overall response

Description	The percentage 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.
Time Frame	Baseline, Week 16
Analysis Population Description	Full Analysis Set (FAS). Due to premature study discontinuation, only Plan A was conducted (no data collected for Plan B, as Plan B was not initiated).

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

	Week 2, Week 3, Week 4, Week 8, Week 12	
Number of Participants Analyzed [units: participants]	0	0
Plan B - Percentage of participants achieving overall response (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	(NaN%)	(NaN%)

Plan B - Percentage of participants achieving response in diplopia

Description	The percentage 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.
Time Frame	Baseline, Week 16
Analysis Population Description	Full Analysis Set (FAS). Due to premature study discontinuation, only Plan A was conducted (no data collected for Plan B, as Plan B was not initiated).

	Secukinumab 300 mg	**Placebo**
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	0	0
Plan B - Percentage of participants achieving response in diplopia (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	(NaN%)	(NaN%)

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

Description	Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.
Time Frame	Baseline, Week 16
Analysis Population Description	Full Analysis Set (FAS). Due to premature study discontinuation, only Plan A was conducted (no data collected for Plan B, as Plan B was not initiated).

	Secukinumab 300 mg	Placebo
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	0	0
Plan B - Mean change from Baseline to Week 16 in clinical activity score (CAS) in the study eye. (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	(NaN%)	(NaN%)

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

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.
Time Frame	Baseline, Week 16
Analysis Population Description	Full Analysis Set (FAS). Due to premature study discontinuation, only Plan A was conducted (no data collected for Plan B, as Plan B was not initiated).

	Secukinumab 300 mg	Placebo

Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	0	0
Plan B - Mean change from Baseline to Week 16 in proptosis in the study eye. (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	(NaN%)	(NaN%)

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

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.
Time Frame	Baseline, Week 2, Week 4, Week 8, Week 12, Week 16
Analysis Population Description	Full Analysis Set (FAS). Due to premature study discontinuation, only Plan A was conducted (no data collected for Plan B, as Plan B was not initiated).

	Secukinumab 300 mg	Placebo
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	0	0
Plan B - Mean change from Baseline to Week 16 in the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 1: Visual functioning) (units:)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

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

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.
Time Frame	Baseline, Week 2, Week 4, Week 8, Week 12, Week 16
Analysis Population Description	Full Analysis Set (FAS). Due to premature study discontinuation, only Plan A was conducted (no data collected for Plan B, as Plan B was not initiated).

	Secukinumab 300 mg	**Placebo**
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	0	0
Plan B - Mean change from Baseline to Week 16 in the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) score (score 2: Psychosocial functioning) (units:)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

Plan B - Number of participants with Adverse Events

Description	Due to premature study discontinuation, only Plan A was conducted (Plan B was not initiated) for the secondary endpoint.
Time Frame	From first dose of study treatment until Week 16

Analysis Population Description	Safety Analysis Set (SAF). Due to premature study discontinuation, only Plan A was conducted (no data collected for Plan B, as Plan B was not initiated).

	Secukinumab 300 mg	Placebo
Arm/Group Description	Secukinumab 300 mg subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12	Placebo subcutaneous (s.c.) injection at Baseline, Week 1, Week 2, Week 3, Week 4, Week 8, Week 12
Number of Participants Analyzed [units: participants]	0	0
Plan B - Number of participants with Adverse Events (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	(NaN%)	(NaN%)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	Adverse events are presented for the double-blind treatment period (from first dose of study treatment until Week 16) and for the follow-up/open-label re-treatment period, including AEs in follow up for all patients who received at least one dose of Secukinumab during the entire study up to a maximum of 108 weeks.
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.
Source Vocabulary for Table Default	MedDRA (24.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Secukinumab 300 mg (Double-blind) N = 14	**Placebo (Double-blind) N = 14**	**Any Secukinumab 300 mg (entire study) N = 26**
Arm/Group Description	Secukinumab 300 mg (Double-blind): Double-blind treatment period (from first dose of study treatment until Week 16)	Secukinumab matching placebo (Double-blind): Double-blind treatment period (from first dose of study treatment until Week 16)	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)
Total Number Affected	0	0	0
Total Number At Risk	14	14	26

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Serious Adverse Events

Time Frame	Adverse events are presented for the double-blind treatment period (from first dose of study treatment until Week 16) and for the follow-up/open-label re-treatment period, including AEs in follow up for all patients who received at least one dose of Secukinumab during the entire study up to a maximum of 108 weeks.
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.
Source Vocabulary for Table Default	MedDRA (24.0)
Collection Approach for Table Default	Systematic Assessment

	Secukinumab 300 mg (Double-blind) N = 14	**Placebo (Double-blind) N = 14**	**Any Secukinumab 300 mg (entire study) N = 26**
Arm/Group Description	Secukinumab 300 mg (Double-blind): Double-blind treatment period (from first dose of study treatment until Week 16)	Secukinumab matching placebo (Double-blind): Double-blind treatment period (from first dose of study treatment until Week 16)	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)
Total # Affected by any Serious Adverse Event	1	1	1
Total # at Risk by any Serious Adverse Event	14	14	26
Endocrine disorders			
Graves' disease	1 (7.14%)	0 (0.00%)	1 (3.85%)
Eye disorders			

Endocrine ophthalmopathy	0 (0.00%)	1 (7.14%)	0 (0.00%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events are presented for the double-blind treatment period (from first dose of study treatment until Week 16) and for the follow-up/open-label re-treatment period, including AEs in follow up for all patients who received at least one dose of Secukinumab during the entire study up to a maximum of 108 weeks.
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.
Source Vocabulary for Table Default	MedDRA (24.0)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	Secukinumab 300 mg (Double-blind) N = 14	**Placebo (Double-blind) N = 14**	**Any Secukinumab 300 mg (entire study) N = 26**
Arm/Group Description	Secukinumab 300 mg (Double-blind): Double-blind treatment period (from first dose of study treatment until Week 16)	Secukinumab matching placebo (Double-blind): Double-blind treatment period (from first dose of study treatment until Week 16)	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)

Total # Affected by any Other Adverse Event	12	12	23
Total # at Risk by any Other Adverse Event	14	14	26
Blood and lymphatic system disorders			
Lymphadenopathy	1 (7.14%)	0 (0.00%)	1 (3.85%)
Neutropenia	1 (7.14%)	0 (0.00%)	1 (3.85%)
Ear and labyrinth disorders			
Vertigo	1 (7.14%)	0 (0.00%)	1 (3.85%)
Endocrine disorders			
Thyroid dermatopathy	0 (0.00%)	1 (7.14%)	1 (3.85%)
Eye disorders			
Chalazion	0 (0.00%)	1 (7.14%)	1 (3.85%)
Conjunctival hyperaemia	0 (0.00%)	1 (7.14%)	0 (0.00%)
Conjunctival oedema	0 (0.00%)	1 (7.14%)	0 (0.00%)
Diplopia	1 (7.14%)	1 (7.14%)	1 (3.85%)
Erythema of eyelid	0 (0.00%)	1 (7.14%)	0 (0.00%)
Eye pain	0 (0.00%)	1 (7.14%)	0 (0.00%)
Eye swelling	0 (0.00%)	1 (7.14%)	0 (0.00%)
Metamorphopsia	1 (7.14%)	0 (0.00%)	1 (3.85%)
Ocular discomfort	1 (7.14%)	0 (0.00%)	1 (3.85%)
Pupillary reflex impaired	0 (0.00%)	1 (7.14%)	0 (0.00%)
Swelling of eyelid	1 (7.14%)	1 (7.14%)	1 (3.85%)
Vision blurred	0 (0.00%)	1 (7.14%)	0 (0.00%)
Visual field defect	1 (7.14%)	1 (7.14%)	1 (3.85%)

Gastrointestinal disorders			
Abdominal pain	1 (7.14%)	0 (0.00%)	1 (3.85%)
Diarrhoea	0 (0.00%)	1 (7.14%)	1 (3.85%)
Vomiting	0 (0.00%)	1 (7.14%)	1 (3.85%)
General disorders and administration site conditions			
Fatigue	2 (14.29%)	0 (0.00%)	2 (7.69%)
Injection site erythema	1 (7.14%)	0 (0.00%)	1 (3.85%)
Injection site haematoma	0 (0.00%)	1 (7.14%)	1 (3.85%)
Injection site pain	1 (7.14%)	0 (0.00%)	1 (3.85%)
Injection site pruritus	1 (7.14%)	0 (0.00%)	1 (3.85%)
Injection site swelling	0 (0.00%)	1 (7.14%)	1 (3.85%)
Oedema peripheral	1 (7.14%)	1 (7.14%)	1 (3.85%)
Swelling	0 (0.00%)	1 (7.14%)	0 (0.00%)
Infections and infestations			
Borrelia infection	0 (0.00%)	1 (7.14%)	1 (3.85%)
Bronchitis	0 (0.00%)	1 (7.14%)	1 (3.85%)
COVID-19	4 (28.57%)	6 (42.86%)	10 (38.46%)
Oral candidiasis	1 (7.14%)	0 (0.00%)	1 (3.85%)
Oral herpes	1 (7.14%)	0 (0.00%)	1 (3.85%)
Urinary tract infection	0 (0.00%)	3 (21.43%)	2 (7.69%)
Injury, poisoning and procedural complications			
Fall	1 (7.14%)	0 (0.00%)	1 (3.85%)
Investigations			

Blood thyroid stimulating hormone decreased	1 (7.14%)	0 (0.00%)	1 (3.85%)
Glycosylated haemoglobin increased	1 (7.14%)	0 (0.00%)	1 (3.85%)
Haematocrit decreased	0 (0.00%)	1 (7.14%)	0 (0.00%)
Haemoglobin decreased	0 (0.00%)	1 (7.14%)	0 (0.00%)
Red blood cell count decreased	0 (0.00%)	1 (7.14%)	0 (0.00%)
Thyroxine free decreased	1 (7.14%)	0 (0.00%)	1 (3.85%)
Tri-iodothyronine increased	1 (7.14%)	0 (0.00%)	1 (3.85%)
Metabolism and nutrition disorders			
Type 2 diabetes mellitus	1 (7.14%)	0 (0.00%)	1 (3.85%)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (14.29%)	0 (0.00%)	2 (7.69%)
Back pain	0 (0.00%)	1 (7.14%)	1 (3.85%)
Myalgia	1 (7.14%)	0 (0.00%)	1 (3.85%)
Neck pain	0 (0.00%)	1 (7.14%)	1 (3.85%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma	1 (7.14%)	0 (0.00%)	1 (3.85%)
Nervous system disorders			
Headache	3 (21.43%)	2 (14.29%)	5 (19.23%)
Horner's syndrome	1 (7.14%)	0 (0.00%)	1 (3.85%)
Psychiatric disorders			
Acute stress disorder	1 (7.14%)	0 (0.00%)	1 (3.85%)
Anxiety	1 (7.14%)	0 (0.00%)	1 (3.85%)
Renal and urinary disorders			

Dysuria	0 (0.00%)	1 (7.14%)	0 (0.00%)
Haematuria	0 (0.00%)	1 (7.14%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Dermatitis atopic	1 (7.14%)	0 (0.00%)	1 (3.85%)
Vascular disorders			
Hypertension	1 (7.14%)	2 (14.29%)	3 (11.54%)

Other Relevant Findings

None

Conclusion:

The purpose of this study was to demonstrate the efficacy and safety of secukinumab 300 mg s.c. in adults with active, moderate to severe TED.

Due to the lack of efficacy (no proptosis response) observed on blinded data, this study was terminated early by Novartis. At the time of termination, 28 patients had been randomized, 25 patients had completed the double-blind treatment period, and 23 patients had entered the follow-up period. There were no differences between the secukinumab and the placebo group regarding all endpoints analyzed.

No new safety signals were observed.

The study was well conceived and executed and was successful in answering the scientific question whether IL-17A alone is an appropriate treatment target in patients with active, moderate to severe TED.

Date of Clinical Trial Report

02-May-2024