



Clinical trial results:

A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study to Evaluate the Efficacy and Safety of Botulinum Toxin Type A (AGN-151607) Injections into the Epicardial Fat Pads to Prevent Post-Operative Atrial Fibrillation in Patients Undergoing Open-Chest Cardiac Surgery

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2017-004399-68 |
| Trial protocol | GB DE ES AT SE NL IT |
| Global end of trial date | 06 March 2023 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 16 June 2024 |
| First version publication date | 20 March 2024 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Edits made to clarify text and clarify data table in 1 secondary endpoint. |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | 1925-201-008 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03779841 |
| 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 | 06 March 2023 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 March 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to evaluate the efficacy and safety of botulinum toxin type A (AGN-151607) injections into the epicardial fat pads, foci of ganglionic plexi, to prevent Post-Operative Atrial Fibrillation (POAF) in patients undergoing open-chest cardiac surgery.

Protection of trial subjects:

Prior to the initiation of any screening or study-specific procedures, the investigator or his or her representative explained the nature of the study to the subject or his or her representative and answered all questions regarding this study. The informed consent statement was reviewed and signed and dated by the subject and the person who administered the informed consent. A copy of the signed informed consent was to be given to the subject and the original was to be placed in the subject's medical record.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | United States: 186 |
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Canada: 97 |
| Country: Number of subjects enrolled | Germany: 5 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Spain: 7 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Worldwide total number of subjects | 319 |
| EEA total number of subjects | 31 |

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) | 130 |
| From 65 to 84 years | 189 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 323 subjects were randomized, of which 319 received study drug (Safety Population).

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Injections of placebo were made into each 1 of 5 fat pads. The total injection volume into each fat pad was 1mL. One-time treatment.

| | |
|--|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Other use |

Dosage and administration details:

The placebo solution for injection contained only the excipients of AGN-151607. Subjects received a single dose divided into five equal injections to be administered into five epicardial fat pads during the open-chest surgery.

| | |
|------------------|--------------------|
| Arm title | AGN-151607 (125 U) |
|------------------|--------------------|

Arm description:

Injections of 25 U were made into each 1 of 5 fat pads. The total injection volume into each fat pad was 1 mL. One-time treatment.

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Clostridium botulinum toxin type A |
| Investigational medicinal product code | AGN-151607 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Other use |

Dosage and administration details:

A lyophilized formulation consisting of AGN-151607 was reconstituted. Subjects received a single dose divided into five equal injections to be administered into five epicardial fat pads during the open-chest surgery for total dose of 125 U.

| | |
|------------------|--------------------|
| Arm title | AGN-151607 (250 U) |
|------------------|--------------------|

Arm description:

Injections of 50 U were made into each 1 of 5 fat pads. The total injection volume into each fat pad was 1 mL. One-time treatment.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|------------------------------------|
| Investigational medicinal product name | Clostridium botulinum toxin type A |
| Investigational medicinal product code | AGN-151607 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Other use |

Dosage and administration details:

A lyophilized formulation consisting of AGN-151607 was reconstituted. Subjects received a single dose divided into five equal injections to be administered into five epicardial fat pads during the open-chest surgery for total dose of 250 U.

| Number of subjects in period 1 | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) |
|---------------------------------------|---------|--------------------|--------------------|
| Started | 105 | 105 | 109 |
| Completed | 94 | 87 | 93 |
| Not completed | 11 | 18 | 16 |
| Adverse event, serious fatal | 1 | - | 2 |
| Consent withdrawn by subject | 4 | 8 | 6 |
| Adverse event, non-fatal | 1 | 1 | - |
| Lost to follow-up | 5 | 9 | 8 |

Baseline characteristics

Reporting groups

| | |
|--|--------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Injections of placebo were made into each 1 of 5 fat pads. The total injection volume into each fat pad was 1mL. One-time treatment. | |
| Reporting group title | AGN-151607 (125 U) |
| Reporting group description: | |
| Injections of 25 U were made into each 1 of 5 fat pads. The total injection volume into each fat pad was 1 mL. One-time treatment. | |
| Reporting group title | AGN-151607 (250 U) |
| Reporting group description: | |
| Injections of 50 U were made into each 1 of 5 fat pads. The total injection volume into each fat pad was 1 mL. One-time treatment. | |

| Reporting group values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) |
|-------------------------------------|---------|--------------------|--------------------|
| Number of subjects | 105 | 105 | 109 |
| Age categorical | | | |
| Units: Subjects | | | |
| Between 18 and 64 years | 43 | 42 | 45 |
| ≥ 65 years | 62 | 63 | 64 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 66.8 | 66.8 | 67.2 |
| standard deviation | ± 6.76 | ± 6.54 | ± 7.01 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 14 | 17 | 22 |
| Male | 91 | 88 | 87 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 6 | 8 | 6 |
| Not Hispanic or Latino | 99 | 97 | 103 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| Asian | 1 | 0 | 2 |
| Black or African American | 2 | 2 | 2 |
| White | 102 | 102 | 105 |
| Unknown or Not Reported | 0 | 1 | 0 |
| Type of Surgery | | | |
| CABG = Coronary Artery Bypass Graft | | | |
| Units: Subjects | | | |
| Isolated CABG Surgery | 65 | 68 | 70 |
| Valve only Surgery | 27 | 24 | 27 |
| CABG and Valve Surgery | 13 | 13 | 12 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 319 | | |

| | | | |
|-------------------------------------|-----|--|--|
| Age categorical | | | |
| Units: Subjects | | | |
| Between 18 and 64 years | 130 | | |
| ≥ 65 years | 189 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 53 | | |
| Male | 266 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 20 | | |
| Not Hispanic or Latino | 299 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| Asian | 3 | | |
| Black or African American | 6 | | |
| White | 309 | | |
| Unknown or Not Reported | 1 | | |
| Type of Surgery | | | |
| CABG = Coronary Artery Bypass Graft | | | |
| Units: Subjects | | | |
| Isolated CABG Surgery | 203 | | |
| Valve only Surgery | 78 | | |
| CABG and Valve Surgery | 38 | | |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Placebo |
| Reporting group description: Injections of placebo were made into each 1 of 5 fat pads. The total injection volume into each fat pad was 1mL. One-time treatment. | |
| Reporting group title | AGN-151607 (125 U) |
| Reporting group description: Injections of 25 U were made into each 1 of 5 fat pads. The total injection volume into each fat pad was 1 mL. One-time treatment. | |
| Reporting group title | AGN-151607 (250 U) |
| Reporting group description: Injections of 50 U were made into each 1 of 5 fat pads. The total injection volume into each fat pad was 1 mL. One-time treatment. | |

Primary: Percentage of participants with at least 1 continuous AF (atrial fibrillation or atrial flutter) episode \geq 30 seconds during the first 30 days post-surgery

| | |
|--|--|
| End point title | Percentage of participants with at least 1 continuous AF (atrial fibrillation or atrial flutter) episode \geq 30 seconds during the first 30 days post-surgery |
| End point description: At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained \geq 30 seconds documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest. All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery. | |
| End point type | Primary |
| End point timeframe: First 30 days following the initial intensive care unit (ICU) admission date after open-chest cardiac surgery. | |

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 46.1 | 36.5 | 47.2 | |

Statistical analyses

| | |
|--|------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (125 U) v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1612 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 1.1 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7789 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.37 |

Secondary: Percentage of Time Spent in Atrial Fibrillation or Atrial Flutter (AF Burden) During the First 30 Days Post-surgery

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|-----------------|---|
| End point title | Percentage of Time Spent in Atrial Fibrillation or Atrial Flutter (AF Burden) During the First 30 Days Post-surgery |
|-----------------|---|

End point description:

The proportion of time an individual is in AF (atrial fibrillation or atrial flutter) during a monitoring period (expressed as a percentage) calculated as (the total time spent in AF during the first 30 days post-surgery divided by the total time of analyzable data obtained from the ECG patch during the first 30 days post-surgery) multiplied by 100. The calculation excludes continuous AF episodes < 30 seconds in duration.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|--------------------------------------|--------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 4.84 (± 14.898) | 4.41 (± 14.976) | 5.45 (± 15.821) | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 2 |
|--|-----------------------------------|
| Statistical analysis description: | |
| P-value is obtained from stratified Wilcoxon (Van Elteren) test versus Placebo with type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years) as stratification factors. | |
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8722 |
| Method | stratified Wilcoxon (Van Elteren) |

| Statistical analysis title | Statistical Analysis 1 |
|--|-----------------------------------|
| Statistical analysis description: | |
| P-value is obtained from stratified Wilcoxon (Van Elteren) test versus Placebo with type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years) as stratification factors. | |
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2972 |
| Method | stratified Wilcoxon (Van Elteren) |

Secondary: Percentage of Participants With at Least 1 Event of Symptomatic AF (Atrial Fibrillation or Atrial Flutter) During the First 30 Days Post-surgery

| | |
|-----------------|--|
| End point title | Percentage of Participants With at Least 1 Event of Symptomatic AF (Atrial Fibrillation or Atrial Flutter) During the First 30 Days Post-surgery |
|-----------------|--|

End point description:

At least 1 event of symptomatic AF (atrial fibrillation or atrial flutter) (symptoms occurring within 2 hours of an AF episode). For symptomatic AF, symptoms that occur in the interval that starts two hours prior to the onset of the AF episode and ends two hours after the conclusion of the AF episode will meet the definition of "within 2 hours of an AF episode". AF episode ≥ 30 seconds.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch)

by Day 30 post-surgery.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| First 30 days following the initial ICU admission date after open-chest cardiac surgery. | |

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 13.7 | 13.5 | 13.2 | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9814 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.96 |

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|-------------------|------------------------------|
| Comparison groups | AGN-151607 (250 U) v Placebo |
|-------------------|------------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9715 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.97 |

Secondary: Time to First Occurrence of AF (Atrial Fibrillation or Atrial Flutter) During the First 30 Days Post-surgery

| | |
|--|--|
| End point title | Time to First Occurrence of AF (Atrial Fibrillation or Atrial Flutter) During the First 30 Days Post-surgery |
| End point description: Amount of time (days) to first AF (atrial fibrillation or atrial flutter) occurrence defined by first episode of AF lasting for ≥ 30 seconds. | |
| 99999 = Insufficient number of participants with events | |
| End point type | Secondary |
| End point timeframe: First 30 days following the initial ICU admission date after open-chest cardiac surgery. | |

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|----------------------------------|----------------------|------------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: days | | | | |
| median (confidence interval 95%) | 99999 (9.1 to 99999) | 99999 (99999 to 99999) | 99999 (13.2 to 99999) | |

Statistical analyses

| | |
|--|------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: P-value is from stratified log-rank test versus Placebo with type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years) as stratification factors. | |
| Comparison groups | AGN-151607 (125 U) v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1281 |
| Method | Logrank |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

P-value is from stratified log-rank test versus Placebo with type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years) as stratification factors.

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.882 |
| Method | Logrank |

Secondary: Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 2 Minutes During the First 30 Days Post-surgery

| | |
|-----------------|--|
| End point title | Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 2 Minutes During the First 30 Days Post-surgery |
|-----------------|--|

End point description:

At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained ≥ 2 minutes documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 45.1 | 35.6 | 46.2 | |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7776 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 1.39 |

| | |
|---|------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1623 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 1.1 |

Secondary: Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 5 Minutes During the First 30 Days Post-surgery

| | |
|-----------------|--|
| End point title | Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 5 Minutes During the First 30 Days Post-surgery |
|-----------------|--|

End point description:

At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained ≥ 5 minutes documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 44.1 | 34.6 | 46.2 | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1603 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 1.1 |

| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|-------------------|------------------------------|
| Comparison groups | AGN-151607 (250 U) v Placebo |
|-------------------|------------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6706 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.42 |

Secondary: Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode \geq 6 Minutes During the First 30 Days Post-surgery

| | |
|-----------------|---|
| End point title | Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode \geq 6 Minutes During the First 30 Days Post-surgery |
|-----------------|---|

End point description:

At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained \geq 6 minutes documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 43.1 | 33.7 | 45.3 | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|-------------------|------------------------------|
| Comparison groups | AGN-151607 (125 U) v Placebo |
|-------------------|------------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1583 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.1 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6694 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.43 |

Secondary: Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 30 Minutes During the First 30 Days Post-surgery

| | |
|-----------------|---|
| End point title | Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 30 Minutes During the First 30 Days Post-surgery |
|-----------------|---|

End point description:

At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained ≥ 30 minutes documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 38.2 | 30.8 | 39.6 | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2578 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.18 |

| Statistical analysis title | Statistical Analysis 2 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7526 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.05 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.47 |

Secondary: Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode \geq 1 Hour During the First 30 Days Post-surgery

| | |
|-----------------|--|
| End point title | Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode \geq 1 Hour During the First 30 Days Post-surgery |
|-----------------|--|

End point description:

At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained \geq 1 hour documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 37.3 | 29.8 | 37.7 | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8544 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.03 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.45 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2549 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.18 |

Secondary: Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 4 Hours During the First 30 Days Post-surgery

| | |
|-----------------|---|
| End point title | Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 4 Hours During the First 30 Days Post-surgery |
|-----------------|---|

End point description:

At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained ≥ 4 hours documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 32.4 | 24.0 | 26.4 | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1718 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 1.14 |

| Statistical analysis title | Statistical Analysis 2 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3801 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 1.27 |

Secondary: Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode \geq 6 Hours During the First 30 Days Post-surgery

| | |
|-----------------|---|
| End point title | Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode \geq 6 Hours During the First 30 Days Post-surgery |
|-----------------|---|

End point description:

At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained \geq 6 hours documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 25.5 | 22.1 | 20.8 | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5531 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 1.39 |

| | |
|---|------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4213 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.33 |

Secondary: Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 12 Hours During the First 30 Days Post-surgery

| | |
|-----------------|---|
| End point title | Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 12 Hours During the First 30 Days Post-surgery |
|-----------------|---|

End point description:

At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained ≥ 12 hours documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 15.7 | 14.4 | 17.0 | |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.804 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 1.73 |

Statistical analysis title

Statistical Analysis 2

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7573 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 1.98 |

Secondary: Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 24 Hours During the First 30 Days Post-surgery

| | |
|-----------------|--|
| End point title | Percentage of Participants With at Least 1 Continuous AF (Atrial Fibrillation or Atrial Flutter) Episode ≥ 24 Hours During the First 30 Days Post-surgery |
|-----------------|--|

End point description:

At least one episode of continuous AF (atrial fibrillation or atrial flutter) sustained ≥ 24 hours documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| First 30 days following the initial ICU admission date after open-chest cardiac surgery. | |

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 9.8 | 6.7 | 12.3 | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 2 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5257 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 2.7 |

| Statistical analysis title | Statistical Analysis 1 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4065 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.69 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 1.67 |

Secondary: Percentage of Participants With at Least 1 Continuous Atrial Fibrillation (Excluding Atrial Flutter) Episode ≥ 30 Seconds During the First 30 Days Post-surgery

| | |
|-----------------|---|
| End point title | Percentage of Participants With at Least 1 Continuous Atrial Fibrillation (Excluding Atrial Flutter) Episode ≥ 30 Seconds During the First 30 Days Post-surgery |
|-----------------|---|

End point description:

At least one episode of continuous atrial fibrillation (excluding atrial flutter) sustained ≥ 30 seconds documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 43.1 | 33.7 | 42.5 | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9966 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.35 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1612 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.11 |

Secondary: Percentage of Participants With at Least 1 Continuous Atrial Flutter Episode ≥ 30 Seconds During the First 30 Days Post-surgery

| | |
|-----------------|---|
| End point title | Percentage of Participants With at Least 1 Continuous Atrial Flutter Episode ≥ 30 Seconds During the First 30 Days Post-surgery |
|-----------------|---|

End point description:

At least one episode of continuous atrial flutter sustained ≥ 30 seconds documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 12.7 | 8.7 | 15.1 | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3374 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 1.52 |

| Statistical analysis title | Statistical Analysis 2 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5403 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 2.45 |

Secondary: Percentage of Participants With at Least 1 Continuous Atrial Tachycardia Episode (Defined as the Duration of the Longest Supraventricular Tachycardia [SVT] Run) \geq 30 Seconds During the First 30 Days Post-surgery

| | |
|-----------------|--|
| End point title | Percentage of Participants With at Least 1 Continuous Atrial Tachycardia Episode (Defined as the Duration of the Longest Supraventricular Tachycardia [SVT] Run) \geq 30 Seconds During the First 30 Days Post-surgery |
|-----------------|--|

End point description:

At least one episode of continuous atrial tachycardia sustained \geq 30 seconds documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 2.9 | 11.5 | 7.5 | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years).

| | |
|---|------------------------------|
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0163 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 3.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.16 |
| upper limit | 13.42 |

| | |
|---|------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1101 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 9.64 |

Secondary: Percentage of Participants With at Least 1 Continuous Episode of Either Atrial Fibrillation or Atrial Flutter or Atrial Tachycardia ≥ 30 Seconds During the First 30 Days Post-surgery

| | |
|-----------------|--|
| End point title | Percentage of Participants With at Least 1 Continuous Episode of Either Atrial Fibrillation or Atrial Flutter or Atrial Tachycardia ≥ 30 Seconds During the First 30 Days Post-surgery |
|-----------------|--|

End point description:

At least one episode of continuous atrial fibrillation or atrial flutter or atrial tachycardia sustained ≥ 30 seconds documented by monitoring ECG measurements using ECG patches (ePatch) placed on the participant's chest.

All randomized participants who received study treatment and had at least 1 post-dose ECG (by ePatch) by Day 30 post-surgery.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

First 30 days following the initial ICU admission date after open-chest cardiac surgery.

| End point values | Placebo | AGN-151607 (125 U) | AGN-151607 (250 U) | |
|-----------------------------------|-----------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 102 | 104 | 106 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 48.0 | 41.3 | 51.9 | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (125 U) v Placebo |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3339 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.16 |

| Statistical analysis title | Statistical Analysis 2 |
|---|------------------------------|
| Statistical analysis description: | |
| P-values and Risk Ratios (and their corresponding 95% CI) for each pairwise comparison of AGN-151607 versus Placebo are obtained from Cochran-Mantel-Haenszel (CMH) test controlling for type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). | |
| Comparison groups | AGN-151607 (250 U) v Placebo |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4614 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.42 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The length of this study was up to 367 days post single dose study treatment, plus up to 28 days before the first study day (randomization, Day 1).

Adverse event reporting additional description:

Of the 323 subjects enrolled and included in the All-cause mortality data table, 4 did not receive treatment and, therefore, did not go beyond the 28-Day screening period. The median time that the 319 subjects who received a single treatment of Placebo, AGN-151607 125 Units, or AGN-151607250 Units was 371.0, 372.0 and 371.0 days, respectively.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 25.1 |

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | PLACEBO |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | AGN-151607_250_U |
|-----------------------|------------------|

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | AGN-151607_125_U |
|-----------------------|------------------|

Reporting group description: -

| Serious adverse events | PLACEBO | AGN-151607_250_U | AGN-151607_125_U |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 36 / 105 (34.29%) | 28 / 109 (25.69%) | 38 / 105 (36.19%) |
| number of deaths (all causes) | 1 | 2 | 0 |
| number of deaths resulting from adverse events | 1 | 2 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| LUNG NEOPLASM | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NON-SMALL CELL LUNG CANCER | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| LUNG ADENOCARCINOMA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RENAL CANCER | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| Vascular disorders | | | |
| SHOCK HAEMORRHAGIC | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| AORTIC PERFORATION | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| THROMBOSIS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERTENSION | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTERMITTENT CLAUDICATION | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ORTHOSTATIC HYPOTENSION | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HAEMATOMA | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 2 / 105 (1.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYREXIA | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 109 (0.92%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 3 / 105 (2.86%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 2 / 109 (1.83%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 1 / 109 (0.92%) | 2 / 105 (1.90%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| HAEMOTHORAX | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| DYSпноEA EXERTIONAL | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| DYSпноEA | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 109 (0.92%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIAPHRAGMATIC PARALYSIS | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| ASPIRATION | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PULMONARY OEDEMA | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY FAILURE | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| Psychiatric disorders | | | |
| MENTAL STATUS CHANGES | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| BLOOD CREATINE PHOSPHOKINASE INCREASED | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| HAEMOGLOBIN DECREASED | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTERNATIONAL NORMALISED RATIO INCREASED | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| ELECTROENCEPHALOGRAM ABNORMAL | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| CORONARY SINUS INJURY | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| FALL | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERIPROCEDURAL MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| POST PROCEDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 0 / 109 (0.00%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| POSTOPERATIVE ILEUS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PROCEDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| TRANSFUSION-RELATED ACUTE LUNG INJURY | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| SUBDURAL HAEMATOMA | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VASCULAR GRAFT OCCLUSION | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| VASCULAR PROCEDURE COMPLICATION | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| Cardiac disorders | | | |
| AORTIC VALVE INCOMPETENCE | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 4 / 109 (3.67%) | 6 / 105 (5.71%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 6 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ATRIAL FLUTTER | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | 5 / 109 (4.59%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ATRIOVENTRICULAR BLOCK | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| ATRIOVENTRICULAR BLOCK COMPLETE | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 2 / 109 (1.83%) | 2 / 105 (1.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| BRADYCARDIA | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 2 / 109 (1.83%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC ARREST | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC FAILURE ACUTE | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| ACUTE MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIOGENIC SHOCK | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| ACUTE LEFT VENTRICULAR FAILURE | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| PERICARDIAL EFFUSION | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| NODAL RHYTHM | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MYOCARDIAL ISCHAEMIA | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| CORONARY ARTERY PERFORATION | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| CORONARY ARTERY DISEASE | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERICARDITIS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| FACIAL PARALYSIS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LOSS OF CONSCIOUSNESS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TRANSIENT ISCHAEMIC ATTACK | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 109 (0.92%) | 2 / 105 (1.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SYNCOPE | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 109 (0.92%) | 3 / 105 (2.86%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MYASTHENIA GRAVIS | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| ENCEPHALOPATHY | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| DIZZINESS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 0 / 109 (0.00%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CEREBRAL ISCHAEMIA | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| BELL'S PALSY | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| AMYOTROPHIC LATERAL SCLEROSIS | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| BLOOD LOSS ANAEMIA | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANAEMIA | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 2 / 105 (1.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COAGULOPATHY | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| THROMBOCYTOSIS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| Eye disorders | | | |
| DIPLOPIA | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 2 / 109 (1.83%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| MELAENA | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ILEUS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | | |
|------------------------------|---|-----------------|-----------------|-----------------|
| GASTROINTESTINAL HAEMORRHAGE | subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DYSPHAGIA | subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| DIARRHOEA | subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| AORTO-OESOPHAGEAL FISTULA | subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hepatobiliary disorders | | | | |
| CHOLECYSTITIS ACUTE | subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| Renal and urinary disorders | | | | |
| ACUTE KIDNEY INJURY | subjects affected / exposed | 2 / 105 (1.90%) | 1 / 109 (0.92%) | 0 / 105 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HAEMATURIA | subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NEPHROLITHIASIS | subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 1 / 105 (0.95%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| URINARY RETENTION | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ROTATOR CUFF SYNDROME | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| Infections and infestations | | | |
| APPENDICITIS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENDOCARDITIS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIVERTICULITIS | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MEDIASTINITIS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 2 / 105 (1.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| COLONIC ABSCESS | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| CELLULITIS | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 1 / 109 (0.92%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHITIS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 0 / 105 (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 |
| BACTERAEMIA | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 PNEUMONIA | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| OSTEOMYELITIS | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 109 (0.92%) | 2 / 105 (1.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEPSIS | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 0 / 109 (0.00%) | 0 / 105 (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 |
| URINARY TRACT INFECTION | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 105 (0.00%) | 1 / 109 (0.92%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| WOUND INFECTION | | | |
| subjects affected / exposed | 0 / 105 (0.00%) | 0 / 109 (0.00%) | 1 / 105 (0.95%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| LACTIC ACIDOSIS | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 1 / 109 (0.92%) | 0 / 105 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 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-151607_250_U | AGN-151607_125_U |
|--|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 86 / 105 (81.90%) | 94 / 109 (86.24%) | 84 / 105 (80.00%) |
| Vascular disorders | | | |
| HYPOTENSION | | | |
| subjects affected / exposed | 15 / 105 (14.29%) | 17 / 109 (15.60%) | 10 / 105 (9.52%) |
| occurrences (all) | 18 | 20 | 10 |
| HYPERTENSION | | | |
| subjects affected / exposed | 8 / 105 (7.62%) | 6 / 109 (5.50%) | 7 / 105 (6.67%) |
| occurrences (all) | 9 | 6 | 7 |
| General disorders and administration site conditions | | | |
| PYREXIA | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 5 / 109 (4.59%) | 8 / 105 (7.62%) |
| occurrences (all) | 2 | 6 | 8 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 13 / 105 (12.38%) | 10 / 109 (9.17%) | 10 / 105 (9.52%) |
| occurrences (all) | 15 | 10 | 11 |
| FATIGUE | | | |
| subjects affected / exposed | 7 / 105 (6.67%) | 5 / 109 (4.59%) | 3 / 105 (2.86%) |
| occurrences (all) | 8 | 5 | 3 |

| | | | |
|---|-------------------|-------------------|-------------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | 6 / 109 (5.50%) | 7 / 105 (6.67%) |
| occurrences (all) | 1 | 6 | 7 |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 14 / 105 (13.33%) | 22 / 109 (20.18%) | 10 / 105 (9.52%) |
| occurrences (all) | 15 | 24 | 11 |
| DYSPNOEA | | | |
| subjects affected / exposed | 13 / 105 (12.38%) | 13 / 109 (11.93%) | 3 / 105 (2.86%) |
| occurrences (all) | 19 | 13 | 4 |
| COUGH | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 7 / 109 (6.42%) | 3 / 105 (2.86%) |
| occurrences (all) | 7 | 7 | 3 |
| ATELECTASIS | | | |
| subjects affected / exposed | 12 / 105 (11.43%) | 18 / 109 (16.51%) | 11 / 105 (10.48%) |
| occurrences (all) | 12 | 20 | 11 |
| Psychiatric disorders | | | |
| INSOMNIA | | | |
| subjects affected / exposed | 16 / 105 (15.24%) | 12 / 109 (11.01%) | 17 / 105 (16.19%) |
| occurrences (all) | 16 | 12 | 17 |
| ANXIETY | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | 5 / 109 (4.59%) | 3 / 105 (2.86%) |
| occurrences (all) | 6 | 5 | 4 |
| DELIRIUM | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | 6 / 109 (5.50%) | 2 / 105 (1.90%) |
| occurrences (all) | 2 | 6 | 2 |
| Injury, poisoning and procedural complications | | | |
| VASOPLEGIA SYNDROME | | | |
| subjects affected / exposed | 3 / 105 (2.86%) | 13 / 109 (11.93%) | 5 / 105 (4.76%) |
| occurrences (all) | 3 | 13 | 5 |
| PROCEDURAL PAIN | | | |
| subjects affected / exposed | 20 / 105 (19.05%) | 21 / 109 (19.27%) | 20 / 105 (19.05%) |
| occurrences (all) | 20 | 21 | 21 |
| Cardiac disorders | | | |
| SINUS TACHYCARDIA | | | |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 7 / 105 (6.67%) 8 | 2 / 109 (1.83%) 2 | 1 / 105 (0.95%) 1 |
| PALPITATIONS | | | |
| subjects affected / exposed occurrences (all) | 7 / 105 (6.67%) 10 | 6 / 109 (5.50%) 6 | 4 / 105 (3.81%) 6 |
| BRADYCARDIA | | | |
| subjects affected / exposed occurrences (all) | 4 / 105 (3.81%) 4 | 4 / 109 (3.67%) 4 | 7 / 105 (6.67%) 8 |
| ATRIAL FLUTTER | | | |
| subjects affected / exposed occurrences (all) | 6 / 105 (5.71%) 6 | 7 / 109 (6.42%) 7 | 5 / 105 (4.76%) 6 |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed occurrences (all) | 32 / 105 (30.48%) 38 | 35 / 109 (32.11%) 40 | 31 / 105 (29.52%) 37 |
| TACHYCARDIA | | | |
| subjects affected / exposed occurrences (all) | 4 / 105 (3.81%) 4 | 12 / 109 (11.01%) 12 | 4 / 105 (3.81%) 6 |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed occurrences (all) | 8 / 105 (7.62%) 10 | 5 / 109 (4.59%) 5 | 4 / 105 (3.81%) 4 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed occurrences (all) | 27 / 105 (25.71%) 28 | 30 / 109 (27.52%) 30 | 19 / 105 (18.10%) 20 |
| Gastrointestinal disorders | | | |
| VOMITING | | | |
| subjects affected / exposed occurrences (all) | 4 / 105 (3.81%) 4 | 7 / 109 (6.42%) 7 | 2 / 105 (1.90%) 2 |
| NAUSEA | | | |
| subjects affected / exposed occurrences (all) | 25 / 105 (23.81%) 25 | 29 / 109 (26.61%) 30 | 25 / 105 (23.81%) 27 |
| CONSTIPATION | | | |
| subjects affected / exposed occurrences (all) | 10 / 105 (9.52%) 10 | 6 / 109 (5.50%) 6 | 7 / 105 (6.67%) 9 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|--|--|--|
| DERMATITIS CONTACT subjects affected / exposed occurrences (all) | 5 / 105 (4.76%) 5 | 6 / 109 (5.50%) 6 | 2 / 105 (1.90%) 2 |
| Musculoskeletal and connective tissue disorders MUSCULOSKELETAL CHEST PAIN subjects affected / exposed occurrences (all) | 12 / 105 (11.43%) 12 | 9 / 109 (8.26%) 9 | 11 / 105 (10.48%) 12 |
| Infections and infestations URINARY TRACT INFECTION subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all) | 4 / 105 (3.81%) 4 5 / 105 (4.76%) 5 | 6 / 109 (5.50%) 6 6 / 109 (5.50%) 6 | 6 / 105 (5.71%) 7 10 / 105 (9.52%) 12 |
| Metabolism and nutrition disorders HYPOPHOSPHATAEMIA subjects affected / exposed occurrences (all) HYPOKALAEMIA subjects affected / exposed occurrences (all) HYPERVOLAEMIA subjects affected / exposed occurrences (all) HYPERGLYCAEMIA subjects affected / exposed occurrences (all) | 5 / 105 (4.76%) 5 3 / 105 (2.86%) 3 18 / 105 (17.14%) 19 14 / 105 (13.33%) 16 | 7 / 109 (6.42%) 7 9 / 109 (8.26%) 9 23 / 109 (21.10%) 23 17 / 109 (15.60%) 17 | 6 / 105 (5.71%) 6 3 / 105 (2.86%) 3 24 / 105 (22.86%) 24 17 / 105 (16.19%) 19 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 25 September 2020 | The purpose of this protocol amendment was to clarify specific points within the protocol based on clinical experience to date. These changes did not impact the safety assessment of botulinum toxin type A or alter the risk-benefit ratio for study participants. Administrative edits were also made, but not specifically noted (eg, corrected spelling, punctuation, grammar, abbreviations, and style errors) including global edits required for consistency (eg, “study drug”, “participants”, abbreviation use). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported