Clinical trial results:
A Phase 3, Multicenter Study to Evaluate the Safety and Efficacy of AGN-151586 for the Treatment of Glabellar Lines

Summary

EudraCT number	2021-003667-10
Trial protocol	HU
Global end of trial date	17 March 2023

Results information

Result version number	v1
This version publication date	27 March 2024
First version publication date	27 March 2024

Trial information

Trial identification

Sponsor protocol code	M21-500

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05248867
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.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	17 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and efficacy of AGN-151586 for the treatment of glabellar lines (GL) in participants with moderate to severe GL.

This was a 12-week study in which eligible subjects were enrolled into the study containing 2 treatment periods, double-blind period and open-label period. Participants were randomly assigned to receive AGN-151586 or placebo. Participants received either AGN-151586 or Placebo administered as 5 intramuscular injections to the glabellar complex on Day 1. Participants meeting retreatment criteria may have received an open-label treatment of AGN-151586 during the study.

Protection of trial subjects:

Subjects signed and dated an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 March 2022
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	Canada: 64
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Hungary: 40
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	United States: 434
Worldwide total number of subjects	638
EEA total number of subjects	140

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)	586
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who didn’t meet eligibility criteria were allowed to be rescreened. Rescreening only occurred after discussion with the Sponsor. Rescreening could only occur once for any given potential subject; however, if the original screen failure was due to ineligible Frown Wrinkle Scale (FWS) grade(s), the subject was not permitted to rescreen.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received 5 intramuscular injections of placebo in the glabellar complex on Day 1. Based on meeting the retreatment criteria, the participants may have also received 1 open-label treatment of AGN-151586 on Day 43.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo solution for injection

Arm title	AGN-151586

Arm description:

Participants received 5 intramuscular injections of AGN-151586 in the glabellar complex on Day 1. Based on meeting the retreatment criteria, participants may also have received 1 open-label treatment of AGN-151586 on Day 43.

Arm type	Experimental
Investigational medicinal product name	AGN-151586
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

AGN-151586 solution for injection

Number of subjects in period 1	Placebo	AGN-151586
Started	156	482
Completed	148	454
Not completed	8	28
Other, not specified	3	8
Lost to follow-up	-	3
Withdrawal by subject due to adverse event	-	3
Withdrawal by subject	5	14

Period 2	
Period 2 title	Open-label period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/None

Arm description:

Participants received placebo injections during the Double-blind Period but did not meet all the retreatment criteria on Day 43. Participants were followed weekly in the Open-label Period until the Facial Wrinkle Scale (FWS) grades assessed by both investigator and participant returned to moderate or severe (investigator and participant grades did not need to match) before being discontinued from the study after completing either the Early Exit or Study Exit Visit.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo/AGN-151586

Arm description:

Participants received placebo injections during the Double-blind Period and met all the retreatment criteria on Day 43. A single open-label treatment with AGN-151586 was administered on Day 43. Participants were followed for approximately 6 weeks (through Day 84).

Arm type	Experimental
Investigational medicinal product name	AGN-151586
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

AGN-151586 solution for injection

Arm title	AGN-151586/None

Arm description:

Participants received AGN-151586 during the Double-blind Period but did not meet all the retreatment criteria on Day 43. Participants were followed weekly in the Open-label Period until the Facial Wrinkle Scale (FWS) grades assessed by both investigator and participant returned to moderate or severe (investigator and participant grades did not need to match) before being discontinued from the study after completing either the Early Exit or Study Exit Visit.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	AGN-151586/AGN-151586

Arm description:

Participants received AGN-151586 during the Double-blind Period and met all the retreatment criteria on Day 43. An additional open-label treatment with AGN-151586 was administered on Day 43. Participants were followed for approximately 6 weeks (through Day 84).

Arm type	Experimental
Investigational medicinal product name	AGN-151586
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

AGN-151586 solution for injection

Number of subjects in period 2	Placebo/None	Placebo/AGN-151586	AGN-151586/None
Started	3	145	17
Completed	0	143	0
Not completed	3	2	17
Other, not specified	-	-	4
Lost to follow-up	-	-	5
Withdrawal by subject due to adverse event	-	1	-
COVID-19 infection	-	-	1
Withdrawal by subject	3	1	7

Number of subjects in period 2	AGN-151586/AGN-151586
Started	437
Completed	426
Not completed	11
Other, not specified	-
Lost to follow-up	2
Withdrawal by subject due to adverse event	-
COVID-19 infection	-
Withdrawal by subject	9

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received 5 intramuscular injections of placebo in the glabellar complex on Day 1. Based on meeting the retreatment criteria, the participants may have also received 1 open-label treatment of AGN-151586 on Day 43.	

Reporting group title	AGN-151586
Reporting group description:	
Participants received 5 intramuscular injections of AGN-151586 in the glabellar complex on Day 1. Based on meeting the retreatment criteria, participants may also have received 1 open-label treatment of AGN-151586 on Day 43.	

Reporting group values	Placebo	AGN-151586	Total
Number of subjects	156	482	638
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	47.6	47.1	
standard deviation	± 12.48	± 12.75	-
Gender categorical Units: Subjects			
Female	137	429	566
Male	19	53	72
Ethnicity Units: Subjects			
Hispanic or Latino	14	49	63
Not Hispanic or Latino	142	433	575
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	3	16	19
Native Hawaiian or Other Pacific Islander	2	2	4
Black or African American	5	21	26
White	142	432	574
More than one race	3	11	14
Unknown or Not Reported	0	0	0
Facial Wrinkle Scale (FWS) at Maximum Frown - Participant			
Participants' assessment of the severity of glabellar lines (GL) at maximum frown was performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity.			
Units: Subjects			
0 = None	0	0	0

1 = Mild	1	3	4
2 = Moderate	41	149	190
3 = Severe	114	330	444
Facial Wrinkle Scale (FWS) at Maximum Frown - Investigator			
Investigators' assessment of the severity of glabellar lines (GL) at maximum frown was performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity.			
Units: Subjects			
0 = None	0	0	0
1 = Mild	1	2	3
2 = Moderate	41	149	190
3 = Severe	114	331	445

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received 5 intramuscular injections of placebo in the glabellar complex on Day 1. Based on meeting the retreatment criteria, the participants may have also received 1 open-label treatment of AGN-151586 on Day 43.

Reporting group title	AGN-151586

Reporting group description:

Participants received 5 intramuscular injections of AGN-151586 in the glabellar complex on Day 1. Based on meeting the retreatment criteria, participants may also have received 1 open-label treatment of AGN-151586 on Day 43.

Reporting group title	Placebo/None

Reporting group description:

Participants received placebo injections during the Double-blind Period but did not meet all the retreatment criteria on Day 43. Participants were followed weekly in the Open-label Period until the Facial Wrinkle Scale (FWS) grades assessed by both investigator and participant returned to moderate or severe (investigator and participant grades did not need to match) before being discontinued from the study after completing either the Early Exit or Study Exit Visit.

Reporting group title	Placebo/AGN-151586

Reporting group description:

Participants received placebo injections during the Double-blind Period and met all the retreatment criteria on Day 43. A single open-label treatment with AGN-151586 was administered on Day 43. Participants were followed for approximately 6 weeks (through Day 84).

Reporting group title	AGN-151586/None

Reporting group description:

Participants received AGN-151586 during the Double-blind Period but did not meet all the retreatment criteria on Day 43. Participants were followed weekly in the Open-label Period until the Facial Wrinkle Scale (FWS) grades assessed by both investigator and participant returned to moderate or severe (investigator and participant grades did not need to match) before being discontinued from the study after completing either the Early Exit or Study Exit Visit.

Reporting group title	AGN-151586/AGN-151586

Reporting group description:

Participants received AGN-151586 during the Double-blind Period and met all the retreatment criteria on Day 43. An additional open-label treatment with AGN-151586 was administered on Day 43. Participants were followed for approximately 6 weeks (through Day 84).

Primary: Percentage of Participants With a Grade 0 or 1 and a ≥2-grade Improvement From Baseline on the FWS According to Both Investigator and Subject Assessments of Glabellar Lines (GL) Severity at Maximum Frown at Day 7 [US FDA]

End point title	Percentage of Participants With a Grade 0 or 1 and a ≥2-grade Improvement From Baseline on the FWS According to Both Investigator and Subject Assessments of Glabellar Lines (GL) Severity at Maximum Frown at Day 7 [US FDA]

End point description:

[Primary endpoint for the United States FDA] Percentage of participants achieving a Grade 0 or 1 (none or mild) and a ≥2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to both investigator and participant assessments of glabellar lines (GL) severity at maximum frown at Day 7 are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis population: Intent-to-Treat (ITT) population: all randomized participants, analyzed according to the treatment groups to which they were randomized. Multiple imputation was used for missing data.

End point type	Primary

End point timeframe:

Baseline, Day 7 (Double-blind period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	482		
Units: percentage of participants				
number (confidence interval 95%)	0.6 (0.0 to 1.9)	60.0 (55.5 to 64.4)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	59.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	54.7
upper limit	63.9

Notes:

[1] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Primary: Percentage of Participants With a ≥2-grade Improvement From Baseline on the FWS According to Participant Assessment of Glabellar Lines (GL) Severity at Maximum Frown at Day 7 [European Union Regulatory Agencies]

End point title	Percentage of Participants With a ≥2-grade Improvement From Baseline on the FWS According to Participant Assessment of Glabellar Lines (GL) Severity at Maximum Frown at Day 7 [European Union Regulatory Agencies]

End point description:

[Primary endpoint for European Union regulatory agencies] Percentage of participants with a ≥2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to participant assessment of glabellar lines (GL) severity at maximum frown at Day 7 are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Primary

End point timeframe:

Baseline, Day 7 (Double-blind period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)	0.8 (0.0 to 2.3)	61.0 (55.9 to 66.0)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	60.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	54.9
upper limit	65.4

Notes:

[2] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Primary: Percentage of Participants With a ≥2-grade Improvement From Baseline on the FWS According to Investigator Assessment of Glabellar Lines (GL) Severity at Maximum Frown at Day 7 [European Union Regulatory Agencies]

End point title	Percentage of Participants With a ≥2-grade Improvement From Baseline on the FWS According to Investigator Assessment of Glabellar Lines (GL) Severity at Maximum Frown at Day 7 [European Union Regulatory Agencies]

End point description:

[Primary endpoint for European Union regulatory agencies] Percentage of participants with a ≥2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to investigator assessment of glabellar lines (GL) severity at maximum frown at Day 7 are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11)

total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Primary

End point timeframe:

Baseline, Day 7 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)	0.8 (0.0 to 2.3)	72.1 (67.5 to 76.7)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	71.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	66.5
upper limit	76.2

Notes:

[3] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Primary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events[4]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. The investigator assesses the relationship of each event to the use of study drug. A serious adverse event (SAE) is an event that results in death, is life-threatening, requires or prolongs hospitalization, results in a congenital anomaly, persistent or significant disability/incapacity or is an important medical event that, based on medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent any of the outcomes listed above. Treatment-emergent adverse events/treatment-emergent serious adverse events (TEAEs/TESAEs) are defined as any event that began or worsened in severity on or after the first dose of study drug.

End point type	Primary

End point timeframe:

From Day 1 to Day 43 (Double-blind Period) and from Day 43 to Day 84 (Open-label Period)

Notes:

[4] - 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: Descriptive data are summarized for this end point per protocol.

End point values	Placebo	AGN-151586	Placebo/None	Placebo/AGN-151586
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	156[5]	482[6]	0[7]	145[8]
Units: participants				
Any TEAE (n=156, 482, 0, 145, 0, 437)	44	118		32
TESAE (n=156, 482, 0, 145, 0, 437)	1	3		0

Notes:

[5] - Subjects treated with ≥ 1 dose of study drug, analyzed by actual Tx received

[6] - Subjects treated with ≥ 1 dose of study drug, analyzed by actual Tx received

[7] - Subjects didn't receive Tx during Open-label Period/weren't analyzed for TEAEs during OL Period

[8] - Subjects treated with ≥ 1 dose of study drug, analyzed by actual Tx received

End point values	AGN-151586/None	AGN-151586/AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	437[10]		
Units: participants				
Any TEAE (n=156, 482, 0, 145, 0, 437)		90		
TESAE (n=156, 482, 0, 145, 0, 437)		1		

Notes:

[9] - Subjects didn't receive Tx during Open-label Period/weren't analyzed for TEAEs during OL Period

[10] - Subjects treated with ≥ 1 dose of study drug, analyzed by actual Tx received

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Grade 0 or 1 and a ≥2-grade Improvement From Baseline on the FWS According to Both Investigator and Participant Assessments of Glabellar Lines (GL) Severity at Maximum Frown Over Time [US FDA]

End point title	Percentage of Participants With a Grade 0 or 1 and a ≥2-grade Improvement From Baseline on the FWS According to Both Investigator and Participant Assessments of Glabellar Lines (GL) Severity at Maximum Frown Over Time [US FDA]

End point description:

[Secondary endpoint for the United States FDA] Percentage of participants achieving a Grade 0 or 1 (none or mild) and a ≥2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to both investigator and participant assessments of glabellar lines (GL) severity at maximum frown over time are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hours 8, 12, 24, 36, and 48, Days 7, 14, 21, 28, 35, and 43 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	482		
Units: percentage of participants				
number (confidence interval 95%)				
Hour 8	0.0 (0.0 to 0.0)	7.1 (4.8 to 9.3)		
Hour 12	0.6 (0.0 to 1.9)	15.9 (12.6 to 19.2)		
Hour 24	0.6 (0.0 to 1.9)	30.4 (26.3 to 34.6)		
Hour 36	0.6 (0.0 to 1.9)	43.2 (38.7 to 47.6)		
Hour 48	0.6 (0.0 to 1.9)	50.1 (45.6 to 54.6)		
Day 7	0.6 (0.0 to 1.9)	60.0 (55.5 to 64.4)		
Day 14	0.0 (0.0 to 0.0)	25.3 (21.4 to 29.2)		
Day 21	0.0 (0.0 to 0.0)	2.7 (1.3 to 4.2)		
Day 28	0.0 (0.0 to 0.0)	0.2 (0.0 to 0.6)		
Day 35	0.0 (0.0 to 0.0)	0.4 (0.0 to 1.0)		
Day 43	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Grade 0 or 1 and a ≥2-grade Improvement From Baseline on the FWS According to Investigator Assessment of Glabellar Lines (GL) Severity at Maximum Frown Over Time [US FDA]

End point title	Percentage of Participants With a Grade 0 or 1 and a ≥2-grade Improvement From Baseline on the FWS According to Investigator Assessment of Glabellar Lines (GL) Severity at Maximum Frown Over Time [US FDA]

End point description:

[Secondary endpoint for the United States FDA] Percentage of participants with a Grade 0 or 1 (none or mild) and at least a 2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to investigator assessment of glabellar lines (GL) severity at maximum frown over time are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hours 8, 12, 24, 36, and 48, Days 7, 14, 21, 28, 35, and 43 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	482		
Units: percentage of participants				
number (confidence interval 95%)				
Hour 8	1.3 (0.0 to 3.0)	11.0 (8.2 to 13.8)		
Hour 12	0.7 (0.0 to 2.0)	20.2 (16.6 to 23.8)		
Hour 24	0.6 (0.0 to 1.9)	37.4 (33.1 to 41.8)		
Hour 36	0.7 (0.0 to 2.0)	53.1 (48.6 to 57.6)		
Hour 48	0.6 (0.0 to 1.9)	62.2 (57.9 to 66.6)		
Day 7	0.6 (0.0 to 1.9)	72.6 (68.6 to 76.6)		
Day 14	0.0 (0.0 to 0.0)	32.3 (28.1 to 36.6)		
Day 21	0.0 (0.0 to 0.0)	5.2 (3.2 to 7.3)		
Day 28	0.0 (0.0 to 0.0)	1.3 (0.3 to 2.2)		
Day 35	0.0 (0.0 to 0.0)	0.4 (0.0 to 1.0)		
Day 43	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Grade 0 or 1 and a ≥2-grade Improvement From Baseline on the FWS According to Participant Assessment of Glabellar Lines (GL) Severity at Maximum Frown Over Time [US FDA]

End point title	Percentage of Participants With a Grade 0 or 1 and a ≥2-grade Improvement From Baseline on the FWS According to Participant Assessment of Glabellar Lines (GL) Severity at Maximum Frown Over Time [US FDA]

End point description:

[Secondary endpoint for the United States FDA] Percentage of participants with a Grade 0 or 1 (none or mild) and at least a 2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to participant assessment of glabellar lines (GL) severity at maximum frown over time are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hours 8, 12, 24, 36, and 48, Days 7, 14, 21, 28, 35, and 43 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	482		
Units: percentage of participants				
number (confidence interval 95%)				
Hour 8	0.0 (0.0 to 0.0)	8.1 (5.7 to 10.5)		
Hour 12	0.7 (0.0 to 2.0)	18.5 (15.0 to 22.0)		
Hour 24	0.6 (0.0 to 1.9)	32.1 (27.9 to 36.3)		
Hour 36	0.6 (0.0 to 1.9)	44.4 (40.0 to 48.9)		
Hour 48	1.9 (0.0 to 4.1)	51.8 (47.3 to 56.3)		
Day 7	0.6 (0.0 to 1.9)	63.3 (58.9 to 67.6)		
Day 14	0.0 (0.0 to 0.0)	29.8 (25.6 to 34.0)		
Day 21	0.0 (0.0 to 0.0)	4.2 (2.4 to 6.1)		
Day 28	0.0 (0.0 to 0.0)	1.9 (0.7 to 3.1)		
Day 35	1.3 (0.0 to 3.0)	1.2 (0.3 to 2.2)		
Day 43	0.0 (0.0 to 0.0)	0.8 (0.0 to 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 5 (Overall Satisfaction) for GL at Day 7 [US FDA]

End point title	Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 5 (Overall Satisfaction) for GL at Day 7 [US FDA]

End point description:

[Secondary endpoint for the United States FDA] The FLSQ is a validated measure that assesses treatment expectations, treatment satisfaction, and psychosocial impact of GL from the participant perspective. Participants assessed their overall satisfaction with their glabellar lines using a 5-point verbal descriptor scale (VDS): very dissatisfied, mostly dissatisfied, neither dissatisfied nor satisfied, mostly satisfied, and very satisfied. The percentage of participants mostly satisfied or very satisfied is reported. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Day 7 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	482		
Units: percentage of participants				
number (confidence interval 95%)	5.1 (1.7 to 8.6)	77.6 (73.9 to 81.4)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	72.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	67.4
upper limit	77.6

Notes:

[11] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 5 (Overall Satisfaction) for GL at Hour 24 [United States FDA]

End point title	Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 5 (Overall Satisfaction) for GL at Hour 24 [United States FDA]

End point description:

[Secondary endpoint for the United States FDA] The FLSQ is a validated measure that assesses treatment expectations, treatment satisfaction, and psychosocial impact of GL from the participant perspective. Participants assessed their overall satisfaction with their glabellar lines using a 5-point verbal descriptor scale (VDS): very dissatisfied, mostly dissatisfied, neither dissatisfied nor satisfied, mostly satisfied, and very satisfied. The percentage of participants mostly satisfied or very satisfied is reported. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Hour 24 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	482		
Units: percentage of participants				
number (confidence interval 95%)	17.3 (11.4 to 23.2)	59.2 (54.8 to 63.6)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	41.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	34.5
upper limit	49.3

Notes:

[12] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 4 (Natural Look) for GL at Day 7 [US FDA]

End point title	Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 4 (Natural Look) for GL at Day 7 [US FDA]

End point description:

[Secondary endpoint for the United States FDA] The FLSQ is a validated measure that assesses treatment expectations, treatment satisfaction, and psychosocial impact of GL from the participant perspective. Participants assessed their satisfaction with natural look using a 5-point verbal descriptor scale (VDS): very dissatisfied, mostly dissatisfied, neither dissatisfied nor satisfied, mostly satisfied, and very satisfied. The percentage of participants mostly satisfied or very satisfied is reported. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Day 7 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	482		
Units: percentage of participants				
number (confidence interval 95%)	9.0 (4.5 to 13.5)	78.5 (74.8 to 82.2)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	69.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	63.7
upper limit	75.3

Notes:

[13] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With a ≥20-point Improvement From Baseline in FLO-11 Total Scores for GL at Day 7 [European Union Regulatory Agencies]

End point title	Percentage of Participants With a ≥20-point Improvement From Baseline in FLO-11 Total Scores for GL at Day 7 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] The Facial Lines Outcomes (FLO-11) Questionnaire is an 11-item validated measure that assesses appearance-related psychological impacts of glabellar lines (GL) from the participant's perspective. Items 1-10 are assessed on an 11-point numeric rating scale that ranges from 0 (Not at all) to 10 (Very much), with higher scores indicating negative impact. Item 11 is scored in the reverse direction. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50 were included. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Day 7 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)	8.5 (3.7 to 13.2)	66.6 (61.8 to 71.5)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	58.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.3
upper limit	65

Notes:

[14] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With a ≥2-grade Improvement From Baseline on the FWS According to Participant Assessment of GL Severity at Maximum Frown at Hour 24 [European Union Regulatory Agencies]

End point title	Percentage of Participants With a ≥2-grade Improvement From Baseline on the FWS According to Participant Assessment of GL Severity at Maximum Frown at Hour 24 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Percentage of participants with a ≥2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to participant assessment of glabellar lines (GL) severity at maximum frown at Hour 24 are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hour 24 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)	0.8 (0.0 to 2.3)	30.9 (26.2 to 35.7)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	30.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.2
upper limit	35.1

Notes:

[15] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With a ≥2-grade Improvement From Baseline on the FWS According to Investigator Assessment of GL Severity at Maximum Frown at Hour 24 [European Union Regulatory Agencies]

End point title	Percentage of Participants With a ≥2-grade Improvement From Baseline on the FWS According to Investigator Assessment of GL Severity at Maximum Frown at Hour 24 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Percentage of participants with a ≥2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to investigator assessment of glabellar lines (GL) severity at maximum frown at Hour 24 during the Double-Blind Period are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hour 24 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)	0.8 (0.0 to 2.3)	36.5 (31.5 to 41.4)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	35.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.5
upper limit	40.9

Notes:

[16] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With a ≥1-grade Improvement From Baseline on FWS According to Participant Assessment of GL Severity at Maximum Frown at Hour 24 [European Union Regulatory Agencies]

End point title	Percentage of Participants With a ≥1-grade Improvement From Baseline on FWS According to Participant Assessment of GL Severity at Maximum Frown at Hour 24 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Percentage of participants with a ≥1-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to participant assessment of glabellar lines (GL) severity at maximum frown at Hour 24 are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hour 24 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)	11.5 (6.0 to 17.0)	64.1 (59.2 to 69.1)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	52.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	45.2
upper limit	60

Notes:

[17] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With a ≥1-grade Improvement From Baseline on FWS According to Investigator Assessment of GL Severity at Maximum Frown at Hour 24 [European Union Regulatory Agencies]

End point title	Percentage of Participants With a ≥1-grade Improvement From Baseline on FWS According to Investigator Assessment of GL Severity at Maximum Frown at Hour 24 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Percentage of participants with a ≥1-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to investigator assessment of glabellar lines (GL) severity at maximum frown at Hour 24 are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hour 24 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)	13.8 (7.9 to 19.8)	72.5 (67.9 to 77.1)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	58.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.1
upper limit	66.1

Notes:

[18] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 5 (Overall Satisfaction) for GL at Hour 24 [European Union Regulatory Agencies]

End point title	Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 5 (Overall Satisfaction) for GL at Hour 24 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] The FLSQ is a validated measure that assesses treatment expectations, treatment satisfaction, and psychosocial impact of GL from the participant perspective. Participants assessed their overall satisfaction with their glabellar lines using a 5-point verbal descriptor scale (VDS): very dissatisfied, mostly dissatisfied, neither dissatisfied nor satisfied, mostly satisfied, and very satisfied. The percentage of participants mostly satisfied or very satisfied is reported. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to

the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary
End point timeframe:	
Hour 24 (Double-blind Period)	

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)	16.2 (9.8 to 22.5)	58.7 (53.6 to 63.7)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	42.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	34.4
upper limit	50.6

Notes:

[19] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 4 (Natural Look) for GL at Day 7 [European Union Regulatory Agencies]

End point title	Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 4 (Natural Look) for GL at Day 7 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] The FLSQ is a validated measure that assesses treatment expectations, treatment satisfaction, and psychosocial impact of GL from the participant perspective. Participants assessed their satisfaction with natural look using a 5-point verbal descriptor scale (VDS): very dissatisfied, mostly dissatisfied, neither dissatisfied nor satisfied, mostly satisfied, and very satisfied. The percentage of participants mostly satisfied or very satisfied is reported. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary
End point timeframe:	
Day 7 (Double-blind Period)	

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)	7.7 (3.1 to 12.3)	77.7 (73.3 to 82.0)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	70
Confidence interval	
level	95 %
sides	2-sided
lower limit	63.7
upper limit	76.3

Notes:

[20] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Time to the First ≥1-grade Improvement From Baseline on the FWS According to Participant Assessment of GL Severity at Maximum Frown [European Union Regulatory Agencies]

End point title	Time to the First ≥1-grade Improvement From Baseline on the FWS According to Participant Assessment of GL Severity at Maximum Frown [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Time to the first ≥1-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to participant assessment of glabellar lines (GL) severity at maximum frown is reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. For those who did not improve at least 1 grade from Baseline, censoring occurred at the latest visit during the treatment period for which FWS data were available.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50.

End point type	Secondary

End point timeframe:

From Baseline to Day 43 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: days				
median (full range (min-max))	41.9 (0 to 69)	1.0 (0 to 45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the First ≥1-grade Improvement From Baseline on the FWS According to Investigator Assessment of GL Severity at Maximum Frown [European Union Regulatory Agencies]

End point title	Time to the First ≥1-grade Improvement From Baseline on the FWS According to Investigator Assessment of GL Severity at Maximum Frown [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Time to the first ≥1-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to investigator assessment of glabellar lines (GL) severity at maximum frown is reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. For those who did not improve at least 1 grade from Baseline, censoring occurred at the latest visit during the treatment period for which FWS data were available.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50.

End point type	Secondary

End point timeframe:

From Baseline to Day 43 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: days				
median (full range (min-max))	41.0 (0 to 69)	0.7 (0 to 45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ≥2-grade Improvement From Baseline on the FWS According to Participant Assessment of GL Severity at Maximum Frown Over Time [European Union Regulatory Agencies]

End point title	Percentage of Participants With ≥2-grade Improvement From Baseline on the FWS According to Participant Assessment of GL Severity at Maximum Frown Over Time [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Percentage of participants with at least a 2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to participant assessment of glabellar lines (GL) severity at maximum frown over time are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hours 8, 12, 24, 36, and 48, Days 7, 14, 21, 28, 35, and 43 (Double-blind period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)				
Hour 8	0.0 (0.0 to 0.0)	7.6 (4.9 to 10.3)		
Hour 12	0.8 (0.0 to 2.3)	17.7 (13.8 to 21.7)		
Hour 24	0.8 (0.0 to 2.3)	30.9 (26.2 to 35.7)		
Hour 36	0.8 (0.0 to 2.3)	44.0 (38.9 to 49.1)		
Hour 48	2.3 (0.0 to 4.9)	50.1 (45.0 to 55.3)		
Day 7	0.8 (0.0 to 2.3)	61.0 (55.9 to 66.0)		

Day 14	0.0 (0.0 to 0.0)	30.5 (25.6 to 35.3)		
Day 21	0.0 (0.0 to 0.0)	4.6 (2.4 to 6.9)		
Day 28	0.0 (0.0 to 0.0)	1.9 (0.5 to 3.3)		
Day 35	1.5 (0.0 to 3.7)	1.4 (0.2 to 2.5)		
Day 43	0.0 (0.0 to 0.0)	0.8 (0.0 to 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ≥2-grade Improvement From Baseline on the FWS According to Investigator Assessment of GL Severity at Maximum Frown Over Time [European Union Regulatory Agencies]

End point title	Percentage of Participants With ≥2-grade Improvement From Baseline on the FWS According to Investigator Assessment of GL Severity at Maximum Frown Over Time [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Percentage of participants with at least a 2-grade improvement from Baseline on the Facial Wrinkle Scale (FWS) according to investigator assessment of glabellar lines (GL) severity at maximum frown over time are reported. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hours 8, 12, 24, 36, and 48, Days 7, 14, 21, 28, 35, and 43 (Double-blind period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)				
Hour 8	1.5 (0.0 to 3.7)	10.9 (7.7 to 14.1)		
Hour 12	0.8 (0.0 to 2.3)	18.6 (14.5 to 22.6)		
Hour 24	0.8 (0.0 to 2.3)	36.5 (31.5 to 41.4)		
Hour 36	0.8 (0.0 to 2.3)	53.3 (48.1 to 58.4)		
Hour 48	0.8 (0.0 to 2.3)	61.7 (56.6 to 66.7)		
Day 7	0.8 (0.0 to 2.3)	72.1 (67.5 to 76.7)		

Day 14	0.0 (0.0 to 0.0)	32.8 (27.9 to 37.7)		
Day 21	0.0 (0.0 to 0.0)	5.4 (3.0 to 7.7)		
Day 28	0.0 (0.0 to 0.0)	1.1 (0.0 to 2.2)		
Day 35	0.0 (0.0 to 0.0)	0.3 (0.0 to 0.8)		
Day 43	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Return to Baseline FWS According to Participant Assessment of FWS at Maximum Frown After Achieving Responder Definition on Day 7 [European Union Regulatory Agencies]

End point title	Time to Return to Baseline FWS According to Participant Assessment of FWS at Maximum Frown After Achieving Responder Definition on Day 7 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Time to return to Baseline (Baseline criterion of Moderate or Severe) on the Facial Wrinkle Scale (FWS) according to participant assessment of FWS at maximum frown after achieving responder definition on Day 7 is reported. Responder definition was a rating of None or Mild on the FWS. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. For those who maintained their response, censoring occurred at the latest visit during the treatment period for which FWS was available.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized subjects, analyzed according treatment groups to which they were randomized with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Those who didn't meet responder definition on Day 7 were excluded from analysis; analysis was limited to those that responded.

End point type	Secondary

End point timeframe:

From Baseline to Day 43 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	251		
Units: days				
median (full range (min-max))	28.0 (15 to 43)	21.0 (8 to 50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Return to Baseline FWS According to Investigator Assessment of FWS at Maximum Frown After Achieving Responder Definition on Day 7 [European Union Regulatory Agencies]

End point title	Time to Return to Baseline FWS According to Investigator Assessment of FWS at Maximum Frown After Achieving Responder Definition on Day 7 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] Time to return to Baseline (Baseline criterion of Moderate or Severe) on the Facial Wrinkle Scale (FWS) according to investigator assessment of FWS at maximum frown after achieving responder definition on Day 7 is reported. Responder definition was a rating of None or Mild on the FWS. Assessments were performed using the 4-grade Facial Wrinkle Scale (FWS), where 0=none, 1=mild, 2=moderate, and 3=severe. Higher scores indicate more severity. For those who maintained their response, censoring occurred at the latest visit during the treatment period for which FWS was available.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized subjects, analyzed according treatment groups to which they were randomized with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Those who didn't meet responder definition on Day 7 were excluded from analysis; analysis was limited to those who responded.

End point type	Secondary

End point timeframe:

From Baseline to Day 43 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	280		
Units: days				
median (full range (min-max))	15.0 (15 to 15)	21.0 (8 to 50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 5 (Overall Satisfaction) for GL Over Time [European Union Regulatory Agencies]

End point title	Percentage of Participants With Achievement of Mostly Satisfied or Very Satisfied on the Facial Lines Satisfaction Questionnaire (FLSQ) Follow-up Version Item 5 (Overall Satisfaction) for GL Over Time [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] The FLSQ is a validated measure that assesses treatment expectations, treatment satisfaction, and psychosocial impact of GL from the participant perspective. Participants assessed their overall satisfaction with their glabellar lines using a 5-point verbal descriptor scale (VDS): very dissatisfied, mostly dissatisfied, neither dissatisfied nor satisfied, mostly satisfied, and very satisfied. The percentage of participants mostly satisfied or very satisfied is reported. Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Hours 8, 24, and 48, Days 7, 14, 21, 28, 35, and 43 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: percentage of participants				
number (confidence interval 95%)				
Hour 8	14.3 (8.2 to 20.4)	33.1 (28.3 to 38.0)		
Hour 24	16.2 (9.8 to 22.5)	58.7 (53.6 to 63.7)		
Hour 48	8.5 (3.7 to 13.2)	71.4 (66.7 to 76.0)		
Day 7	4.6 (1.0 to 8.3)	76.9 (72.5 to 81.2)		
Day 14	5.8 (1.7 to 10.0)	69.9 (65.1 to 74.7)		
Day 21	2.5 (0.0 to 5.2)	61.4 (56.3 to 66.5)		
Day 28	4.7 (0.9 to 8.4)	56.1 (50.9 to 61.2)		
Day 35	3.8 (0.5 to 7.2)	58.3 (53.2 to 63.4)		
Day 43	4.8 (1.1 to 8.6)	58.1 (52.9 to 63.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a ≥4-point Improvement From Baseline in FLO-11 Item 10 (Look Angry) for GL at Day 7 [European Union Regulatory Agencies]

End point title	Percentage of Participants With a ≥4-point Improvement From Baseline in FLO-11 Item 10 (Look Angry) for GL at Day 7 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] The Facial Lines Outcomes (FLO-11) Questionnaire is an 11-item validated measure that assesses appearance-related psychological impacts of glabellar lines (GL) from the participant's perspective. Items 1-10 are assessed on an 11-point numeric rating scale that ranges from 0 (Not at all) to 10 (Very much), with higher scores indicating negative impact. Item 11 is scored in the reverse direction. Participants answered FLO-11 Item 10 (Look Angry). Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, and a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Participants with a score that could improve at least 4 points from Baseline were included. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Day 7 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	353		
Units: percentage of participants				
number (confidence interval 95%)	5.6 (1.6 to 9.7)	54.5 (49.2 to 59.7)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	Placebo v AGN-151586
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	48.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	42.2
upper limit	55.4

Notes:

[21] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Percentage of Participants With a ≥4-point Improvement From Baseline in FLO-11 Item 5 (Look Less Attractive) for GL at Day 7 [European Union Regulatory Agencies]

End point title	Percentage of Participants With a ≥4-point Improvement From Baseline in FLO-11 Item 5 (Look Less Attractive) for GL at Day 7 [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] The Facial Lines Outcomes (FLO-11) Questionnaire is an 11-item validated measure that assesses appearance-related psychological impacts of glabellar lines (GL) from the participant's perspective. Items 1-10 are assessed on an 11-point numeric rating scale that ranges from 0 (Not at all) to 10 (Very much), with higher scores indicating negative impact. Item 11 is scored in the reverse direction. Participants answered FLO-11 Item 5 (Look Less Attractive). Percentages are rounded off to nearest single decimal.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, and a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Participants with a score that could improve at least 4 points from Baseline were included. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Baseline, Day 7 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	362		
Units: percentage of participants				
number (confidence interval 95%)	3.9 (0.5 to 7.3)	48.1 (42.9 to 53.3)		

Statistical analyses

Statistical analysis title	AGN-151586 vs Placebo
Comparison groups	AGN-151586 v Placebo
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	44.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	38
upper limit	50.4

Notes:

[22] - P-value was based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator site, toxin use history (for aesthetic purposes), and baseline Facial Wrinkle Scale score at maximum frown after using multiple imputation for missing data.

Secondary: Mean Global Assessment of Change in Glabellar Lines (GAC-GL) at Maximum Frown Over Time [European Union Regulatory Agencies]

End point title	Mean Global Assessment of Change in Glabellar Lines (GAC-GL) at Maximum Frown Over Time [European Union Regulatory Agencies]

End point description:

[Secondary endpoint for European Union regulatory agencies] The GAC-GL Questionnaire assesses the appearance of the participant’s GL "now”in comparison with their perspective before treatment. Participants assessed the change in their glabellar lines at maximum frown using a 7-point verbal descriptor scale (VDS): very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse. Higher scores indicate more improvement.

Analysis Population: Intent-to-Treat (ITT) Population: all randomized participants, analyzed according to the treatment groups to which they were randomized, with a Baseline Facial Lines Outcome (FLO-11) total score (transformed) of ≤50. Multiple imputation was used for missing data.

End point type	Secondary

End point timeframe:

Hours 24 and 48, Days 7, 14, 21, 28, 35, and 43 (Double-blind Period)

End point values	Placebo	AGN-151586		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	368		
Units: units on a scale				
least squares mean (standard error)				
Hour 24	0.2 (± 0.10)	1.4 (± 0.07)		
Hour 48	0.1 (± 0.09)	1.9 (± 0.06)		
Day 7	0.1 (± 0.08)	2.2 (± 0.06)		
Day 14	0.1 (± 0.10)	1.5 (± 0.07)		
Day 21	0.1 (± 0.10)	0.5 (± 0.07)		
Day 28	0.1 (± 0.10)	0.2 (± 0.07)		
Day 35	0.1 (± 0.10)	0.0 (± 0.07)		
Day 43	0.1 (± 0.09)	0.0 (± 0.06)		

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality reported from enrollment to study end; median time on follow-up was 85 days for Placebo, AGN-151586, Placebo/AGN-151586, and AGN-151586/AGN-151586 groups; 50 days for Placebo/None group; and 53 days for the AGN-151586/None group.

Adverse event reporting additional description:

TEAEs/SAEs collected Day 1-43 (Double-blind Period) + Day 43-84 (Open-label Period) for those who rcvd Tx. Open-label Period Placebo/None and AGN-151586/None groups didn't receive Tx during Open-label Period and therefore weren't analyzed for TEAEs during that Period. TEAEs experienced by these subjects were recorded during Double-blind Period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received 5 intramuscular injections of placebo in the glabellar complex on Day 1. Based on meeting the retreatment criteria, the participants may have also received 1 open-label treatment of AGN-151586 on Day 43.

Reporting group title	AGN-151586

Reporting group description:

Participants received 5 intramuscular injections of AGN-151586 in the glabellar complex on Day 1. Based on meeting the retreatment criteria, participants may also have received 1 open-label treatment of AGN-151586 on Day 43.

Reporting group title	AGN-151586/None

Reporting group description:

Participants received AGN-151586 during the Double-blind Period but did not meet all the retreatment criteria on Day 43. Participants were followed weekly in the Open-label Period until the Facial Wrinkle Scale (FWS) grades assessed by both investigator and participant returned to moderate or severe (investigator and participant grades did not need to match) before being discontinued from the study after completing either the Early Exit or Study Exit Visit. Participants in the Open-label Period AGN-151586/None group did not receive treatment during the Open-label Period and therefore were not analyzed for treatment-emergent adverse events during the Open-label period. TEAEs experienced by these participants were recorded during the Double-blind Period

Reporting group title	Placebo/AGN-151586

Reporting group description:

Participants received placebo injections during the Double-blind Period and met all the retreatment criteria on Day 43. A single open-label treatment with AGN-151586 was administered on Day 43. Participants were followed for approximately 6 weeks (through Day 84).

Reporting group title	AGN-151586/AGN-151586

Reporting group description:

Participants received AGN-151586 during the Double-blind Period and met all the retreatment criteria on Day 43. An additional open-label treatment with AGN-151586 was administered on Day 43. Participants were followed for approximately 6 weeks (through Day 84).

Reporting group title	Placebo/None

Reporting group description:

Participants received placebo injections during the Double-blind Period but did not meet all the retreatment criteria on Day 43. Participants were followed weekly in the Open-label Period until the Facial Wrinkle Scale (FWS) grades assessed by both investigator and participant returned to moderate or severe (investigator and participant grades did not need to match) before being discontinued from the study after completing either the Early Exit or Study Exit Visit. Participants in the Open-label Period Placebo/None group did not receive treatment during the Open-label Period and therefore were not analyzed for treatment-emergent adverse events during the Open-label period. TEAEs experienced by these participants were recorded during the Double-blind Period.

Serious adverse events	Placebo	AGN-151586	AGN-151586/None
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 156 (0.64%)	3 / 482 (0.62%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	1 / 156 (0.64%)	0 / 482 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 156 (0.00%)	1 / 482 (0.21%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 156 (0.00%)	1 / 482 (0.21%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 156 (0.00%)	0 / 482 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPOCALCAEMIA			
subjects affected / exposed	0 / 156 (0.00%)	1 / 482 (0.21%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo/AGN-151586	AGN-151586/AGN-151586	Placebo/None
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 145 (0.00%)	1 / 437 (0.23%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	0 / 145 (0.00%)	0 / 437 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 145 (0.00%)	0 / 437 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 145 (0.00%)	0 / 437 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	0 / 145 (0.00%)	1 / 437 (0.23%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPOCALCAEMIA			
subjects affected / exposed	0 / 145 (0.00%)	0 / 437 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	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	Placebo	AGN-151586	AGN-151586/None
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 156 (5.77%)	31 / 482 (6.43%)	0 / 17 (0.00%)
Nervous system disorders			
HEADACHE			
subjects affected / exposed	9 / 156 (5.77%)	31 / 482 (6.43%)	0 / 17 (0.00%)
occurrences (all)	10	35	0

Non-serious adverse events	Placebo/AGN-151586	AGN-151586/AGN-151586	Placebo/None
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 145 (5.52%)	14 / 437 (3.20%)	0 / 3 (0.00%)
Nervous system disorders			
HEADACHE			
subjects affected / exposed	8 / 145 (5.52%)	14 / 437 (3.20%)	0 / 3 (0.00%)
occurrences (all)	8	16	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2022	Protocol amendment 2 • Added FLSQ Item 5 at Day 7 as the third secondary endpoint • Planned balanced enrollment between moderate and severe GL severity at maximum frown • Added information re: no anticipated additional risk to subjects with use of AGN-151586 with regard to COVID-19; added information regarding anticipated risks with the use of AGN-151586 and provided overall benefit:risk conclusion • Indicated that specified endpoints will be evaluated outside of gated hierarchical testing; added estimand for FLSQ Item 5 at Day 7 • Clarified when visits will occur relative to treatment • Updated eligibility criteria to exclude those with personal/family history of prolonged QT; with clinically significant abnormal vital sign value at screening or Baseline Day 1 visit, removed specification of serum/urine pregnancy tests; semi-permanent make-up (e.g., microblading) not permitted in the 6-month period before Baseline Day 1 visit • Noted that at least 10 days must elapse since first COVID-19 positive test in asymptomatic subjects or at least 10 days since recovery • Added additional safety retreatment criteria, including no ongoing AEs that may place subject at increased risk following exposure to AGN-151586 and no clinically significant abnormality in safety assessments at retreatment visit • Updated COVID-19 language including recommendation that study drug be given ± 7 days from SARS-CoV-2 vaccine administration; added statement that any prior toxin therapy for aesthetics or therapeutic treatment at any time and COVID-19 vaccination history must be recorded • Clarified that subjects who are missing assessments or data due to COVID-19 pandemic and are missing data for the primary endpoints will count as though they hypothetically continued in the study • Added as-observed sensitivity analysis and NRI sensitivity analysis • Updated study start and end definition • Revised abbreviated physical exam on Day 7 (including retreatment Day 7) to a full exam

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported