Title Page

Protocol Title: 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

Protocol Number: 1925-201-008

Product: AGN-151607

Brief Protocol Title: Botulinum toxin type A (AGN-151607) for the prevention of post-operative atrial fibrillation in patients undergoing open-chest cardiac surgery

Study Acronym: NOVA Study: NeurOtoxin for the preVention of post-operative Atrial fibrillation in cardiac surgery patients

Development Phase: 2

Sponsor Name and Legal Registered Address:
Allergan Sales LLC, 5 Giralda Farms, Madison, NJ 07940, USA.
Allergan Ltd, 1st Floor, Marlow International, Parkway, Marlow, Buckinghamshire, SL7 1YL, United Kingdom.

Regulatory Agency Identifying Numbers:
IND Number: 135000
EudraCT Number: 2017-004399-68

Emergency Telephone Number: Refer to the study contacts page

SAE Reporting Fax Number/Email:
Email to: IR-Clinical-SAE@allergan.com
Fax: +1-714-796-9504
Back-up Fax: +1-714-246-5295

Sponsor Signatory:
[redacted] MD, PhD, FACC
[redacted] Internal Medicine, Women's Health, Urology, & Anti-Infectives

The signature of the sponsor signatory is collected on the protocol approval page.

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	[redacted]
Amendment 1	[redacted]

Amendment 1 (25 Sep 2020)

Overall Rationale for the Amendment

This summary includes changes made to Protocol 1925-201-008 Amendment 1 (dated 25 Sep 2020). The purpose of this protocol amendment is to clarify specific points within the protocol based on clinical experience to date. These changes will 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).

Summary of Changes in Global Protocol Amendment

Section No. and Name	*Description of Change*	*Brief Rationale*
Global change	• Text was revised throughout as needed regarding time period ECG patch is to be worn post-surgery: "for a full 30 days post-surgery". This change may not be universally reflected in text related to statistical analyses where original text was more often retained.	• To clarify that the ECG patch should be worn for a full 30 days
	• Text was revised throughout as needed regarding the 30-day cut-off post-discharge and 60-day cut-off post-surgery.	• For clarification and consistency
	• References were updated	• To include/update references published after original protocol was finalized
Title page	Study acronym was added	For clarification
Section 1.1, Synopsis	Revised text as needed to align with in-text revisions	For consistency
Section 1.2, Schema	Revised as needed to align with in-text revisions	For consistency
Section 1.3, Schedule of Activities	All footnotes were sequentially renumbered	For consistency and accuracy following addition and deletion of footnotes in the original protocol

Section No. and Name	*Description of Change*	*Brief Rationale*
	• A new footnote 'a' was added to "Screening": ***Screening and randomization activities can occur on the same day. If screening and randomization occur on the same day, all assessments for Visit 1 and Visit 2 should be completed. Duplicate assessments (eg, laboratory assessments) do not have to be completed twice; please note a 12-lead ECG is required both before and after surgery.***	• To clarify that screening activities can take place on the same day as randomization
	• Current footnote 'b' was revised: These visits are optional and are only required if the participant is still hospitalized. Participants may remain in the hospital beyond Day 6, based on the recovery from surgery. The ***study visit*** procedures will have to be performed each day until discharge	• For clarification
	• Current footnote 'c' was revised: In case of early discontinuation, attempts will be made to follow-up with the participant. ~~for 3 months post dose.~~	• To clarify that follow-up must occur as soon as possible after sponsor is notified of potential early discontinuation
	• Current footnote 'd' was revised: Day 367 must be at least 7 days and ***should be*** no more than 14 days after Visit 13 (Day 360).	• To clarify visit window
	• A new footnote 'f' was added to "Physical examination" Day 360: ***Physical examinations should be conducted where feasible. If the participant cannot attend the study visit, then the physical examination can be omitted, with sponsor approval.***	• To provide guidance regarding feasibility of study assessments being conducted
	• Current footnote 'h' was revised: Laboratory assessments (hematology, chemistry, coagulation and urinalysis) to be performed at screening, Day 1 and day of discharge. The day of discharge can be from Day 3 onwards. ~~Once discharged the participant does not have to return until Day 30 (Visit 8).~~	• To allow for remote assessments
	• A new footnote 'i' was added to "Laboratory assessments" Days 60, 90, and 360: ***Laboratory assessments should be conducted where feasible. If the participant cannot attend the study visit and/or an in-home assessment is not feasible, then the laboratory assessments can be omitted, after sponsor approval.***	• To provide guidance regarding feasibility of study assessments being conducted
	• Current footnote 'j' was revised: On Visit 2, Day 1, two 12-lead ECGs will be performed; 1 before surgery and 1 after surgery. PFT should be performed ~~after vital signs and ECG~~ ***at a reasonable time apart from vital signs and ECG to avoid confounding ECG and vital signs data.***	• Clarified timing of when assessments should be conducted in relation to other assessments

Section No. and Name	*Description of Change*	*Brief Rationale*
	• A new footnote 'k' was added to "12-lead ECG" at Days 60, 90, 180, 270, and 360: ***12-lead ECGs should be conducted where feasible. If the participant cannot attend the study visit and/or an in-home assessment is not feasible, then the 12-lead ECG can be omitted, after sponsor approval.***	• To provide guidance regarding feasibility of study assessments being conducted
	• A new footnote l was added to "ECG patch" Day 30: ***ECG patch must be worn for a full 30 days post-surgery, even if Day 30 visit occurs prior to Day 30 due to window allowance.***	• To clarify that the ECG patch should be worn for a full 30 days
	• Current footnote 'm' was revised: ECG patch must be used ~~for first 30 days after surgery and~~ during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits.	• Clarified that footnote m was only regarding visits 9 to 13
	• Current footnote 'n' was revised: Vital signs taken after a participant has been in a resting position for a minimum of 5 minutes; include blood pressure, pulse, respiration rate, and body temperature. On Visit 2, Day 1, vital signs will be measured before and after surgery. ~~PFT should be performed after vital signs and ECG~~.	• Guidance regarding PFTs was moved to footnote i and r
	• Current footnote 'r' was revised: Pulmonary function to be assessed using a ~~bedside~~ spirometer and will include forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1), 3 seconds (FEV_3) and 6 seconds (FEV_6). ***Note, if local policies contraindicate or prohibit PFT assessments due to potential for viral spread or microbial precautions, then the PFT is not required after explicit approval from the sponsor.***	• To provide guidance regarding feasibility of study assessments being conducted
	• "EuroSCORE II" and corresponding footnote (footnote 't') was added to the SoA: ***Impaired prognosis defined as EuroSCORE II > 7% perioperative mortality at screening is exclusionary.***	• Included guidance regarding EuroSCORE II in the SoA for consistency
	• A new footnote 'u' was added to "Serum sampling for immunogenicity assessment": ***Serum collection should be conducted where feasible. If the participant cannot attend the study visit and/or an in-home assessment is not feasible, then the serum collection can be omitted, after sponsor approval.***	• To provide guidance regarding feasibility of study assessments being conducted

Section No. and Name	*Description of Change*	*Brief Rationale*
	• Former footnotes h and n were deleted: ~~[h]: AF symptom diary must be used for first 30 days after surgery (or until early discontinuation if before Day 30) and during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits. The diary should be returned to the site and be part of the medical records.~~ ~~[n]Day 367 must be at least 7 days and no more than 14 days after Visit 13 (Day 360).~~	• Additional clarification was provided in newly added footnotes
Section 2.3, Benefit/Risk Assessment	Text was revised: [redacted] More detailed information about the known and expected benefits and risks and expected AEs of AGN-151607 may be found in the IB.	[redacted]
Section 3, Objectives and Endpoints; Section 9.4.1.3, Secondary Efficacy Variables	The following secondary efficacy endpoints were added: • ***Percentage of participants with at least 1 continuous AF episode ≥ 6 hours during the first 30 days post-surgery*** ***Percentage of participants with at least 1 continuous AF episode ≥ 12 hours during the first 30 days post-surgery***	New secondary efficacy endpoints were added to include events lasting longer than 6 hours and 12 hours.
Section 3, Objectives and Endpoints; Section 8.1.4.4, Re-hospitalization and Days Spent in Hospital, Table 8-7 Section 9.4.1.4, Additional Efficacy Variables	The following additional efficacy endpoints was revised: Number of ***non-arrhythmia*** cardiovascular re-hospitalizations within 30 days post-discharge	For clarification

Section No. and Name	***Description of Change***	***Brief Rationale***
Section 3, Objectives and Endpoints; Section 8.1.3.3 Clinically Important Tachycardia in Atrial Fibrillation; Section 9.4.1.4 Additional Efficacy Variables	The following safety endpoint was revised: • Percentage of participants with clinically important tachycardia in AF (defined as heart rate ≥ 100 bpm for at least 2 minutes) ~~with or without systolic blood pressure < 100 mm Hg)~~	Updated definition of safety endpoint
Section 3, Objectives and Endpoints	The following quality of life endpoints were added/deleted: • ***Healthcare resource utilization (eg, setting, provider, reason for visit)*** • ~~Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)~~ • ~~Number and type of diagnostic and therapeutic tests and procedures~~	For clarification
Section 4.1, Overall Design	The number of projected study sites was revised: It is projected that a total of approximately 20 to ~~30~~ ***40*** sites (North America and Europe) will enroll a total of approximately 330 participants for this Phase 2 study.	For accuracy
Section 5, Study Population; Rational for Inclusion and Exclusion Criteria	Text was revised regarding IC 6.01: • Inclusion criterion 6.01 is to ensure participants have ~~a regular sinus rhythm~~ ***no detected arrhythmias*** in the 48 hours prior to surgery ~~so~~ ***that could impact study conduct***. ~~only POAF is measured~~	To clarify inclusion criteria 6.01
Section 5.1, Inclusion Criteria	• Inclusion Criterion 2.01 was expanded: Participants who are scheduled to undergo open-chest cardiac surgery. Includes: coronary artery bypass graft (CABG) and/or valve repair/replacement. ***Inclusionary valve repair/replacement procedures for the primary reason for surgery include:*** • ***Aortic valve repair/replacement*** • ***Mitral valve repair/replacement*** • ***Combination of aortic and tricuspid valve repair/replacement*** • ***Combination of mitral and tricuspid valve repair/replacement*** • ***CABG/valve combination procedures (when valvular procedure is one of the 4 sub-bulleted procedures immediately above)*** ***Left Atrial Appendage (LAA) procedures are allowed if CABG and/or valve repair or replacement is the qualifying surgical procedure, but is not a qualifying surgical procedure on its own.***	• To further clarify inclusionary valve repair/replacement procedures for primary surgery

Section No. and Name	*Description of Change*	*Brief Rationale*
	• Inclusion Criterion 6.01 was revised: In sinus rhythm for the last 48 hours prior ***to randomization based on standard-of-care assessments and study ECGs (note: continuous ECG monitoring for 48 hours is not required***; ~~surgery~~ prior history of paroxysmal atrial fibrillation [AF] is acceptable).	• To clarify inclusion criteria 6.01
Section 5.2, Exclusion Criteria	• Exclusion Criterion 1.07 was revised: Severe (> 55 mm ***left atrial diameter***) ***left*** atrial enlargement	• To clarify the measurement and atria
	• Exclusion Criterion 1.09 was revised: Presence or history of symptomatic atrioventricular block > 1st degree within the last 30 days (***note: presence of a pacemaker is not exclusionary per se***)	• To clarify pacemaker is not exclusionary if other criteria are satisfied
	• Exclusion Criterion 1.10 was added: ***Exclusionary valve repair/replacement procedures include:*** • ***Combination of aortic and mitral valve repair/replacement*** • ***Isolated tricuspid valve repair/replacement***	• To further clarify exclusionary valve repair/replacement procedures for primary surgery
	• Exclusion Criterion 2.05 was revised: Prior ***open-chest, sternotomy*** cardiac surgery	• To clarify which prior cardiac surgeries are excluded
	• Exclusion Criterion 4.02 was revised: Impaired prognosis defined as EuroSCORE II > 7% perioperative mortality ***at screening is exclusionary.***	• To clarify the timepoint of the assessment
Section 6.1, Study Interventions; Table 6-1 Treatments Administered	Text was added: ***Each of the 5 fat pads must be injected as part of the study procedure. However, in the event where 1 fat pad is missing or is not accessible, the injection procedure can continue and only 4 mL of interventional product or placebo shall be injected. If, upon initial evaluation (ie, if injections have not yet occurred), 3 fat pads or fewer are accessible, the injection procedure should be aborted. If any injections of study intervention have already been made when the surgeon determines they are unable to inject 4 or more fat pads, the participant should remain in the study.*** Table footnote was deleted: [a] ~~Each 1 of the 5 fat pads must be injected as part of the study procedure. However, in the event where 1 fat pad is missing or is not accessible, the injection procedure can continue and only 4 mL of interventional product or placebo shall be injected. If 3 fat pads or less are accessible, the injection procedure must be aborted.~~	To clarify the decision to proceed (or not) based on initial inspection of accessible fat pads

Section No. and Name	*Description of Change*	*Brief Rationale*
Section 6.2, Preparation/Handling/ Storage/Accountability	Text was revised: All unused study intervention and used kits ~~must~~ ***should*** be returned to the sponsor or designee at the termination of the study. Unit counts will be performed when the study intervention is returned, and all study intervention must be accounted for. ***Accountability logs for destroyed materials should be maintained at the site to ensure all study intervention is accounted for. Study intervention may be destroyed on site if required by local/institutional policies after sponsor approval of destruction process and documentation.***	For improved accuracy
Section 6.5.2, Permitted Interventions	Text was revised: • Dosage information including dose, ***route of administration,*** and frequency	For additional guidance
Section 6.5.3, Rescue Medicine or Procedure	• Text was added: Standard-of-care is allowable at any time during the study. The date and time of any medication administration, as well as the name, ***indication,*** and dosage regimen of the medication (***ie, dose, route of administration, and frequency***), should be recorded. • Text was revised: ***An intervention to treat an*** ~~A catheter-based ablation for~~ arrhythmia is allowed during follow-up as clinically warranted in the judgement of the treating physician and/or site-based investigator physician.	• To provide guidance regarding all required information needed • For clarification
Section 6.5.4, Prohibited Intervention During the Study	Text was revised: ~~Participants are prohibited from using aminoglycoside antibiotics or other medicinal products that interfere with neuromuscular transmission (eg, neuromuscular blocking agents) for 60 days post-surgery.~~ Please refer to Section 6.5.1 for prohibited interventions during the washout period prior to surgery. ***Administration of aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution for 60 days post-surgery, as the effect of the toxin may be potentiated.***	To align with current guidance for available botulinum neurotoxins
Section 7.2, Participant Discontinuation/Withdrawal from the Study	The following bullet point was revised: • See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. In case of early discontinuation, attempts will be made to follow-up with the participant ~~for 3 months post-dose~~.	For consistency

Section No. and Name	*Description of Change*	*Brief Rationale*
Section 8, Study Assessments and Procedures	• An additional bullet point was added: • ***Visits 4, 5, 6, and 7 are optional and are only required if the participant is still hospitalized. Participants may remain in the hospital beyond Day 6, based on the recovery from surgery. The study visit procedures will have to be performed each day until discharge.***	• To clarify all procedures required prior to discharge for patients having extended hospital stay
	• An additional bullet point was added: • ***Study visits after the index surgery may be conducted at the participant's home or other designated location in accordance with local ethics and/or IRB regulations, as well as with sponsor approval.***	• To include language regarding at home visits
	• Text was revised: • … However, testing of blood samples (including during unscheduled visits or samples for which local laboratory values are already available) ~~must~~ ***should*** be conducted by the central laboratory.	• For clarification
	• Text was added: • Local laboratory results are required only in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. ***Local laboratory results collected at the screening visit can be used to determine participants' eligibility if central laboratory results are not available***. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.	• For clarification and consistency
Section 8.1.1, Occurrence of Post-Operative Atrial Fibrillation	Text was added: The occurrence of POAF will be monitored through Day 30 and for 7 days after each ***of the following*** study visit***s: Day 60, Day 90, Day 180, Day 270, and Day 360*** by ECG patches placed on the upper left region of the chest (Table 8 1).	For consistency

Section No. and Name	***Description of Change***	***Brief Rationale***
Section 8.1.1, Occurrence of Post-Operative Atrial Fibrillation; Table 8-1	• "Post-surgery" was added to text: Through Day 367 (continuously through Day 30 ***post-surgery*** and during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits)	• For clarification
	• Text was revised to include new timepoints Occurrence of POAF: ***7. Continuous AF ≥ 6 hours*** ***8. Continuous AF ≥ 12 hours*** Time to first occurrence of POAF ***7. Continuous AF ≥ 6 hours*** ***8. Continuous AF ≥ 12 hours***	• Endpoints expanded to include multiple definitions
Section 8.1.3.2, Symptomatic Post-Operative Atrial Fibrillation	Text was revised: ~~From Day 1 to Day 30~~ ***While the participant is wearing the ECG patch,*** if ~~the~~ symptoms of AF occur, the actual symptom will be documented by the participant in a symptom diary. Participants will be instructed by the site staff ***or designee*** on the appropriate completion of the symptom diary and instructions will be included with each diary.	For clarification
Section 8.1.3.2, Symptomatic Post-Operative Atrial Fibrillation; Table 8-3	• Text was revised: Through Day 30 ***and for 7 days after each of the following study visits: Day 60, Day 90, Day 180, Say 270, and Day 360***	• For consistency
	• The following bullet point was deleted: • ~~Symptoms will be assigned to the nearest AF within a 30-minute time window~~	• For clarification
Section 8.1.4.1, Need for Medical Intervention, Table 8-4	Text was revised: Procedural intervention (ie, cardioversion, pacemaker implantation, ablation, additional ***cardiac*** surgery)	For clarification and consistency
Section 8.1.4.4, Re-hospitalization and Days Spent in Hospital, Table 8-7	Text was added: • ***Binary measure (Y/N) of all-cause hospitalizations within 30 days post-discharge*** • ***Binary measure (Y/N) of non-arrhythmia cardiovascular hospitalizations within 30 days post-discharge*** • ***Binary measure (Y/N) of arrhythmia hospitalizations within 30 days post-discharge***	• Binary measures were added for clarity; text was clarified regarding number of days spent in the hospital 60 days post-surgery
	• Number of days spent in the hospital within 60 days post-surgery ***for all cause hospitalizations*** • ***Number of days spent in the hospital within 6 days post-surgery for non-arrhythmia cardiovascular hospitalizations*** • ***Number of days spent in the hospital within 60 days post-surgery for arrythmia hospitalization***	

Section No. and Name	*Description of Change*	*Brief Rationale*
Section 8.2.3, Electrocardiograms	"Designee" was added: • Sites ***or designee*** shall transmit all study-required ECGs obtained to the ECG vendor.	For clarification
Section 8.2.5, Pulmonary Function Tests	Text was added: Study participant pulmonary function will be assessed at the screening visit and Day 30 using forced procedures and compared across all 3 study groups (refer to study reference guide). ***Note, if local policies contraindicate or prohibit PFT assessments due to potential for viral spread or microbial precautions, then the PFT is not required after explicit approval from the sponsor. If PFT assessments are not prohibited by local regulations/policies, then the PFTs should be conducted.***	Updated for accuracy
Section 8.2.7 Immunogenicity Assessments	Newly created section. Text was moved from Section 8.8 Biomarkers and Other Assessments to Section 8.2 Safety Assessments creating a new subsection 8.2.7 ***Blood samples will be collected from all participants prior to dosing on Day 1 and at the Day 30 and Day 90 follow-up visits. A 2-tier assay approach will be used for the detection of binding and neutralizing antibodies to AGN-151607 in human serum. In tier 1, serum samples will be screened using a validated enzyme-linked immunosorbent assay (ELISA). The positive samples will subsequently be immune depleted to confirm that the antibodies were specifically binding to AGN-151607 and then titered to assess the magnitude of antibodies present. In tier 2, only samples that are considered positive in the ELISA will be tested for neutralizing antibodies to AGN-151607 using a validated assay.*** ***Samples may be stored for a maximum of 2 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to AGN-151607.***	For improved consistency

Section No. and Name	*Description of Change*	*Brief Rationale*
Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Event Information	Text was added: ***Assessment of causality to both the study intervention and the study procedures are required for reporting each SAE. For the purpose of causality assessment, "study procedure" on the SAE reporting form means the procedure of injecting the study intervention into the epicardial fat pads. It does not include any other study procedures (eg, the open-chest surgery and related procedures). Therefore, the check box on the SAE form titled "Causal Relationship to Study Procedure" should only be checked if, in the investigator's judgement, the SAE was related to the injection procedure into the epicardial fat pads. The cardiac surgery procedure the study participant is undergoing (eg, CABG and/or valve repair/replacement) and any other procedures the participants may have during the study are NOT considered the study procedure for the purpose of SAE reporting causality assessment.***	For clarification
Section 8.8.1 Immunogenicity Assessments	~~Blood samples will be collected from all participants prior to dosing on Day 1 and at the Day 30 and Day 90 follow-up visits. A 2-tier assay approach will be used for the detection of binding and neutralizing antibodies to AGN-151607 in human serum. In tier 1, serum samples will be screened using a validated enzyme-linked immunosorbent assay (ELISA). The positive samples will subsequently be immune depleted to confirm that the antibodies were specifically binding to AGN-151607 and then titered to assess the magnitude of antibodies present. In tier 2, only samples that are considered positive in the ELISA will be tested for neutralizing antibodies to AGN-151607 using a validated assay.~~ ~~Samples may be stored for a maximum of 2 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to AGN-151607.~~	Section was moved to new subsection 8.2.7 for consistency

Section No. and Name	***Description of Change***	***Brief Rationale***
Section 8.9, Medical Resource Utilization and Health Economics	Text was revised: Medical resource utilization and health economics data, associated with medical encounters, will be collected by the investigator and study-site personnel ***or designee*** for all participants throughout the study. ***• Healthcare resource utilization (eg, setting, provider, reason for visit)*** ~~• Number and type of diagnostic and therapeutic tests and procedures~~ ~~• Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).~~	For clarification
Section 9.1, Statistical Hypotheses	Text was revised: ***Details regarding adjustment for multiple comparisons for other efficacy variables will be discussed in the SAP.*** ~~There will be no adjustment for multiple comparisons for all other efficacy variables.~~	For clarification and to refer readers to the SAP
Section 9.3, Populations for Analyses	Text was revised: • The modified intent-to-treat (mITT) population will consist of all randomized participants who received study intervention and had at least 1 post-dose ECG by ***Day 30 post-surgery*** ~~day of discharge~~. Analyses will be based on randomized intervention.	For consistency
Section 9.4.1, Efficacy Analysis	Text was added to include new timepoints and text was revised to reflect the addition: The ECG measurements collected for AF episodes post-surgery will be used to provide ~~7~~ ***9*** different definitions for POAF for use in statistical analyses, namely: ***7. At least 1 continuous AF episode ≥ 6 hours*** ***8. At least 1 continuous AF episode ≥ 12 hours***	Endpoints expanded to include multiple definitions
Section 9.4.1.1, Primary Efficacy Variables	Text was revised: For primary efficacy consideration, POAF will be defined as any continuous episode of AF lasting 30 seconds or more during the-first 30 days post-surgery. The primary efficacy variable is the percentage of participants with at least 1 continuous AF episode ≥ 30 seconds during the first 30 days post-surgery. ***AF will be defined as the detection of either AF or atrial flutter.***	For clarification
Section 9.4.1.4, Additional Efficacy Variables	Text was added: • ***Binary measure (Y/N) of all-cause hospitalizations within 30 days post-discharge*** • ***Binary measure (Y/N) of non-arrhythmia cardiovascular hospitalizations within 30 days post-discharge*** • ***Binary measure (Y/N) of arrhythmia hospitalizations within 30 days post-discharge***	For consistency

Section No. and Name	*Description of Change*	*Brief Rationale*
Section 9.4.1.5, Secondary and Additional Efficacy Analyses	Text was deleted: ICU and hospital length of stay will be compared between groups using t-tests as well as linear regression models with adjustment for POAF baseline risk factors. The data in both groups will first be examined for normality. Should the data have a normal distribution, it will be analyzed using an unadjusted t-test. In the event of significant skewedness, the Wilcoxon rank-sum test will be used. [redacted]	This is exploratory analysis, and could be performed post-hoc if necessary.
Section 10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations	Text was added: •Providing oversight of the overall conduct of the study at the site ***or at any home visits*** and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)	For clarification
Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting; AE of Special Interest	Text was revised: ***Serious AESIs should be reported to the sponsor within 24 hours using the same reporting procedures for SAE reporting. Nonserious AESIs should be reported using the same procedures as nonserious AEs reporting by capturing the AE information in the source document and entering them into the eCRF. The Serious Adverse Event/Adverse Event of Special Interest Form for Interventional Studies should not be used to report any nonserious AESIs.*** ~~Non-serious AESIs should be reported to the sponsor within 72 hours and serious AESIs should be reported to the sponsor within 24 hours. The AESI form should be used for reporting the AESI even is a serious outcome may not apply.~~	For clarification
Section 11, References	References were added as needed.	To reflect new or updated references within the protocol

Table of Contents

List of Tables

1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Protocol Number: 1925-201-008

Brief Title: Botulinum toxin type A (AGN-151607) for the prevention of post-operative atrial fibrillation in patients undergoing open-chest cardiac surgery

Study Rationale:

Post-operative atrial fibrillation (POAF) occurs at high rates despite standard-of-care therapies and is associated with problematic outcomes, eg, medical/procedural interventions, extended length of stay in the intensive care unit (ICU) and hospital, and rehospitalization. Nonclinical studies have demonstrated that injections of botulinum toxin type A into discrete regions of the heart can prevent atrial fibrillation (AF) and 2 clinical studies have demonstrated that botulinum toxin type A injections can prevent POAF with no noted safety issues.

Objectives and Endpoints:

Objectives	Endpoints
Primary	**Primary Efficacy**
• To compare the efficacy of AGN-151607 with placebo to prevent post-operative atrial fibrillation (POAF) in participants who are undergoing open-chest cardiac surgery	• Percentage of participants with at least 1 continuous atrial fibrillation (AF) episode ≥ 30 seconds during the first 30 days post-surgery
• To compare the efficacy of AGN-151607 with placebo to reduce AF burden in participants who are undergoing open-chest cardiac surgery	• Percentage of time spent in AF (AF burden) during the first 30 days post-surgery • Percentage of participants with at least 1 event of symptomatic AF during the first 30 days post-surgery • Time to first occurrence of AF during the first 30 days post-surgery

Objectives	Endpoints
Secondary	**Secondary Efficacy**
• To compare the efficacy of AGN-151607 with placebo to prevent POAF using alternative definitions for AF in participants who are undergoing open-chest cardiac surgery	• Percentage of participants with at least 1 continuous AF episode ≥ 2 minutes during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 5 minutes during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 30 minutes during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 1 hour during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 4 hours during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 6 hours during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 12 hours during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 24 hours during the first 30 days post-surgery
Safety	**Safety Assessments**
• To compare the safety of AGN-151607 with placebo in participants undergoing open-chest cardiac surgery	• Adverse events (AEs), physical examination, clinical laboratory tests, vital signs, electrocardiogram (ECGs), pulmonary function • Potential immunogenicity response

Overall Study Design:

This is 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 POAF in participants undergoing open-chest cardiac surgery.

Key inclusion criteria:

- 55 to 90 years of age, inclusive, at the time of signing the informed consent
- Scheduled to undergo open-chest cardiac surgery. Includes: coronary artery bypass graft (CABG) and/or valve repair/replacement (inclusionary valve repair/replacement procedures for the primary reason for surgery include: aortic or mitral valve repair/replacement; combination of aortic and tricuspid valve repair/replacement; combination of mitral and tricuspid valve repair/replacement; CABG/valve combination procedures [when valvular procedure is one of the 4 sub-bulleted procedures immediately

above]; left atrial appendage [LAA] procedures are allowed if CABG and/or valve repair/replacement is the qualifying surgical procedure, but is not a qualifying surgical procedure on its own).

- In sinus rhythm for the last 48 hours prior to randomization based on standard-of-care assessments and study ECGs (note: continuous ECG monitoring for 48 hours is not required; prior history of paroxysmal AF is acceptable)
- Willing to wear an electrocardiogram (ECG) patch for a full 30 days post-surgery and for 7 days after each study visit

Key exclusion criteria:

- Any medical condition that may put the participant at increased risk with exposure to botulinum toxin type A, including diagnosed muscular dystrophy (eg, Duchenne's muscular dystrophy), myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, mitochondrial disease, or any other significant disease which might interfere with neuromuscular function
- Participants with presence or history of any of the following within 3 months prior to the Day 1 visit that may indicate a vulnerable respiratory state per the investigator's clinical judgment: aspiration pneumonia, lower respiratory tract infections, uncontrolled asthma, severe chronic obstructive pulmonary disease or otherwise compromised respiratory function
- Permanent/persistent AF
- Has a known allergy or sensitivity to any botulinum toxin type A preparation; has a known allergy or sensitivity to medical adhesive (eg, ECG patch adhesive; hydrogel-based adhesive)
- Severe (> 55mm left atrial diameter) left atrial enlargement
- Left ventricular ejection fraction (LVEF) < 25%; presence or history of symptomatic atrioventricular block > 1st degree within the last 30 days (note: presence of a pacemaker is not exclusionary per se)
- Exclusionary valve repair/replacement procedures include combination of aortic and mitral valve repair/replacement; isolated tricuspid valve repair/replacement.
- Prior or concomitant therapy with Class I or III antiarrhythmic drugs unless proper washout was documented
- Botulinum toxin type A (of any serotype) use within 6 months of randomization
- Has been immunized for any botulinum toxin type A serotype as determined by participant medical history
- Preoperative need for inotropes/vasopressors or intra-aortic balloon pump
- Prior open-chest, sternotomy cardiac surgery
- History of ablation for AF
- Planned ablation procedure for AF at the time of surgery
- Emergency surgery
- Impaired prognosis defined as EuroSCORE II > 7% perioperative mortality at screening is exclusionary

The use of any concomitant medication, prescription or over-the-counter, including vitamins, and/or herbal supplements, is to be recorded in the participant's records at each visit along with the reason the medication is taken.

Screening may occur up to 28 days before randomization on Day 1, Visit 2.

An independent data safety monitoring board (DSMB) will meet throughout the course of this study.

Study visits after the index surgery may be conducted at the participant's home or other designated location in accordance with local ethics and/or IRB regulations, as well as with sponsor approval.

Number of Participants:

Approximately 400 participants will be screened to achieve approximately 330 randomly assigned to study intervention, in order to have an estimated 300 participants complete all the efficacy assessments up to Day 60 (100 participants per intervention group; Section 9.2).

Number of Sites:

It is projected that a total of approximately 20 to 40 sites (North America and Europe) will enroll participants.

Intervention Groups and Study Duration:

This Phase 2, placebo-controlled study will evaluate the efficacy and safety of one-time injections of AGN-151607 125 U (25 U per fat pad) and 250 U (50 U per fat pad) distributed across each of the 5 major epicardial fat pads for the prevention of POAF in participants undergoing open-chest cardiac surgery. Injections will be administered during the open-chest cardiac surgery. Primary and secondary efficacy will be assessed for 30 days post-surgery; participants will be followed for additional efficacy and safety through Day 367 post-surgery.

Prior to the database lock, an interim analysis of all efficacy data will be performed when all randomized participants have completed the Day 60 visit, or exited the study earlier.

Data Monitoring Committee: No

1.2. Schema

D = study day; TC = telephone call; U = units; V = Visit
[a] Hospital discharge could take more than 6 days.

1.3. Schedule of Activities (SoA)

Study Period	Screening[a]	Days 1 to 60									Day 61 through Day 360					Early Disc[c]
Visit Number	V1	V2	V3	V4[b]	V5[b]	V6[b]	V7[b]	TC1	V8	V9	V10	V11	V12	V13	TC2	
Day Number	(up to 28 days)	D1	D2	D3	D4	D5	D6	D14	D30	D60	D90	D180	D270	D360	D367[d]	
Visit Windows	-	-	-	-	-	-	-	± 3d	± 3d	± 3d	± 7d	± 7d	± 7d	± 7d	V13 + 7d (+ 7d)	-
Informed consent	X															
Inclusion and exclusion criteria	X[e]	X														
Demography	X															
Physical examination	X								X					X[f]		X
Medical history	X															
Urine pregnancy test (for women of childbearing potential)[e,g]	X	X														
Laboratory assessments[e,h]	X	X					X		X	X[i]	X[i]			X[i]		X
Sample collection for biomarker assessment[e]		X	X	X	X											
12-lead ECG[j]	X	X	X	X	X	X	X		X	X[k]	X[k]	X[k]	X[k]	X[k]		X
ECG patch		X	X	X	X	X	X	X	X[l]	X[m]	X[m]	X[m]	X[m]	X[m]	X	
Vital signs[e,n]	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Height	X															
Body weight and abdominal circumference	X													X		X
Dispense AF symptom diary and train participant on proper use[o]	X															
AF symptom diary review[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X														
Study intervention[p]		X														
Assessment of fat pads and injection procedure		X														
AE/SAE review[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PFT[r]	X								X							
Concomitant medication and concurrent procedure review[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening[a]	Days 1 to 60									Day 61 through Day 360					Early Disc[c]
Visit Number	V1	V2	V3	V4[b]	V5[b]	V6[b]	V7[b]	TC1	V8	V9	V10	V11	V12	V13	TC2	
Day Number	(up to 28 days)	D1	D2	D3	D4	D5	D6	D14	D30	D60	D90	D180	D270	D360	D367[d]	
Visit Windows	-	-	-	-	-	-	-	± 3d	± 3d	± 3d	± 7d	± 7d	± 7d	± 7d	V13 + 7d (+ 7d)	-
AFEQT	X								X		X	X				X[s]
AFSS	X								X		X	X				X[s]
DASI	X								X		X	X				X[s]
EuroSCORE II[t]	X															
SF-12v2	X								X		X	X				X[s]
EQ-5D-5L	X								X		X	X				X[s]
Record discharge from ICU		X	X	X	X	X	X									
Record discharge from hospital			X	X	X	X	X									
Record any additional healthcare resource utilization								X	X	X	X	X	X	X	X	X
Serum sampling for immunogenicity assessment[u]	X								X		X					

AE = adverse event; AF = atrial fibrillation; AFEQT = Atrial Fibrillation Effect on Quality-of-life Questionnaire; AFSS = University of Toronto Atrial Fibrillation Severity Scale; D(d) = day; DASI = Duke Activity Status Index; Disc = discontinuation; ECG = electrocardiogram; EQ-5D-5L = A measure of health-related quality of life developed by the EuroQol Group; FU = follow-up; ICU = intensive care unit; PFT = pulmonary function test; SAE = serious adverse event; SF-12v2 = Short Form-12 Health Survey, version 2; TC = telephone call; V = visit

[a] Screening and randomization activities can occur on the same day. If screening and randomization occur on the same day, all assessments for Visit 1 and Visit 2 should be completed. Duplicate assessments (eg, laboratory assessments) do not have to be completed twice; please note a 12-lead ECG is required both before and after surgery.

[b] These visits are optional and are only required if the participant is still hospitalized. Participants may remain in the hospital beyond Day 6, based on the recovery from surgery. The study visit procedures will have to be performed each day until discharge.

[c] In case of early discontinuation, attempts will be made to follow-up with the participant.

[d] Day 367 must be at least 7 days and should be no more than 14 days after Visit 13 (Day 360).

[e] On Day 1, assessments to be performed prior to surgery.

[f] Physical examinations should be conducted where feasible. If the participant cannot attend the study visit, then the physical examination can be omitted, after sponsor approval.

[g] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

[h] Laboratory assessments (hematology, chemistry, coagulation and urinalysis) to be performed at screening, Day 1 and day of discharge. The day of discharge can be from Day 3 onwards.

[i] Laboratory assessments should be conducted where feasible. If the participant cannot attend the study visit and/or an in-home assessment is not feasible, then the laboratory assessments can be omitted, after sponsor approval.

[j] On Visit 2, Day 1, two 12-lead ECGs will be performed; 1 before surgery and 1 after surgery. PFT should be performed at a reasonable time apart from vital signs and ECG to avoid confounding ECG and vital signs data.

[k] 12-lead ECGs should be conducted where feasible. If the participant cannot attend the study visit and/or an in-home assessment is not feasible, then the 12-lead ECG can be omitted, after sponsor approval.

[l] ECG patch must be worn for a full 30 days post-surgery, even if Day 30 visit occurs prior to Day 30 due to window allowance.

[m] ECG patch must be used during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits.

[n] Vital signs taken after a participant has been in a resting position for a minimum of 5 minutes; include blood pressure, pulse, respiration rate, and body temperature. On Visit 2, Day 1, vital signs will be measured before and after surgery.

[o] AF symptom diary must be used for first 30 days after surgery (or until early discontinuation if before Day 30) and during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits. The diary should be returned to the site and be part of the medical records.

[p] Unblinded site pharmacist or designee will prepare drug; injected by investigator who is blinded to study intervention.

[q] Method of detecting AEs and SAEs: care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

[r] Pulmonary function to be assessed using a spirometer and will include forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV_1), 3 seconds (FEV_3) and 6 seconds (FEV_6). Note, if local policies contraindicate or prohibit PFT assessments due to potential for viral spread or microbial precautions, then the PFT is not required after explicit approval from the sponsor.

[s] If participant withdraws after Day 180, these early discontinuation procedures will not be performed.

[t] Impaired prognosis defined as EuroSCORE II > 7% perioperative mortality at screening is exclusionary.

[u] Serum collection should be conducted where feasible. If the participant cannot attend the study visit and/or an in-home assessment is not feasible, then the serum collection can be omitted, after sponsor approval.

2. Introduction

Allergan has developed a botulinum toxin type A neurotoxin complex, AGN-151607, for the prevention of post-operative atrial fibrillation (POAF) in patients undergoing cardiac surgery. AGN-151607 will be injected intraoperatively into discrete targets of the heart, namely the epicardial fat pads near the pulmonary veins and atria. The administration of AGN-151607 is intended to neuromodulate the ganglionic plexi in these regions, thus lowering the risk of developing POAF.

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia with uncoordinated atrial activation and, consequently, ineffective atrial contraction (January 2014). Characteristics on an electrocardiogram (ECG) include:

1) Irregular R-R intervals
2) Absence of distinct P waves
3) Irregular atrial activity

AF is a common complication of cardiac surgery, occurring post-operatively in 30% to 60% of patients undergoing coronary artery bypass and/or cardiac valve surgical procedures, with an unchanged incidence over past decades (Mostafa 2012).

POAF is associated with recurrent AF, longer hospital stays (including in intensive-care settings), increased healthcare costs (in-hospital and post-discharge), higher risk of stroke, and increased mortality (Arsenault 2013; Kertai 2014; LaPar 2014; Mathew 2004); all of which reflect an increased clinical burden due to POAF, including the need for medical/procedural interventions.

Cardiac surgery via median sternotomy (open-chest or “open-heart” surgery) yields access to the epicardial fat pads, ie, the cardiac autonomic ganglionic plexi, which contain a rich network of nerves. These autonomic nerves have been targeted in several, customarily used ablative procedures to attenuate AF, both post-operative and more broadly. Surgical and catheter-based interventions (eg, ablations, surgical excisions of tissue) of the autonomic nervous tissue near the left atrial ostia of the pulmonary veins, including the epicardial fat pads, have demonstrated positive results in the prevention of recurrent AF (Katritsis 2011; Katritsis 2013; Pokushalov 2013; Gillinov 2016).

Based on 1) the effectiveness of ablative and surgical intervention on cardiac autonomic nerve foci, 2) the general safety of these procedures involving tissue disruption, and 3) a goal to avoid permanent destruction of cardiac tissue, temporary neuromodulation has been hypothesized to be an effective approach as preventative therapy of POAF in cardiac surgery patients. Pursuant to this hypothesis, several recent nonclinical and clinical studies were performed, showing that neuromodulation with botulinum toxin type A, injected into discrete epicardial fat pads at the time of open-chest surgery, reduces the incidence of POAF (Tsuboi 2002; Oh 2010; Oh 2011; Pokushalov 2015; Lo 2016; Waldron 2019). Nonclinical proof-of-concept studies have shown that injections of botulinum toxin type A into the epicardial fat pads of dogs in an open-chest cardiac surgical procedure, and using a rapid atrial pacing model of atrial arrhythmia, led to

suppression of AF and reduced vulnerability to provoked AF. No adverse safety findings were reported in these studies (Tsuboi 2002; Oh 2010; Oh 2011; Lo 2016).

Based on these findings, a clinical proof-of-concept study in 60 participants undergoing open-chest, coronary artery bypass grafting (CABG) cardiac surgery was conducted by an independent investigator (Pokushalov 2015). In this randomized, placebo-controlled, double-blind study, participants received epicardial injections of either botulinum toxin A (50 U of botulinum toxin A [incobotulinumtoxinA, Xeomin®] per fat pad; total of 200 U), or placebo, into 4 discrete fat pads. This study demonstrated that, over 30 days of follow-up, POAF occurred at a statistically significantly lower incidence in participants receiving intraoperative botulinum toxin type A injections (7% of participants) into epicardial fat pads compared with placebo injections (30% of participants). This study also reported that it was practical to administer botulinum toxin type A (total of 200 U) into the epicardial fat pads of these participants undergoing open-chest cardiac surgery and did not lead to safety problems, with follow-up through 3-years (Pokushalov 2015; Romanov 2019).

Following the Pokushalov publication, investigators at Duke University Medical Center conducted a clinical trial (Waldron 2019) in 130 participants undergoing open-chest, CABG and/or valve surgery. In this randomized, placebo-controlled, double-blind study, participants received epicardial injections of either botulinum toxin type A (50 U of botulinum toxin type A (onabotulinumtoxinA, [BOTOX®]) per fat pad; total of 250 U) or placebo into 5 discrete fat pads. This study demonstrated, over a mean follow-up of 6 days, that POAF occurred at a lower incidence in participants receiving intraoperative botulinum toxin type A injections (36.5% of participants) into epicardial fat pads compared with placebo injections (47.8% of participants). In addition, this study demonstrated that injections of a total of 250 U of botulinum toxin type A (50 U per fat pad) were safe and tolerable, with no increases in adverse events (AEs) or serious adverse events (SAEs) (Waldron 2019).

Based on the effectiveness and safety of targeting the ganglionic plexi of the cardiac autonomic nervous system to attenuate AF, the extensive nonclinical and clinical data with botulinum toxin type A (particularly, with onabotulinumtoxinA) administration for multiple indications and into different organ systems, and a sound mechanism for temporary neuromodulation in cardiac surgery patients, Allergan is developing a novel botulinum toxin type A intervention (AGN-151607) for the prevention of POAF to be administered during open-chest cardiac surgery.

AGN-151607 is a highly purified and animal- and human-product-free formulation of botulinum toxin type A. The mechanism of action of AGN-151607 is [redacted] Botulinum neurotoxins exert their effect on cholinergic motor nerve terminals through a sequential process: 1) binding to presynaptic cholinergic motor axon terminals, 2) internalization or entry into the nerve terminal, and 3) exertion of the pharmacologic action (ie, inhibition of acetylcholine release) within the nerve terminal; these processes have been documented for several types of nerves, including autonomic nerves, and are relevant for neuromodulation in autonomic epicardial targets.

Allergan designed this development program based on the problematic nature of POAF in patients, a long-standing unmet need (the paucity of safe and effective therapies), the encouraging results from nonclinical and initial clinical studies demonstrating temporary neuromodulation with botulinum toxin type A in open-chest cardiac surgery patients, and the general safety of botulinum toxin type A across multiple organs and patient types. If this development program demonstrates efficacy of AGN-151607, combined with an acceptable safety profile, then this will be the first effective, preventive treatment for POAF in more than 20 years and could thus reduce the clinical burden observed in these cardiac surgery patients.

2.1. Study Rationale

POAF occurs at high rates despite standard-of-care therapies and is associated with problematic outcomes, eg, medical/procedural interventions, extended length of stay in the intensive care unit (ICU) and hospital, and rehospitalization. Nonclinical studies have demonstrated that injections of botulinum toxin type A into discrete regions of the heart can prevent AF and 2 clinical studies have demonstrated that botulinum toxin type A injections can prevent POAF with no noted safety issues.

This Phase 2, placebo-controlled study will evaluate the efficacy and safety of one-time injections of AGN-151607 125 U (25 U per fat pad) and 250 U (50 U per fat pad) distributed across each of the 5 major epicardial fat pads for the prevention of POAF in participants undergoing open-chest cardiac surgery. Injections will be administered during the open-chest cardiac surgery. Primary and secondary efficacy will be assessed for 30 days post-surgery; participants will be followed for additional efficacy and safety through Day 367 post-surgery.

2.2. Background

POAF is a serious condition, associated with: recurrent AF, longer hospital stays (including in intensive-care settings), increased healthcare costs (in-hospital and post-discharge), higher risk of stroke, and increased mortality (Arsenault 2013; Kertai 2014; LaPar 2014; Mathew 2004); all of which reflect an increased clinical burden due to POAF, including the need for medical/procedural interventions.

Current standard-of-care therapies have been unable to successfully prevent POAF in cardiac surgery patients and most conventional therapies are applicable only after AF occurs. Thus, there is an unmet need in this patient population to prevent the occurrence of POAF. Recent non-clinical and clinical data suggest that neuromodulation with botulinum toxin type A, injected into discrete epicardial fat pads, can prevent POAF.

AGN-151607 is purified from [redacted] *Clostridium botulinum* [redacted]

A detailed description of the chemistry, pharmacology, toxicology of AGN-151607 is provided in the investigator's brochure (IB).

2.3. Benefit/Risk Assessment

Patients undergoing cardiac surgery are at a high risk of developing POAF. POAF is associated with a number of negative outcomes, such as need for medical/procedural interventions, extended length of stay in the ICU and hospital, and rehospitalization. Treatment with one-time injections of AGN-151607 may prevent the occurrence of POAF in these cardiac-surgery patients and thus represents a distinct potential for benefit. In addition, the injection of botulinum toxin type A into discrete epicardial fat pads has been shown to be safe and tolerable in cardiac surgery patients during 2 separate clinical trials, with up to 3 years of follow-up reported (Pokushalov 2015; Waldron 2019; Romanov 2019). Injections of AGN-151607 will be administered in addition to standard-of-care therapies, such as beta-blockers, as needed.

[redacted]

The AE profile of AGN-151607 has not yet been fully characterized in humans. However, extensive safety data are available from clinical studies and post-marketing experience with BOTOX. BOTOX experience is considered relevant to the current program, having a similar dose range and other similarities with AGN-151607, as outlined in the IB.

[redacted]

More detailed information about the known and expected benefits and risks and expected AEs of AGN-151607 may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	Primary efficacy
• To compare the efficacy of AGN-151607 with placebo to prevent post-operative atrial fibrillation (POAF) in participants who are undergoing open-chest cardiac surgery	• Percentage of participants with at least 1 continuous atrial fibrillation (AF) episode ≥ 30 seconds during the first 30 days post-surgery
Secondary	Secondary efficacy
• To compare the efficacy of AGN-151607 with placebo to reduce AF burden in participants who are undergoing open-chest cardiac surgery	• Percentage of time spent in AF (AF burden) during the first 30 days post-surgery • Percentage of participants with at least 1 event of symptomatic AF during the first 30 days post-surgery • Time to first occurrence of AF during the first 30 days post-surgery
• To compare the efficacy of AGN-151607 with placebo to prevent POAF using alternative definitions for AF in participants who are undergoing open-chest cardiac surgery	• Percentage of participants with at least 1 continuous AF episode ≥ 2 minutes during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 5 minutes during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 30 minutes during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 1 hour during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 4 hours during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 6 hours during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 12 hours during the first 30 days post-surgery • Percentage of participants with at least 1 continuous AF episode ≥ 24 hours during the first 30 days post-surgery
Safety	Safety assessments
• To compare the safety of AGN-151607 with placebo in participants undergoing open-chest cardiac surgery	• AEs, physical examination, clinical laboratory tests, vital signs, ECGs, pulmonary function • Potential immunogenicity response

Objectives	Endpoints
Additional	Additional efficacy
• To compare the clinical benefit of AGN-151607 with placebo in participants who are undergoing open-chest cardiac surgery	• Percentage of participants with clinically important tachycardia in AF (defined as heart rate ≥ 100 bpm for at least 2 minutes) • Percentage of participants needing pharmacologic intervention (ie, anticoagulation, antiarrhythmic drugs) during the first 30 days post-surgery due to AF • Percentage of participants needing pharmacologic intervention (ie, anticoagulation, antiarrhythmic drugs) from Day 31 to Day 360 post-surgery due to AF • Percentage of participants needing procedural intervention (ie, cardioversion, ablation, additional surgery) during the first 30 days post-surgery due to AF • Percentage of participants needing procedural intervention (ie, cardioversion, ablation, additional surgery) from Day 31 to Day 360 post-surgery due to AF • Time to first prescription of pharmacologic intervention due to POAF during the first 30 days post-surgery and length of time that prescription is taken • Time of POAF resolution from first dose of prescription of pharmacologic intervention • Time to first procedural intervention due to POAF during the first 30 days post-surgery • Time of POAF resolution from first procedural intervention due to AF • Length of stay in the ICU and reason • Length of stay in hospital and reason • Number of all-cause re-hospitalizations within 30 days post-discharge • Number of non-arrhythmia cardiovascular re-hospitalizations within 30 days post-discharge • Number of arrhythmia re-hospitalizations within 30 days post-discharge • Number of days spent in the hospital: within 30 days post-discharge and within 60 days post-surgery • Percentage of participants with any occurrence of AF as defined in the primary and secondary endpoints during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits • Percentage of time spent in AF (AF burden) during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits • Percentage of participants with at least 1 event of symptomatic AF during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits

Objectives	Endpoints
Tertiary/Exploratory	
[redacted]	

4. Study Design

4.1. Overall Design

This is 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 POAF in participants undergoing open-chest cardiac surgery. It is projected that a total of approximately 20 to 40 sites (North America and Europe) will enroll a total of approximately 330 participants for this Phase 2 study.

There will be a total of 3 intervention arms randomized in 1:1:1 fashion to receive a one-time injection of:

- 125 U of AGN-151607 (25 U per fat pad)
- 250 U of AGN-151607 (50 U per fat pad)
- Placebo

The randomization will be stratified by age (< 65, ≥ 65 years) and type of surgery (presence/absence of valve surgery).

This study intervention will be the administration of a one-time injection of either placebo or AGN-151607 during the open-chest surgery. Primary and secondary efficacy assessments will be performed through Day 30. Additional and exploratory assessments will be assessed through Day 367. All participants will be followed through Day 367 for safety assessments. POAF usually occurs within 2 to 5 days of surgery. However, Pokushalov et al (Pokushalov 2015), found in their study that episodes of POAF were recorded up to 18 days after surgery. Therefore, a 30-day cut off for the primary endpoint is appropriate to mostly fully capture occurrences of POAF. Assessments of clinical benefits and resource-utilization are customarily over a period of 60 days post-surgery (Gillinov 2016). Accordingly, a 60-day cut off was selected for this study to capture resource-utilization outcomes. Finally, based on prior clinical data, the effect of botulinum toxin type A is estimated to be 3 to 6 months. There will be a 12-month follow-up for the study.

Inflammation plays a key role in the etiology of multiple cardiac conditions including the development of POAF. The mechanism of action of AGN-151607 [redacted].

Approximately 400 participants will be screened to achieve approximately 330 randomly assigned to study intervention, in order to have an estimated 300 participants complete all the efficacy assessments up to Day 60 (100 participants per intervention group; Section 9.2).

One database lock is planned for this study and will occur when all participants have completed the study or exited earlier. Prior to the database lock, an interim analysis of all efficacy data will be performed when all randomized participants have completed the Day 60 visit or exited the study earlier. The final analysis will occur when all participants have completed the 12-month safety follow-up or have exited the study earlier. The details of all analyses will be provided in the SAP which will be finalized before the interim analysis.

An independent data safety monitoring board (DSMB) will meet throughout the course of this study.

4.1.1. Clinical Hypotheses

Injection of AGN-151607 into epicardial fat pads near the pulmonary veins and atria will prevent the occurrence of POAF, reduce the incidence of negative outcomes known to be associated with POAF, favorably impact health care resources utilization, and be well-tolerated and safe in patients undergoing open-chest cardiac surgery.

4.2. Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, dose-ranging study to assess the efficacy and safety of a one-time injection of AGN-151607 in open-chest cardiac surgery participants. The use of placebo is justified as all participants will receive standard-of-care therapies, such as beta-blockers. Participants who experience POAF during the trial will be treated as per investigator judgement and local standards of care. All medications and procedures will be recorded. AF symptoms and quality of life outcomes will be collected through patient reported assessments.

4.3. Justification for Dose

There are 2 doses of AGN-151607 which will be tested: 250 U and 125 U.

The highest dose planned for this study is 250 U (50 U per epicardial fat pad) of AGN-151607. The dose was selected based on prior clinical experience. There have been 2 clinical trials conducted by external investigators which have injected 50 U per fat pad of botulinum toxin type A (non-AGN-151607) in cardiac-surgery participants. One of these trials injected a total of 250 U of BOTOX (50 U into 5 epicardial fat pads; Waldron 2019) and the other injected a total of 200 U of Xeomin (50 U into 4 epicardial fat pads; Pokushalov 2015; Romanov 2019). In both studies, these doses were found to be safe and well-tolerated.

The lower dose planned for this study is 125 U (25 U per epicardial fat pad) of AGN-151607. This dose was selected to determine whether a lower dose would provide a similar efficacy and safety profile as the higher dose.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities (SoA, Section 1.3) for the last participant in the study globally. A participant is considered to have completed the primary and secondary efficacy part of the study if he/she has completed the Day 60 (Visit 9). A participant is considered to have completed the full study if he/she has completed the Day 367.

5. Study Population

The study population consists of participants undergoing open-chest cardiac surgery who have given informed consent to participate.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Participants must be 55 to 90 years of age, inclusive, at the time of signing the informed consent.
2.	**Type of Participant and Surgical Characteristics**
2.01	Participants who are scheduled to undergo open-chest cardiac surgery. Includes: coronary artery bypass graft (CABG) and/or valve repair/replacement. Inclusionary valve repair/replacement procedures for the primary reason for surgery include: • Aortic valve repair/replacement • Mitral valve repair/replacement • Combination of aortic and tricuspid valve repair/replacement • Combination of mitral and tricuspid valve repair/replacement • CABG/valve combination procedures (when valvular procedure is one of the 4 sub-bulleted procedures immediately above) • Left Atrial Appendage (LAA) procedures are allowed if CABG and/or valve repair or replacement is the qualifying surgical procedure, but is not a qualifying surgical procedure on its own.
3.	**Sex**
3.01	Male or female

4.	**Contraceptives**
4.01	Male participants willing to minimize the risk of inducing pregnancy up to Day 60.
	A male participant must agree to use contraception as detailed in Appendix 7, Section 10.7 of this protocol until Day 60 and refrain from donating sperm during this period.
4.02	Female participants willing to minimize the risk of inducing pregnancy up to Day 60. A female participant is eligible to participate if she is not pregnant (has a negative urine pregnancy result prior to randomization) not breastfeeding, and at least 1 of the following conditions applies: a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 7, Section 10.7 OR b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 7, Section 10.7 of this protocol until after Day 60.
5.	**Informed Consent**
5.01	Capable of giving signed informed consent as described in Appendix 1, Section 10.1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
5.02	Written informed consent from the participant has been obtained prior to any study-related procedures.
5.03	Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data Protection consent (European Union [EU] sites).
6.	**Other**
6.01	In sinus rhythm for the last 48 hours prior to randomization based on standard-of-care assessments and study ECGs (note: continuous ECG monitoring for 48 hours is not required; prior history of paroxysmal AF is acceptable).
6.02	Willing to wear an ECG patch for a full 30 days post-surgery and for 7 days after each study visit
6.03	Able, as assessed by the investigator, and willing to follow study instructions and likely to complete required study visit.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Any uncontrolled clinically significant medical condition other than the one under study that, in the investigator's opinion, would put the participant at an unacceptable risk with exposure to botulinum toxin type A.
1.02	Any medical condition that may put the participant at increased risk with exposure to botulinum toxin type A, including diagnosed muscular dystrophy (eg, Duchenne's muscular dystrophy), myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, mitochondrial disease, or any other significant disease which might interfere with neuromuscular function.
1.03	Participants with presence or history of any of the following within 3 months prior to the Day 1 visit that may indicate a vulnerable respiratory state per the investigator's clinical judgment: aspiration pneumonia, lower respiratory tract infections, uncontrolled asthma, severe chronic obstructive pulmonary disease, or otherwise compromised respiratory function.
1.04	Permanent/persistent AF
1.05	Has a known allergy or sensitivity to any botulinum toxin type A preparation
1.06	Has a known allergy or sensitivity to medical adhesive (eg, ECG patch adhesive; hydrogel-based adhesive)
1.07	Severe (> 55 mm left atrial diameter) left atrial enlargement
1.08	Left ventricular ejection fraction (LVEF) < 25%
1.09	Presence or history of symptomatic atrioventricular block > 1st degree within the last 30 days (note: presence of a pacemaker is not exclusionary per se)
1.10	Exclusionary valve repair/replacement procedures include: • Combination of aortic and mitral valve repair/replacement • Isolated tricuspid valve repair/replacement
2.	**Prior/Concomitant Therapy**
2.01	Class I or III antiarrhythmic drugs unless proper washout was documented (Section 6.5.1)

2.02	Botulinum toxin type A (of any serotype) use within 6 months of randomization
2.03	Has been immunized for any botulinum toxin type A serotype as determined by participant medical history
2.04	Preoperative need for inotropes/vasopressors or intra-aortic balloon pump
2.05	Prior open-chest, sternotomy cardiac surgery
2.06	History of ablation for AF
2.07	Planned ablation procedure for AF at the time of surgery
2.08	Emergency surgery
3.	**Prior/Concurrent Clinical Study Experience**
3.01	Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study
4.	**Diagnostic Assessments**
4.01	Participants have diagnostic assessments which in the opinion of the investigator prevent participation in the study.
4.02	Impaired prognosis defined as EuroSCORE II > 7% perioperative mortality at screening is exclusionary.
5.	**Other**
5.01	Females who are pregnant, nursing, or planning a pregnancy during the study
5.02	The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study.

Rationale for Inclusion and Exclusion Criteria

- Inclusion criterion 1.01 is to ensure appropriate age of the study population since increased age is associated with higher occurrence of POAF.
- Inclusion criterion 2.01 is to ensure that fat pads are accessible as part of the standard surgical procedure.
- Inclusion criterion 3.01 is to ensure that the study population is representative of the target population which comprises male and female participants.

- Inclusion criteria 4.01 and 4.02 are to minimize risk of pregnancy during the first 60 days of the study. Regarding 4.02 and female participants, the risk of pregnancy will be also minimized by the age criteria.
- Inclusion criteria 5.01 to 5.03 are to ensure protection of the study participants through the informed consent process.
- Inclusion criterion 6.01 is to ensure participants have no detected arrhythmias in the 48 hours prior to surgery that could impact study conduct.
- Inclusion criteria 6.02 and 6.03 is to ensure quality of the study data.
- Exclusion criteria 1.01 to 1.09 are necessary to prevent participants with medical conditions that could increase the risk of AEs with exposure to botulinum toxin type A preparation or have conditions that could confound the results of the study in the analysis of efficacy.
- Exclusion criterion 2.01 is necessary to avoid antiarrhythmic medications so any efficacy the study intervention may have is not reduced.
- Exclusion criteria 2.02 and 2.03 are necessary to avoid any effects of prior botulinum toxin type A or prior surgical procedures influencing the results.
- Exclusion criteria 2.04 to 2.08 are to ensure absence of prior cardiac procedures that may influence POAF and confound the study results.
- Exclusion criterion 3.01 is customary in clinical trials and is necessary to prevent interactions with other investigation products.
- Exclusion criteria 4.01 and 5.02 are necessary to ensure the protection and well-being of the study participants.
- Exclusion criterion 4.02 is to ensure that the perioperative risk of death is compatible with the intended study follow-up duration.
- Exclusion criterion 5.01 is to ensure protection of the fetus and mother during pregnancy.

5.3. Lifestyle Considerations

The ECG-acquisition patch cannot be submerged in water and participants should comply with all other restrictions necessary, ie, those customarily required of patients undergoing open-chest cardiac surgery.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AE.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened unless authorized by the sponsor.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

AGN-151607 is not currently authorized or licensed in any country worldwide.

6.1. Study Intervention Administered

Each of the 5 fat pads must be injected as part of the study procedure. However, in the event where 1 fat pad is missing or is not accessible, the injection procedure can continue and only 4 mL of interventional product or placebo shall be injected. If, upon initial evaluation (ie, injections have not yet occurred), 3 fat pads or fewer are accessible, the injection procedure should be aborted. If any injections of study intervention have already been made when the surgeon determines they are unable to inject 4 or more fat pads, the participant should remain in the study.

Table 6-1 Treatments Administered

Study Intervention Name	AGN-151607	Placebo
Dosage Formulation	[redacted]	
Unit Dose Strength(s)	250 U, 125 U	Not applicable
Route of Administration	Injection into epicardial fat pads	Injection into epicardial fat pads
Dosing Instructions*	Injections of 25 U or 50 U will be made into each 1 of 5 fat pads as described in Section 6.3. The total injection volume in to each fat pad will be 1 mL.	Injections of placebo will be made into each 1 of 5 fat pads as described in Section 6.3. The total injection volume in to each fat pad will be 1 mL.
Packaging and Labeling	Study intervention will be provided in a blinded carton container containing 3 AGN-151607 (50 U or 200 U) vials. Each vial will be labeled as required per country requirement.	Placebo will be provided in a blinded carton container containing 3 vials visually identical to the study intervention. Each vial will be labeled as required per country requirement.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the pre- and intra-operative handling of study interventions, and for the final disposition of unused study interventions, will be provided by the sponsor.

All unused study intervention and used kits should be returned to the sponsor or designee at the termination of the study. Unit counts will be performed when the study intervention is returned, and all study intervention must be accounted for. Accountability logs for destroyed materials should be maintained at the site to ensure all study intervention is accounted for. Study intervention may be destroyed on site if required by local/institutional policies after sponsor approval of destruction process and documentation.

Details on the reconstitution and handling of AGN-151607 can be found in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

At screening, each participant who provides informed consent will be assigned a number that will serve as the participant identification number on all study documents.

An automated Interactive Web Response System (IWRS) assigns the participant's identification number and this will be used to manage the randomization and intervention assignment based on a centralized randomization list prepared by Allergan Biostatistics. The randomization will be stratified by age (< 65, ≥ 65 years) and type of surgery (presence/absence of valve surgery). Within each stratification group, participants will be randomly assigned to one of the intervention groups in a 1:1:1 ratio. Before the study is initiated, the log-in information and instructions for the IWRS will be provided to each site.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

At each study site, a designated staff member will serve as the independent drug reconstitutor (IDR). This person will be responsible for study intervention preparation.

The IDR will prepare the study intervention as described in the Pharmacy Manual. The investigator will inject the reconstituted study intervention according to the study intervention

administration instructions. Administration instructions are further detailed in the Surgical Manual.

The injection volume and intervention administration will be identical for each participant whether they are assigned to the 250 U dose, 125 U dose, or the placebo group.

To maintain data integrity for the study while it is still ongoing, sponsor personnel responsible for performing the interim analysis will be different from the project team personnel who manage and maintain the study conduct activities, including data collection, data clarification, analysis development, safety monitoring, and investigational site monitoring and management.

The project team personnel will be prohibited from accessing the unmasked interim results.

Blinding is critical to the integrity of the clinical trial. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment of the participant. If a participant's study intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

6.4. Study Intervention Compliance

Participants will receive a single dose of AGN-151607 under the direct supervision of study site personnel.

The study site will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

6.5. Concomitant Therapy

The use of any concomitant medication, prescription or over-the-counter, including vitamins, and/or herbal supplements, is to be recorded in the participant's records at each visit along with the reason the medication is taken.

6.5.1. Prohibited Interventions and Washout Before the Study

Participants must discontinue any of the medications listed in Table 6-2 for the specified period prior to surgery. Other medications being used at screening may be continued.

Table 6-2 Prohibited Medications with Required Washout Period

Drug Class/Treatment	Washout Required Prior to Surgery
Class I or Class III antiarrhythmic drugs (eg, amiodarone)	At least 5 half-lives or 5 days, whichever is the longest. In the case of amiodarone, 90 days washout is required.
All types of botulinum toxins	At least 6 months since last treatment with any botulinum toxin

6.5.2. Permitted Interventions

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose, route of administration, and frequency

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/intervention is in question, please contact the sponsor.

The sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.3. Rescue Medicine or Procedure

There will be no rescue medication provided by the sponsor for the study.

Standard-of-care will be used at investigator discretion. The study site will supply medications that will be obtained locally, eg, antiarrhythmics drugs, anticoagulants (eg, anti-vitamin K agents, heparin) and rate-control medication (eg, esmolol, metoprolol, diltiazem).

Standard-of-care is allowable at any time during the study. The date and time of any medication administration, as well as the name, indication, and dosage regimen of the medication (ie, dose, route of administration, and frequency), should be recorded.

An intervention to treat an arrhythmia is allowed during follow-up as clinically warranted in the judgement of the treating physician and/or site-based investigator physician.

6.5.4. Prohibited Interventions During the Study

Please refer to Section 6.5.1 for prohibited interventions during the washout period prior to surgery.

Administration of aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution for 60 days post-surgery, as the effect of the toxin may be potentiated.

6.5.5. Anticoagulation and Stroke Prevention

For participants for whom anticoagulation is indicated, treatment should be provided according to local or organization standards with the goal of achieving *at least one* of the following outcomes prior to discharge:

1) If treated with warfarin, participant must have achieved a target International Normalized Ratio (INR) of 2.0 to 3.0
2) If "bridged" with low molecular weight heparin, participant can be discharged with an INR of less than 2.0

3) If treated with non-vitamin K antagonist oral anticoagulants (NOACs), international guidelines do not mandate routine coagulation testing nor recommend target INR. The investigator should refer to the drug prescribing information for more precise guidance in situation when assessment of the anticoagulation effect is useful.
4) If they are deemed by the site principal investigator to be stable for discharge from an anti-coagulation standpoint

6.6. Dose Modification

Not applicable.

6.7. Intervention after the End of the Study

There will be no intervention following the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and is dosed ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented.

The sponsor should be consulted in advance of withdrawal whenever possible. Every effort should be made to retain participants in the study until completion as much as possible. Participants who are withdrawn from the study may not be re-enrolled but will be asked to undergo all early withdrawal activities. Definitions of the standard terms are provided in Appendix 5, Section 10.5.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Lost to follow-up	
Other	
Physician decision	
Pregnancy	
Protocol deviation	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

7.1. Discontinuation of Study Intervention

Not applicable for a one-time intervention.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. The investigator should follow-up with the sponsor so that any samples can be destroyed.

- See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. In case of early discontinuation, attempts will be made to follow-up with the participant.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Visits 4, 5, 6, and 7 are optional and are only required if the participant is still hospitalized. Participants may remain in the hospital beyond Day 6, based on the recovery from surgery. The study visit procedures will have to be performed each day until discharge.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue in the study.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.
- Study visits after the index surgery may be conducted at the participant's home or other designated location in accordance with local ethics and/or IRB regulations, as well as with sponsor approval.
- Procedures conducted as part of the participant's routine clinical management (eg, chest X-ray or echocardiography) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA. However, testing of blood samples (including during unscheduled visits or samples for which local laboratory values are already available) should be conducted by the central laboratory.
- Local laboratory results are required only in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. Local laboratory results collected at the screening visit can be used to determine participant's eligibility if central laboratory results are not available. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

For the primary, secondary, and additional endpoints, AGN-151607 intervention arms will be compared with placebo. These comparisons are further described in Section 9.4.1.

8.1.1. Occurrence of Post-Operative Atrial Fibrillation

The occurrence of POAF will be monitored through Day 30 and for 7 days after each of the following study visits: Day 60, Day 90, Day 180, Day 270, and Day 360 by ECG patches placed on the upper left region of the chest (Table 8-1).

Table 8-1 Assessment of Post-Operative Atrial Fibrillation

Assessment	Timing	Criteria
Occurrence of POAF[a]	Through Day 367 (continuously through Day 30 post-surgery and during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits)	As measured by ECG: 1. Continuous AF ≥ 30 seconds[b] 2. Continuous AF ≥ 2 minutes 3. Continuous AF ≥ 5 minutes 4. Continuous AF ≥ 30 minutes 5. Continuous AF ≥ 1 hour 6. Continuous AF ≥ 4 hours 7. Continuous AF ≥ 6 hours 8. Continuous AF ≥ 12 hours 9. Continuous AF ≥ 24 hours
Time to first occurrence of POAF	Through Day 367 (continuously through Day 30 post-surgery and during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits)	As measured by ECG: 1. Continuous AF ≥ 30 seconds 2. Continuous AF ≥ 2 minutes 3. Continuous AF ≥ 5 minutes 4. Continuous AF ≥ 30 minutes 5. Continuous AF ≥ 1 hour 6. Continuous AF ≥ 4 hours 7. Continuous AF ≥ 6 hours 8. Continuous AF ≥ 12 hours 9. Continuous AF ≥ 24 hours

AF = atrial fibrillation; ECG = electrocardiogram; POAF = post-operative atrial fibrillation
[a] Multiple AF ***events*** may occur within 30 days
[b] Continuous AF ≥ 30 seconds is the primary endpoint
[c] Follow-up through Day 30 will be the primary endpoint and 7-day follow-up periods will be part of the exploratory endpoints

8.1.2. Primary Efficacy Assessments

The primary efficacy assessment will measure the occurrence of POAF (ie, 30-second cutoff for continuous AF) during the first 30 days post-surgery (Table 8-1).

8.1.3. Secondary Efficacy Assessments

Secondary endpoints will include assessments of the occurrence of POAF according to different definitions of AF (ie, different timing cutoffs for continuous AF), time to first occurrence of POAF, percentage of time spent in AF (AF burden), and percentage of participants with at least 1 event of symptomatic AF, during the first 30 days post-surgery.

8.1.3.1. Percentage of Time Spent in Atrial Fibrillation

ECG patches will continuously monitor for all occurrences and durations of AF through Day 30 (Table 8-2). Based on this information, an analysis will measure the total time spent in AF divided by the time spent in the study. The resulting calculation will represent the percent of time each participant has spent in AF during the first 30 days post-surgery (AF burden).

Table 8-2 Assessment of Atrial Fibrillation Burden

Assessment	Timing	Measurement
Percentage of time spent in AF	Through Day 30	• Continuous ECG monitoring will allow for determining total time spent in AF. This will then be divided by the time spent in the study.

AF = atrial fibrillation; ECG = electrocardiogram

8.1.3.2. Symptomatic Post-operative Atrial Fibrillation

The occurrence of POAF is often associated with the onset of particular symptoms, such as dizziness, palpitations, and fatigue. All participants will be wearing ECG patches with the ability to mark the date and time that a symptom is experienced by simply pressing a button on the ECG patch itself (Table 8-3). While the participant is wearing the ECG patch, if symptoms of AF occur, the actual symptom will be documented by the participant in a symptom diary. Participants will be instructed by the site staff or designee on the appropriate completion of the symptom diary and instructions will be included with each diary.

Table 8-3 Assessment of Symptomatic Post-operative Atrial Fibrillation

Assessment	Timing	Measurement
Occurrence of symptomatic POAF	Through Day 30 and for 7 days after each of the following study visits: Day 60, Day 90, Day 180, Say 270, and Day 360	• Participants will press their ECG patch when they experience a symptom and then log the symptom in a diary. The information will be used to identify cases of symptomatic POAF.

AF = atrial fibrillation; ECG = electrocardiogram; POAF = post-operative atrial fibrillation

8.1.3.3. Clinically Important Tachycardia in Atrial Fibrillation

Clinically important tachycardia in AF is defined as heart rate ≥ 100 bpm for at least 2 minutes. The occurrence of clinically important tachycardia in AF is often associated with the need for pharmacologic or procedural interventions and is therefore likely to be associated with higher resources utilization. Evidence for clinically important tachycardia in AF will be acquired using ECG patches and/or hospital monitoring.

8.1.4. Additional Efficacy Assessments

Additional efficacy endpoints will include assessments of the occurrence of POAF, time to first occurrence of POAF, percentage of time spent in AF (AF burden), and percentage of participants with at least one event of symptomatic AF, based on continuous monitoring of all occurrences of AF during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits, as described in Section 8.1.1, and Section 8.1.3.

8.1.4.1. Need for Medical Intervention

If POAF occurs in cardiac-surgery participants, it is at the discretion of the investigator whether to intervene with customary, accepted treatments of pharmacologic therapies and/or medical procedures (Table 8-4). Such interventions will be captured as additional endpoints, and will support assessing the potential burden caused by the occurrence of POAF.

Table 8-4 Assessment of Pharmacologic Therapies and/or Medical Procedures

Assessment	Timing	Measurement
Pharmacologic intervention (ie, anticoagulation, antiarrhythmic drugs)	Through Day 367	• Timing of prescription and whether it was prescribed due to occurrence of POAF • Length of prescription • Timing of AF resolution, if available
Procedural intervention (ie, cardioversion, pacemaker implantation, ablation, additional ***cardiac*** surgery)	Through Day 367	• Timing of procedure and whether it was assigned due to the occurrence of POAF • Timing of AF resolution, if available

AF = atrial fibrillation; POAF = post-operative atrial fibrillation
A composite endpoint composed of pharmacologic and procedural interventions will also be analyzed.

8.1.4.2. All-cause Length of Stay in the Intensive Care Unit and Hospital

All participants will be in-hospital for the CABG and/or valve surgery. The all-cause length of stay in ICU and discharge to a regular ward and the all-cause length of stay in hospital will be recorded.

Table 8-5 Assessment of All-cause Length of Intensive Care Unit and Hospital Stay

Assessment	Timing	Measurement
Length of stay in the ICU	Through hospital stay	• Time of discharge from ICU to a regular ward • If participant remains in the ICU, reasons must be documented
Length of stay in hospital	Through hospital stay	• Time of discharge from hospital • If participant remains in the hospital, reasons must be documented

ICU = intensive care unit

8.1.4.3. Length of Stay in the Intensive Care Unit and Hospital based on Atrial Fibrillation Status

The length of ICU and hospital stay are dependent on a number of factors, one of which is the occurrence of POAF (Table 8-6). Length of stay in ICU and reason for ICU stay will be recorded. Recommendation for successful anticoagulation therapy if indicated is available in Section 6.5.5.

Table 8-6 Assessment of Length of Intensive Care Unit and Hospital Stay Based on Atrial Fibrillation Status

Assessment	Timing	Measurement
Length of stay in the ICU	Through hospital stay	• Time of discharge from ICU to a regular ward • Reason for ICU stay must be documented, including if it was AF-related
Length of stay in hospital	Through hospital stay	• Time of discharge from hospital • Reason for hospital stay must be documented, including if it was AF-related

AF = atrial fibrillation; ICU = intensive care unit; POAF = post-operative atrial fibrillation

8.1.4.4. Re-hospitalization and Days Spent in Hospital

Re-hospitalizations within 30 days after discharge will be logged with the reason(s) for the re-hospitalization (Table 8-7). In addition, all days spent in the hospital within 60 days after the surgery will be logged with the reason(s) for the re-hospitalization.

Table 8-7 Assessment of Re-Hospitalizations Within 30 Days After Discharge

Assessment	Timing	Measurement
30-day re-hospitalization	Through Day 30 post-discharge	• Number of all-cause hospitalizations within 30 days post-discharge • Number of non-arrhythmia cardiovascular hospitalizations within 30 days post-discharge • Number of arrhythmia hospitalizations within 30 days post-discharge • Binary measure (Y/N) of all-cause hospitalizations within 30 days post-discharge • Binary measure (Y/N) of non-arrhythmia cardiovascular hospitalizations within 30 days post-discharge • Binary measure (Y/N) of arrhythmia hospitalizations within 30 days post-discharge
Days in hospital 60 days after surgery	Through Day 60 post-surgery	• Number of days spent in the hospital within 60 days post-surgery for all-cause hospitalizations • Number of days spent in the hospital within 60 days post-surgery for non-arrhythmia cardiovascular hospitalizations • Number of days spent in the hospital within 60 days post-surgery for arrythmia hospitalization

8.1.5. Additional Endpoints

8.1.5.1. Patient Reported Outcomes

Planned timepoints for all patient reported outcomes (PROs) assessments are provided in the SoA (Section 1.3).

Several PROs will be utilized during this study (Table 8-8) to evaluate the impact of intervention on AF symptoms, activities of daily living, and health-related quality of life.

Table 8-8 Patient Reported Outcomes

Assessment	Timing	Measurement
AFEQT	Screening, Day 30, Day 90, Day 180, (or early discontinuation if necessary[a])	• A questionnaire to assess Health Related Quality of Life (HRQoL) in patients with AF. AFEQT evaluates QoL across 3 domains: symptoms, daily activities and treatment concerns. The questionnaire uses 20 questions on a 7-point Likert scale to measure the overall AFEQT score and treatment satisfaction. • The estimated time to complete the AFEQT questionnaire is approximately 5 to 10 minutes.
AFSS	Screening, Day 30, Day 90, Day 180, (or early discontinuation if necessary[a])	• A self-reported, disease-specific quality of life instrument used to capture subjective and objective ratings of disease burden in patients with AF. The AFSS consists of 19 items. It contains a visual analogue scale, 4 items on AF frequency, duration and severity that are used to calculate AF burden, 4 items on health care utilization, and 7 items regarding the severity of specific symptoms. • The estimated time to complete the AFSS is 5 to 10 minutes.
DASI	Screening, Day 30, Day 90, Day 180, (or early discontinuation if necessary[a])	• A 12-item, self-administered questionnaire which provides a standardized assessment of functional status that uses the patient's ability to perform a set of common activities of daily living to gauge functional capacity. • The estimated time to complete the DASI questionnaire is approximately 5 minutes.
EQ-5D-5L	Screening, Day 30, Day 90, Day 180, (or early discontinuation if necessary[a])	• A standardized measure of health-related quality of life comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The scores on these 5 dimensions can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles. • The estimated time to complete the EQ-5D-5L questionnaire is approximately 5 minutes.
SF-12v2	Screening, Day 30, Day 90, Day 180, (or early discontinuation if necessary[a])	• A 12-item, self-administered health survey standardized across age, disease, and treatment group to measure. Eight health domain scales contribute to the scoring of both the Physical and Mental Component Summary measures. • The estimated time to complete the SF-12v2 questionnaire is approximately 5 to 10 minutes.

AF = atrial fibrillation; AFEQT = Atrial Fibrillation Effect on Quality-of-life Questionnaire; AFSS = University of Toronto Atrial Fibrillation Severity Scale; DASI = Duke Activity Status Index; EQ-5D-5L = A measure of health-related quality of life developed by the EuroQol Group; SF-12v2 = Short Form-12 Health Survey, version 2

[a] If participant withdraws after Day 180, these early discontinuation procedures will not be performed

8.1.6. Exploratory Endpoints

[redacted]

[redacted]

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- BP and pulse measurements will be assessed in a resting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured after 5 minutes of rest and will include temperature, systolic and diastolic BP, pulse, and respiratory rate. Three readings of BP and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

8.2.3. Electrocardiograms

- Sites or designee shall transmit all study-required ECGs obtained to the ECG vendor. If multiple ECGs have been obtained for the same participant on the same date, the first readable ECG shall be entered as the visit ECG, and all others shall be entered as unscheduled. All readable ECGs received by the vendor shall be sent for ECG vendor, cardiologist over-read. The sponsor will receive all ECG data, including vendor cardiologist assessments, in the data transfer, including those ECGs that could not be evaluated.
- On Visit 2, Day 1, two 12-lead ECGs will be performed; 1 before surgery and 1 after surgery.
- A 12-lead ECG will be obtained in the supine or semi-recumbent position as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- The X-axis speed will be a standard 25 mm per second; the ECG tracing will be kept at the study site. Measurements will be recorded for the following parameters in lead II or lead III: heart rate, PR interval, QRS duration, QT interval, and QTc. All ECGs will be clinically interpreted by the investigator or sub-investigator.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2, Section 10.2, for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
  - The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significant during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2, Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5. Pulmonary Function Testing

Study participant pulmonary function will be assessed at the screening visit and Day 30 using forced procedures and compared across all 3 study groups (refer to study reference guide). Note, if local policies contraindicate or prohibit PFT assessments due to potential for viral spread or microbial precautions, then the PFT is not required after explicit approval from the sponsor. If PFT assessments are not prohibited by local regulations/policies, then the PFTs should be conducted.

Spirometry testing will be conducted by a pulmonologist, pulmonary technician, respiratory therapist, nurse, and/or other appropriate personnel trained in this procedure, following the American Thoracic Society (ATS) Standardization of Spirometry guidelines (Miller, 2005). To demonstrate reproducibility of results, participants will be required to perform at least 3 acceptable spirometry maneuvers up to a maximum of 8 attempts. The results of all respiratory measures will be reviewed for clinically significant findings.

The assessments will include the following:

1. Forced vital capacity (FVC) measured from a maximal forced exhalation
2. Forced expiratory volume (FEV) in 1 second (FEV_1), 3 seconds (FEV_3) and 6 seconds (FEV_6)

8.2.6. Suicidal Risk Monitoring

Not applicable.

8.2.7. Immunogenicity Assessments

Blood samples will be collected from all participants prior to dosing on Day 1 and at the Day 30 and Day 90 follow-up visits. A 2-tier assay approach will be used for the detection of binding and neutralizing antibodies to AGN-151607 in human serum. In tier 1, serum samples will be screened using a validated enzyme-linked immunosorbent assay (ELISA). The positive samples will subsequently be immune depleted to confirm that the antibodies were specifically binding to AGN-151607 and then titered to assess the magnitude of antibodies present. In tier 2, only samples that are considered positive in the ELISA will be tested for neutralizing antibodies to AGN-151607 using a validated assay.

Samples may be stored for a maximum of 2 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to AGN-151607.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3, Section 10.3.

AEs will be reported by the participant or, when appropriate, by a caregiver.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs/SAEs from the signing of the ICF until the Day 367 follow-up visit/early discontinuation visit will be collected at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent, will be recorded as an AE.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3, Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Section 10.3. Assessment of causality to both the study intervention and the study procedures are required for reporting each SAE. For the purpose of causality assessment, "study procedure" on the SAE reporting form means the procedure of injecting the study intervention into the

epicardial fat pads. It does not include any other study procedures (eg, the open-chest surgery and related procedures). Therefore, the check box on the SAE form titled "Causal Relationship to Study Procedure" should only be checked if, in the investigator's judgement, the SAE was related to the injection procedure into the epicardial fat pads. The cardiac surgery procedure that the study participant is undergoing (eg, CABG and/or valve repair/replacement) and any other procedures the participants may have during the study are NOT considered the study procedure for the purpose of SAE reporting causality assessment.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs and non-serious AEs of special interest (as defined in Section 8.3.6)] will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, if done, including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)s/independent ethics committees (IECs), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until Day 60.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7, Section 10.7.
- Abnormal pregnancy outcomes (eg, spontaneous or elective abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

An AE of special interest (AESI) for botulinum toxin type A, is possible distant spread of toxin (PDSOT). See Section 9.4.2.1 for further details.

8.3.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study intervention.

Overdose: Unintentional administration of a quantity of the study intervention AGN-151607 given per administration that is above the maximum recommended dose according to the protocol for the study intervention. An overdose for this study will be any dose of AGN-151607 exceeding the higher assigned dose specified in the protocol (ie, more than 250 U)

Underdose: Unintentional administration of a quantity of the study intervention AGN-151607 given per administration that is under the minimum recommended dose according to the protocol. An underdose for this study will be any dose of AGN-151607 less than the lower assigned dose specified in the protocol (ie, less than 125 U).

8.4. Treatment of Overdose

For this study, any dose of AGN-151607 greater than an assigned dose specified in the protocol will be considered an overdose.

Sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

PD parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Collection of samples for biomarker research is also part of this study. Blood samples will be collected from all participants in this study as specified in the SoA (Section 1.3). These samples will be used to test for immunogenicity and will also include biomarkers involved in the inflammatory process and in the autonomic nervous system. The biomarkers to be analyzed will be listed in the SAP.

- Samples will be tested for assessment of biomarkers to evaluate their association with the observed clinical responses to study intervention.

Samples may be stored for a maximum of 2 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of biomarker responses to AGN-151607.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are evaluated in this study (Section 8.1.3 and Section 8.1.5).

Medical resource utilization and health economics data, associated with medical encounters, will be collected by the investigator and study-site personnel or designee for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, ICU])
- Healthcare resource utilization (eg, setting, provider, reason for visit)

9. Statistical Considerations

9.1. Statistical Hypotheses

In general, continuous variables will be summarized by descriptive statistics and will include sample size, mean, standard deviation, median, minimum, and maximum. Nominal variables will be summarized by frequency and percentage. Continuous variables will be analyzed using 2-sample t-test or analysis of variance (ANOVA) techniques for comparisons between treatment groups, and paired t-tests for within-group comparisons. Ordinal variables will be analyzed using Wilcoxon rank-sum or Cochran-Mantel-Haenszel (CMH) tests for pairwise comparisons between groups, and Wilcoxon signed-rank tests for within-group comparisons. Time-to-event data will be analyzed using Cox proportional hazards models or the Kaplan-Meier nonparametric model. Nominal variables will be analyzed using Pearson's chi-square test or, if 25% or more of the cells have expected counts less than 5, Fisher's exact test.

The analyses will include 3 treatment groups: Placebo, 125 U, and 250 U of AGN-151607. Each dose level of AGN-151607 (125 U and 250 U) will be separately compared to placebo. All treatment comparisons will be made at the $\alpha = 0.05$ level (2-sided). To control for multiplicity in comparing 2 doses of AGN-151607 with placebo, the primary efficacy variable will be tested sequentially by first comparing the high dose to placebo. The low dose will be compared to placebo only if the comparison to the high dose is found to be statistically significant. Details regarding adjustment for multiple comparisons for other efficacy variables will be discussed in the SAP.

9.2. Sample Size Determination

A sample size of 100 randomized participants per intervention group will provide approximately 80% power to detect the treatment difference between each of the AGN-151607 doses (assumed equally effective) and placebo for the primary efficacy endpoint. The power calculations are based on the following assumptions:

- The expected incidence of early postoperative AF within 30 days post-surgery will be 47.8% in the placebo group and 27.8% in each of the AGN-151607 groups. This assumption is based on the results observed in the Pokushalov study (Pokushalov 2015) and the Duke University Medical Center clinical trial discussed in Section 2 (Waldron 2019).
- Two-sided Mantel-Haenszel test statistic and a significance level of 0.05 for the test.

Calculations will be performed using commercial software PASS 2008 (Hintze 2008).

Assuming that approximately 10% in each intervention group will drop out early from the study, a total of approximately 330 participants will be randomly assigned to study intervention, in order to have approximately 300 participants complete all the efficacy assessments up to Day 60 visit.

9.3. Populations for Analyses

A study participant is enrolled in the study the moment he or she has signed the ICF.

The analysis populations will consist of participants as defined below:

- The modified intent-to-treat (mITT) population will consist of all randomized participants who received study intervention and had at least 1 post-dose ECG by Day 30 post-surgery. Analyses will be based on randomized intervention.
- The safety population will consist of all participants who received study intervention. Analyses will be based on actual intervention received.

9.4. Statistical Analyses

One database lock is planned for this study and will occur when all participants have completed the study or exited earlier. Prior to the database lock, an interim analysis of all efficacy data will be performed when all randomized participants have completed the Day 60 visit, or exited the study earlier.

The SAP will be developed and finalized before the interim analysis and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary and additional endpoints.

9.4.1. Efficacy Analyses

All efficacy analyses will be based on the mITT Population.

Each participant will be continuously monitored through Day 30, and during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits, for all occurrences of AF episodes as well as the length of time spent in each of the corresponding AF episodes using ECG patches placed on the upper region of the participant's chest.

The ECG measurements collected for AF episodes post-surgery will be used to provide ***9*** different definitions for POAF for use in statistical analyses, namely:

1. At least 1 continuous AF episode ≥ 30 seconds
2. At least 1 continuous AF episode ≥ 2 minutes
3. At least 1 continuous AF episode ≥ 5 minutes
4. At least 1 continuous AF episode ≥ 30 minutes
5. At least 1 continuous AF episode ≥ 1 hour
6. At least 1 continuous AF episode ≥ 4 hours

7. At least 1 continuous AF episode ≥ 6 hours
8. At least 1 continuous AF episode ≥ 12 hours
9. At least 1 continuous AF episode ≥ 24 hours

Based on information collected from continuous monitoring for all occurrences of through Day 30, the percent of time spent in AF will be calculated as the total time spent in AF divided by the time spent in the study at the Day 30 visit.

In addition, similar definition of POAF as well as the derivation of the percent of time in AF will be obtained based on continuous monitoring of all occurrences of AF during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits.

9.4.1.1. Primary Efficacy Variables

For primary efficacy consideration, POAF will be defined as any continuous episode of AF lasting 30 seconds or more during the first 30 days post-surgery. The primary efficacy variable is the percentage of participants with at least 1 continuous AF episode ≥ 30 seconds during the first 30 days post-surgery. AF will be defined as the detection of either AF or atrial flutter.

9.4.1.2. Primary Efficacy Analyses

The proportion of participants with at least 1 continuous AF episode ≥ 30 seconds during the first 30 days post-surgery will be presented for each treatment group. Between-group comparisons will be performed using the CMH test for general association, stratified by type of surgery (presence or absence of valve surgery) and age group (< 65 or ≥ 65 years). Two-sided confidence intervals (95%) will be provided for the differences between treatments. The confidence intervals will be constructed using the normal approximation to the binomial distribution.

The primary efficacy variable will also be analyzed using a logistic regression model adjusting for baseline risk factors of POAF (type of surgery, and age group).

9.4.1.3. Secondary Efficacy Variables

The secondary efficacy variables are:

- Percentage of time spent in AF (AF burden) during the first 30 days post-surgery
- Percentage of participants with at least 1 event of symptomatic AF during the first 30 days post-surgery
- Time to first occurrence of AF during the first 30 days post-surgery
- Percentage of participants with at least 1 continuous AF episode ≥ 2 minutes during the first 30 days post-surgery
- Percentage of participants with at least 1 continuous AF episode ≥ 5 minutes during the first 30 days post-surgery
- Percentage of participants with at least 1 continuous AF episode ≥ 30 minutes during the first-30 days post-surgery

- Percentage of participants with at least 1 continuous AF episode ≥ 1 hour during the first 30 days post-surgery
- Percentage of participants with at least 1 continuous AF episode ≥ 4 hours during the first 30 days post-surgery
- Percentage of participants with at least 1 continuous AF episode ≥ 6 hours during the first 30 days post-surgery
- Percentage of participants with at least 1 continuous AF episode ≥ 12 hours during the first 30 days post-surgery
- Percentage of participants with at least 1 continuous AF episode ≥ 24 hours during the first 30 days post-surgery

9.4.1.4. Additional Efficacy Variables

The additional efficacy variables are:

- Percentage of participants with clinically important tachycardia in AF (defined as heart rate ≥ 100 bpm for at least 2 minutes
- Percentage of participants needing pharmacologic intervention (ie, anticoagulation, antiarrhythmic drugs) during the first 30 days post-surgery due to AF
- Percentage of participants needing pharmacologic intervention (ie, anticoagulation, antiarrhythmic drugs) from Day 31 to Day 360 post-surgery due to AF
- Percentage of participants needing procedural intervention (ie, cardioversion, ablation, additional surgery) during the first 30 days post-surgery due to AF
- Percentage of participants needing procedural intervention (ie, cardioversion, ablation, additional surgery) from Day 31 to Day 360 post-surgery due to AF
- Time to first prescription of pharmacologic intervention due to POAF during the first 30 days post-surgery and length of time that prescription is taken.
- Time of POAF resolution from first dose of prescription of pharmacologic intervention
- Time to first procedural intervention due to POAF during the first-30 days post-surgery.
- Time of POAF resolution from first procedural intervention due to AF
- Length of stay in ICU and reason
- Length of stay in hospital and reason
- Number of all-cause re-hospitalizations within 30 days post-discharge
- Number of non-arrhythmia cardiovascular re-hospitalizations within 30 days post-discharge
- Number of arrhythmia re-hospitalizations within 30 days post-discharge
- Binary measure (Y/N) of all-cause hospitalizations within 30 days post-discharge

- Binary measure (Y/N) of non-arrhythmia cardiovascular hospitalizations within 30 days post-discharge
- Binary measure (Y/N) of arrhythmia hospitalizations within 30 days post-discharge
- Number of days spent in the hospital: within 30 days post-discharge and within 60 days post-surgery
- Percentage of participants with any occurrence of AF as defined in the primary and secondary endpoints during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits
- Percentage of participants with at least 1 event of symptomatic AF during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits
- Percentage of time spent in AF (AF burden) during the first 7 days following Day 60, Day 90, Day 180, Day 270 and Day 360 visits

9.4.1.5. Secondary and Additional Efficacy Analyses

For each efficacy variable with binary categorical response outcome, the response proportions will be analyzed using the same methods used to analyze the primary efficacy variable.

Kaplan-Meier curves for time to event data will be produced by treatment group and compared using the log-rank test. Time to event data will also be compared between treatment groups using Cox proportional hazards models.

ICU and hospital length of stay will be compared between groups using t-tests as well as linear regression models with adjustment for POAF baseline risk factors. The data in both groups will first be examined for normality. Should the data have a normal distribution, it will be analyzed using an unadjusted t-test. In the event of significant skewedness, the Wilcoxon rank-sum test will be used.

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs, physical examination, clinical laboratory tests, vital signs, ECG, pulmonary function, and immunogenicity parameters. For each of physical examination, clinical laboratory, vital sign, and ECG parameters, the last nonmissing safety assessment before the initial dose of treatment will be used as the baseline for all analyses of that safety parameter.

9.4.2.1. Adverse Events

AEs will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

An AE will be considered a treatment-emergent adverse event (TEAE) if it was present after the first dose of study intervention or was present before the date of the first dose of study intervention and increased in severity or became serious after the first dose of study intervention.

The number and percentage of participants reporting TEAEs in each study intervention group will be tabulated by descending percentage in any group, by system organ class, and preferred term, and further categorized by severity and causal relationship to the study intervention. If more than 1 AE is coded to the same participant, the participant will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

The total number of TEAEs by severity and causal relationship to the study intervention will be summarized by study intervention group.

The number and percentage of participants who have treatment-emergent SAEs will be summarized by preferred term and treatment group.

The number and percentage of participants in the Safety Population who have AEs leading to premature discontinuation of the study intervention will be summarized by preferred term and study intervention.

To assess PDSOT, MedDRA preferred terms that may be associated with botulinum toxin effects have been identified over the course of the development programs of botulinum toxin type A by the sponsor and will be used for this study. All AEs associated with PDSOT will be tabulated by system organ class and treatment group; in addition, all PDSOT AEs will be listed by participant.

9.4.2.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline (screening), and changes from baseline at each assessment, will be presented by study intervention for each clinical laboratory assessment.

The criteria for potentially clinically significant (PCS) laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by study intervention at each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive tabular display of participants with PCS postbaseline values will be provided, including the participant number, baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline clinical laboratory values will be provided.

9.4.2.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, respiration rate, temperature, body weight and abdominal circumference, and body mass index) and changes from baseline values at each visit and at the end of study will be presented by treatment group.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria. PCS criteria will be specified in the SAP. The number and percentage of participants with PCS postbaseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available non-PCS

baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive tabular display of participants with PCS postbaseline values will be provided, including the participant number, baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline vital sign values will be provided.

9.4.2.4. Electrocardiograms

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc) and changes from baseline values at each assessment timepoint to the end of study will be presented by treatment group.

Electrocardiographic parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria. PCS criteria will be specified in the SAP. The number and percentage of participants with PCS postbaseline ECG values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator is the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive tabular display of participants with PCS postbaseline values will be provided, including the participant number, baseline, all postbaseline (including non-PCS) values, and change from baseline.

A tabular display showing participants with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

9.4.3. Other Analyses

Fat pads and injection procedure, quality of life outcomes and biomarker analyses, will be described in the SAP.

9.5. Interim Analyses

An interim analysis of all efficacy data will be performed when all randomized participants have completed the Day 60 visit or exited the study earlier. The purpose of this analysis is to identify early trends in the data for administrative planning of following studies. There is no plan to stop the study or drop a treatment arm based on the results from the interim analysis.

The final analysis will occur when all participants have completed the long-term safety follow-up or have exited the study earlier. The details of all analyses will be provided in the SAP which will be finalized before the interim analysis.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH/ISO Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator or designee will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site or at any home visits and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators and sub-investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An independent DSMB will review select safety data at scheduled times during the conduct of the study. Ad hoc meetings of the DSMB may be scheduled to evaluate potential safety signals, as needed. Policies, procedures, and composition of the DSMB are described separately in the DSMB charter for this study.

10.1.6. Posting Clinical Study Data

Study information and tabular study results will be posted to the US National Institutes of Health website www.clinicaltrials.gov.

Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of Allergan.

Clinical study reports, safety updates and annual reports will be provided to regulatory authorities as required.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in compliance with all applicable laws and regulations. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source data are defined as: original documents, data, and records (eg, hospital records, clinical and office charts, diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study). These records include, but are

not limited to, original signed and dated consent forms, relevant observations including records of AEs, and records of all exposure to study intervention.

10.1.9. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.10. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multi-center study except as agreed with Allergan. Allergan is solely responsible for determining what and when to publish.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.11. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit Coagulation (prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT))	RBC indices: MCV MCH MCHC % Reticulocytes	WBC count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	BUN Creatinine Glucose (nonfasting) Hemoglobin A1c	Potassium Sodium Calcium eGFR Chloride Albumin	AST ALT Alkaline phosphatase	Total direct and indirect bilirubin Total protein Lipid profile (cholesterol, triglycerides, HDL cholesterol, LDL cholesterol [calculated])
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)[a]			
Other Screening Tests	• Urine human chorionic gonadotropin (hCG) pregnancy test) as needed-for women of childbearing potential[a]			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; HDL = high density lipoprotein; LDL = low density lipoprotein; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, RBC = red blood cell, WBC = white blood cell

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. **AE of Special Interest (AESI)** An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it. The following AESI(s) have been identified for the study intervention in this protocol: possible distant spread of toxin (PDSOT). Serious AESIs should be reported to the sponsor within 24 hours using the same reporting procedures for SAE reporting. Nonserious AESIs should be reported using the same procedures as nonserious AEs reporting by capturing the AE information in the source document and entering them into the eCRF. The Serious Adverse Event/Adverse Event of Special Interest Form for Interventional Studies should not be used to report any nonserious AESIs.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease); for example: o The test result is associated with accompanying symptoms, and/or o The test result requires additional diagnostic testing or medical/surgical intervention, and/or o The test result is considered to be an AE by the investigator or sponsor. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition

- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.
- The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- An SAE should be reported to the sponsor via the paper forms provided within 24 hours.
- All AE or SAE information will then be recorded in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality. • There may be situations in which a SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs

SAE Reporting
• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE form, sent by overnight mail or courier service. The telephone number is +1-800-678-1605. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

AE	adverse event
AESI	adverse event of special interest
AF	atrial fibrillation
AFEQT	Atrial Fibrillation Effect on Quality-of-life Questionnaire
AFSS	University of Toronto Atrial Fibrillation Severity Scale
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATS	American Thoracic Society
BP	blood pressure
CABG	coronary artery bypass graft
CDISC	Clinical Data Interchange Standards Consortium
CFR	code of federal regulations
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
DASI	Duke Activity Status Index
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
ELISA	enzyme-linked immunosorbent assay
EQ-5D-5L	A measure of health-related quality of life developed by the EuroQol Group
EuroScore II	European System for Cardiac Operative Risk Evaluation II
FDA	US Food and Drug Administration
FEV	forced expiratory volume
FEV_1	forced expiratory volume in 1 second
FEV_3	forced expiratory volume in 3 seconds
FEV_6	forced expiratory volume in 6 seconds
FSH	follicle-stimulating hormone

FVC	forced vital capacity
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRQoL	Health Related Quality of Life
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IDR	independent drug reconstitutor
IEC	independent ethics committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
IWRS	Interactive Web Response System
LAA	left atrial appendage
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NCI	National Cancer Institute
NOAC	non-vitamin K antagonist oral anticoagulant (also referred to as novel oral anticoagulant)
NOEL	no observed effect level
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PDSOT	possible distant spread of toxin
PFT	pulmonary function test
POAF	post-operative atrial fibrillation
PRO	patient reported outcome
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SAP	statistical analysis plan
SF-12v2	Short-Form-12 Health Survey, Version 2

SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
WBC	white blood cell
WOCBP	woman of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Death	The absence of life or state of being dead (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	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
	Clinical Study Sponsor	Allergan
	Trial Phase Classification	Phase 2
	Trial Indication	Post-operative atrial fibrillation
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	367 days
	Planned Region of Investigational Sites	North America and Europe
	Planned Number of Participants	330 participants
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Participant information	Diagnosis Group	Patients undergoing open-chest cardiac surgery
	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	55 years
	Planned Maximum Age of Participants	90 years
	Sex of Participants	Both
	Stable Disease Minimum Duration	Not applicable

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	AGN-151607
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	Botulinum toxin type A
	Dose per Administration	125 U or 250 U
	Dose Units	25 U or 50 U per fat pad
	Dosing Frequency	One-time injection
	Route of Administration	Injection
	Current Therapy or Treatment	Standard-of-care
	Added on to Existing Treatments	Yes
	Control Type	Placebo
	Comparative Treatment Name	Not applicable
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	3
	Trial is Randomized	Yes
	Randomization Quotient	1:1:1
	Trial Blinding Schema	Double blind
	Stratification Factor	Age (< 65, ≥ 65 years) Type of surgery (presence/absence of valve surgery)
	Adaptive Design	No
	Study Stop Rules	No

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

     Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined timeframe in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent until after Day 60 of the study
- Agree to use a male condom with spermicide when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

In addition, male participants with pregnant or breastfeeding partners must also agree to remain abstinent from penile-vaginal intercourse until after Day 60 of the study or to use condom with spermicide. Male participants must refrain from donating sperm until after Day 60 of the study.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a method of contraception (highly effective or acceptable birth control methods) consistently and correctly. Highly effective contraceptive methods are described in Table 10–2.

Table 10–2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine hormone-releasing system (IUS) • Etonogestrel implant (ie, Nexplanon®) Bilateral tubal occlusion Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Acceptable birth control methods that result in a failure of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with spermicide
- Cap, diaphragm, or sponge with spermicide
- Nonhormonal intrauterine device
- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable

Pregnancy Testing:

- WOCBP should only be included after a negative highly sensitive urine pregnancy test at screening and also a negative urine test on Day 1.
- Additional pregnancy testing is not required during the study intervention period.

- Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC.

Collection of Pregnancy Information:

Male Participants with Partners Who Become Pregnant

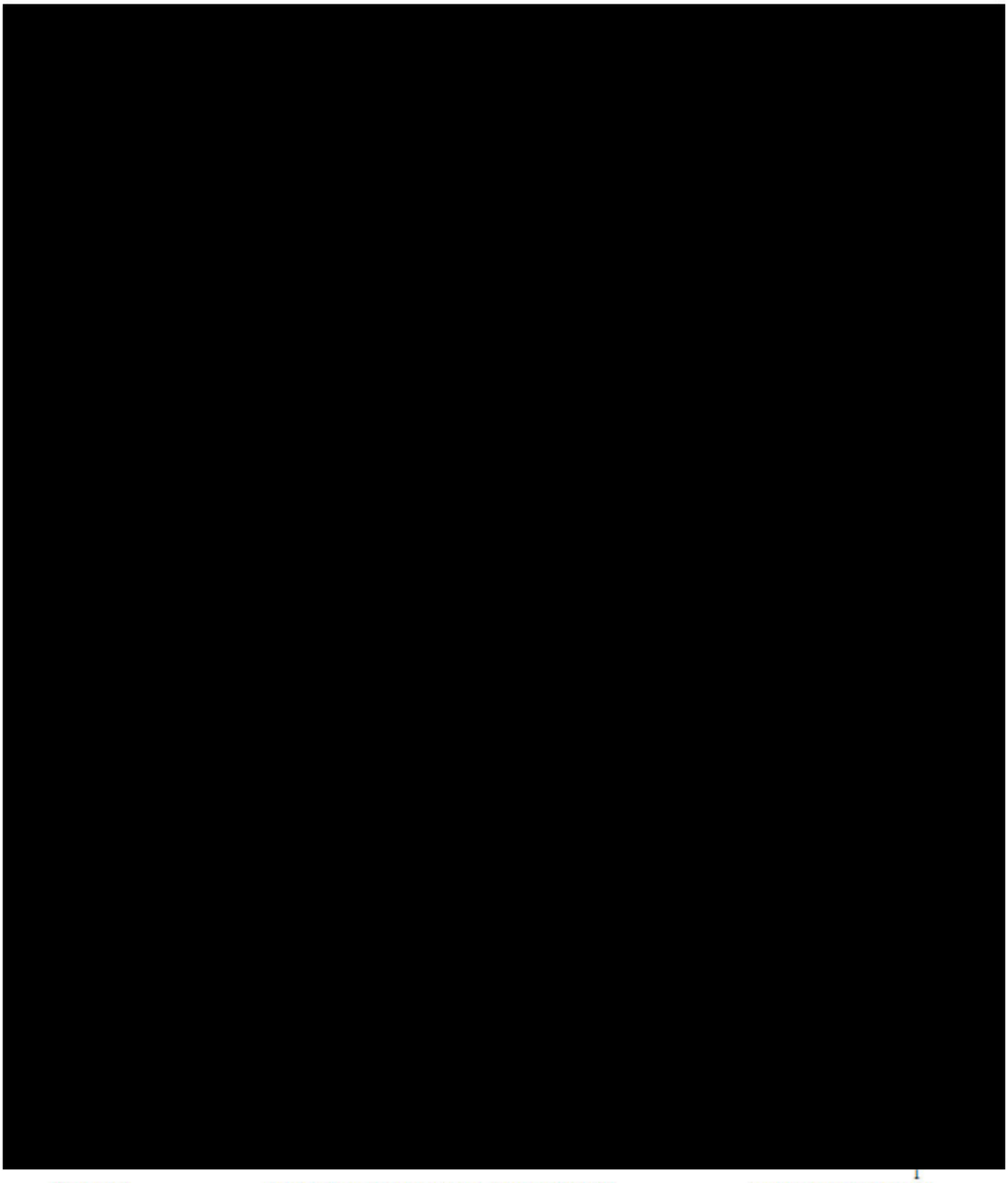
- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant after the start of study intervention and until Day 60. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

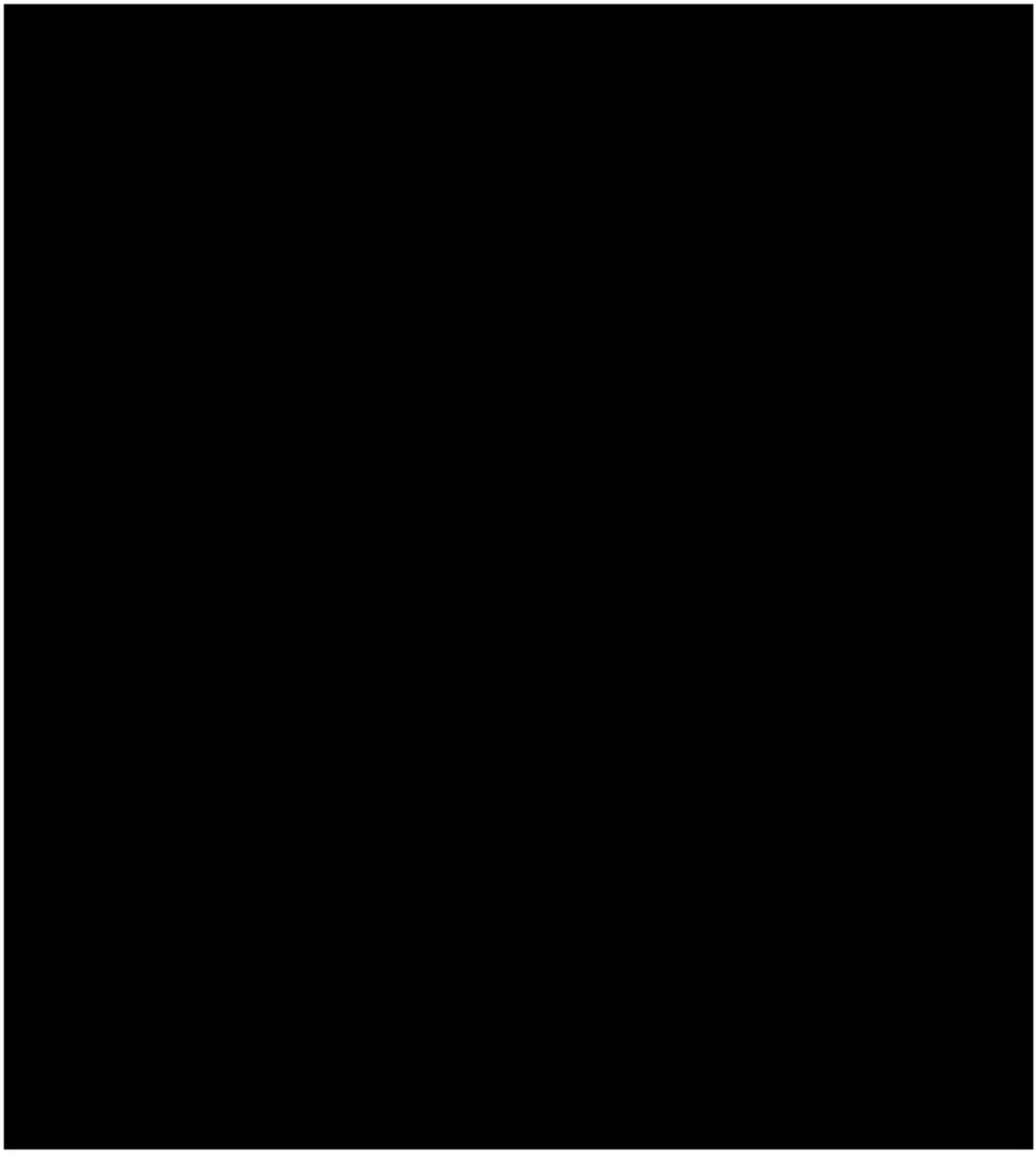
- The investigator will collect pregnancy information on any female participant who becomes pregnant after the start of study intervention and until Day 60. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. A spontaneous or elective abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.8. Appendix 8: Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

Sample questionnaire.

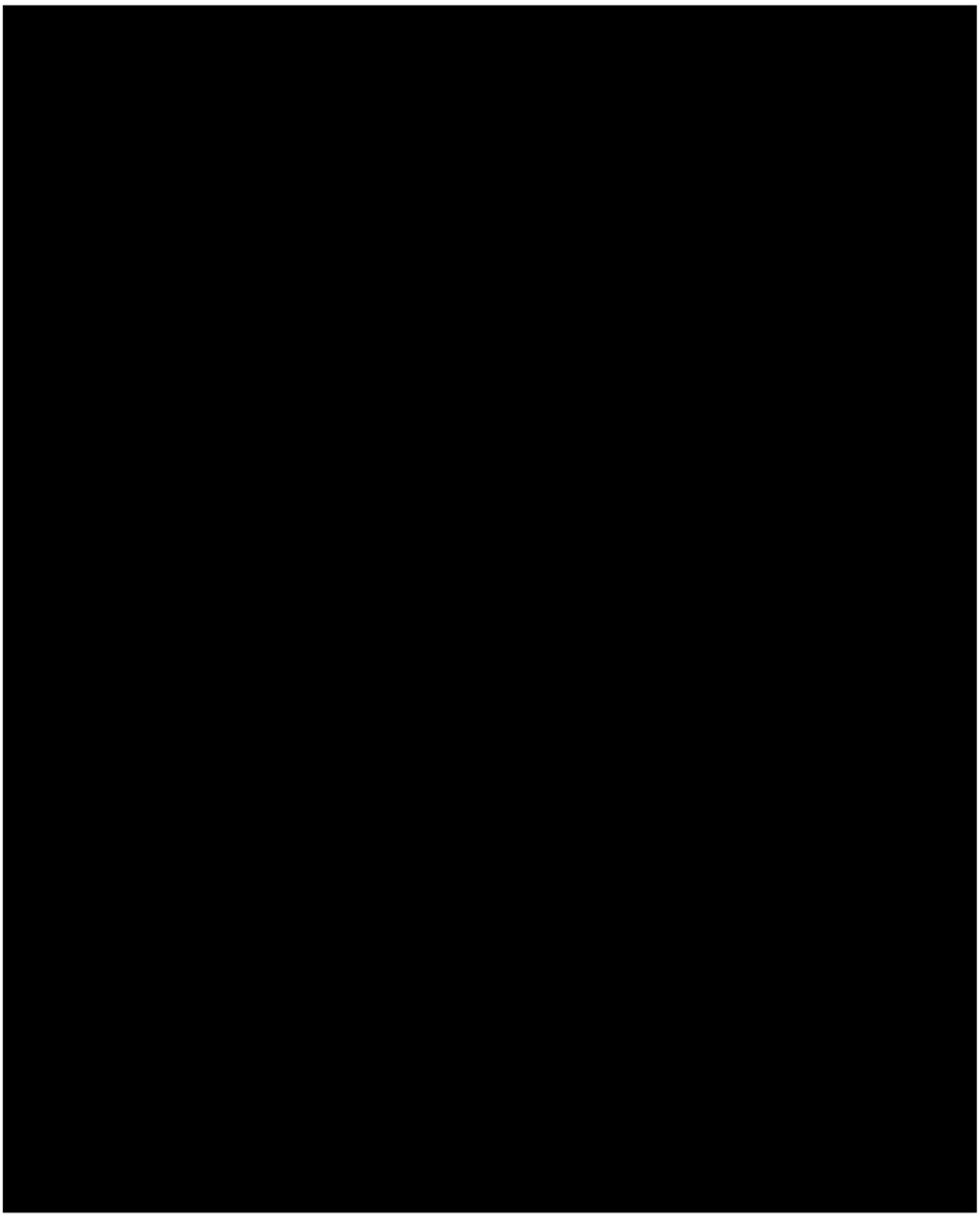


Developed by AFEQT Core Team-John Spertus, MD, Mid America Heart Institute, Kansas City, MO; Paul Dorian, MD, St. Michaels Hospital, Toronto, ON; Rosemary Bubien, RN, University of Alabama, Birmingham, AL; Caroline Burk, Pharm D. M.S; Steven Lewis, PhD; Donna Godejohn, BSN, St. Jude Medical, St. Paul, MN.

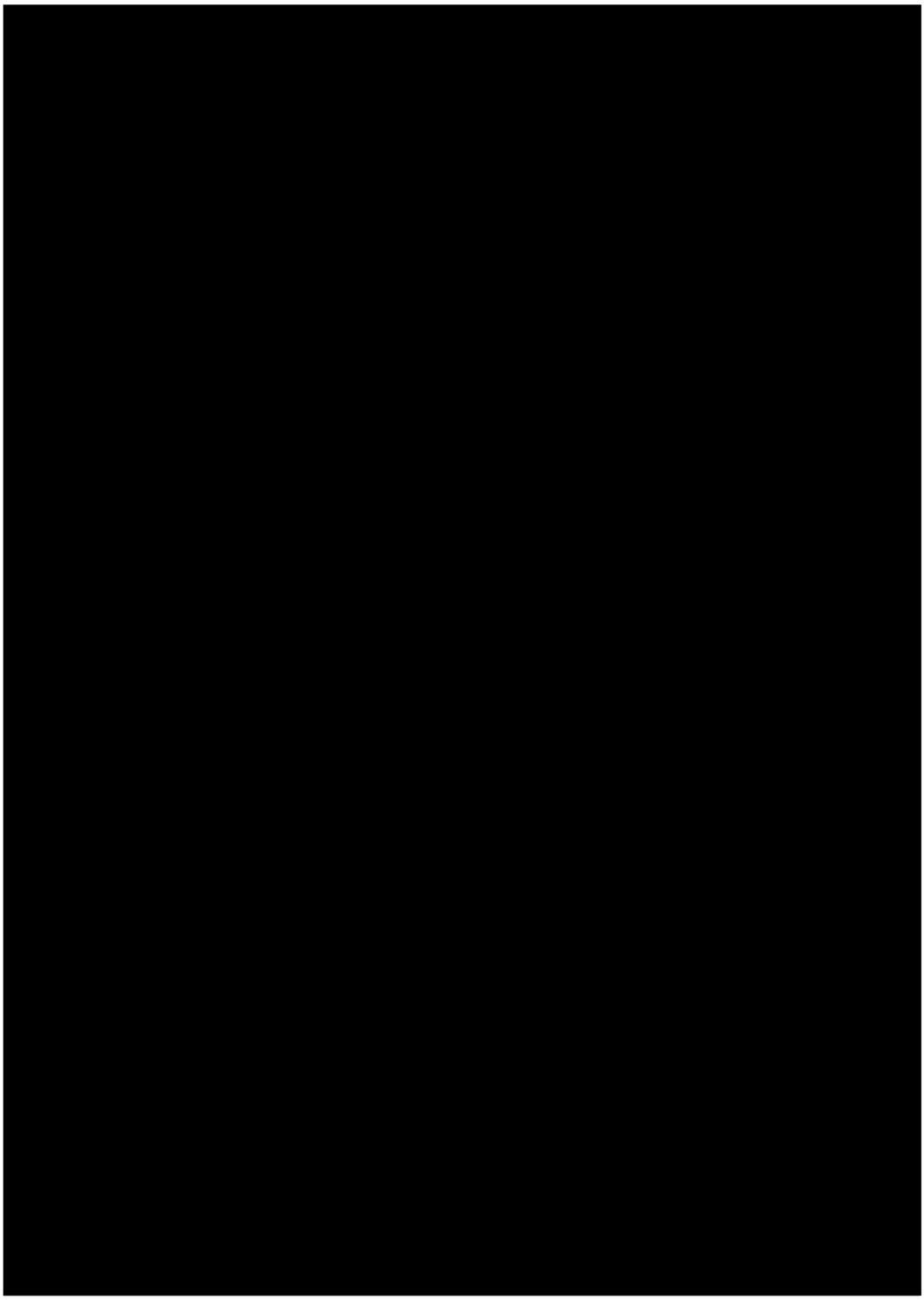


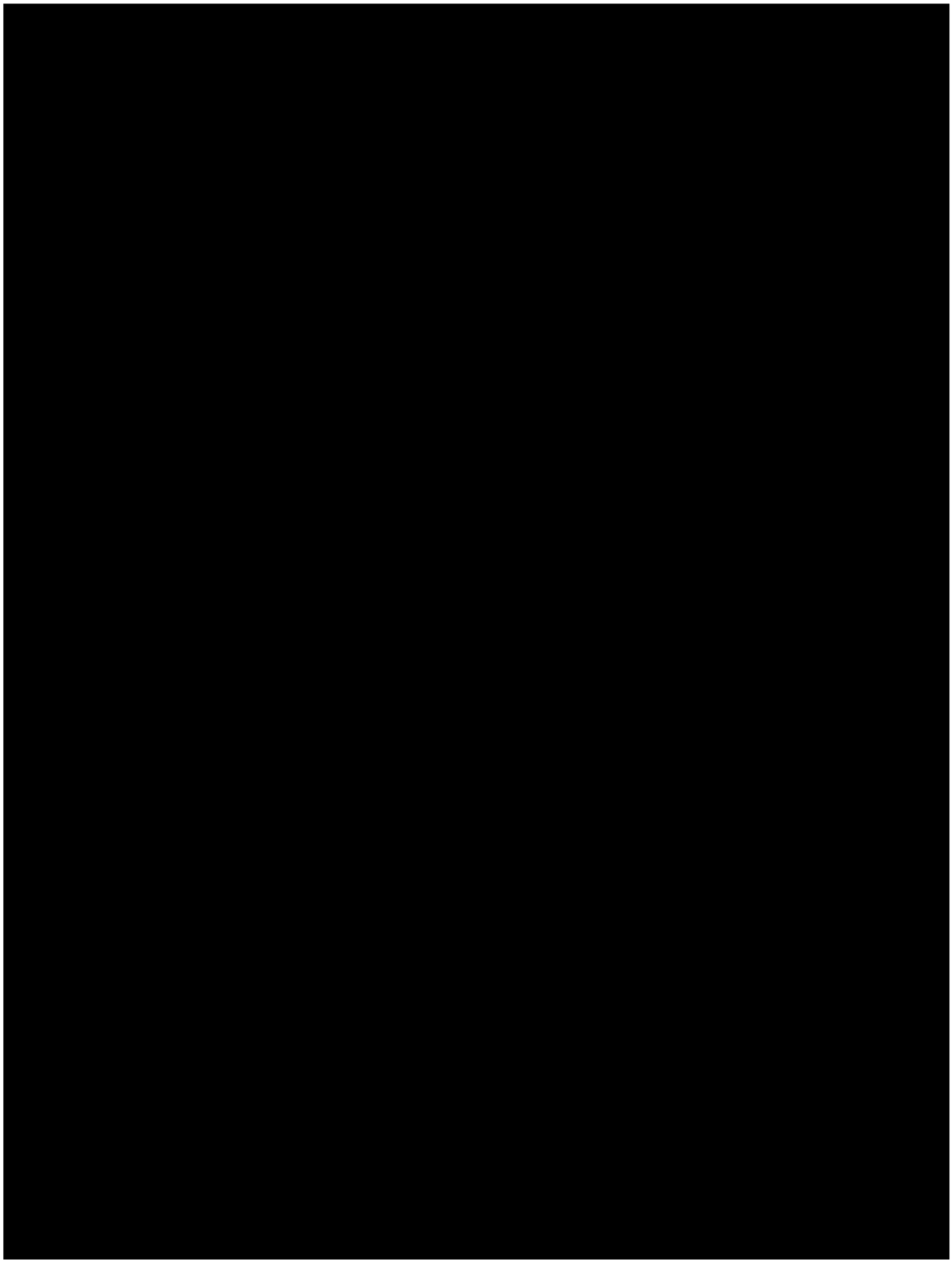
10.9. Appendix 9: University of Toronto Atrial Fibrillation Severity Scale

Sample scale.



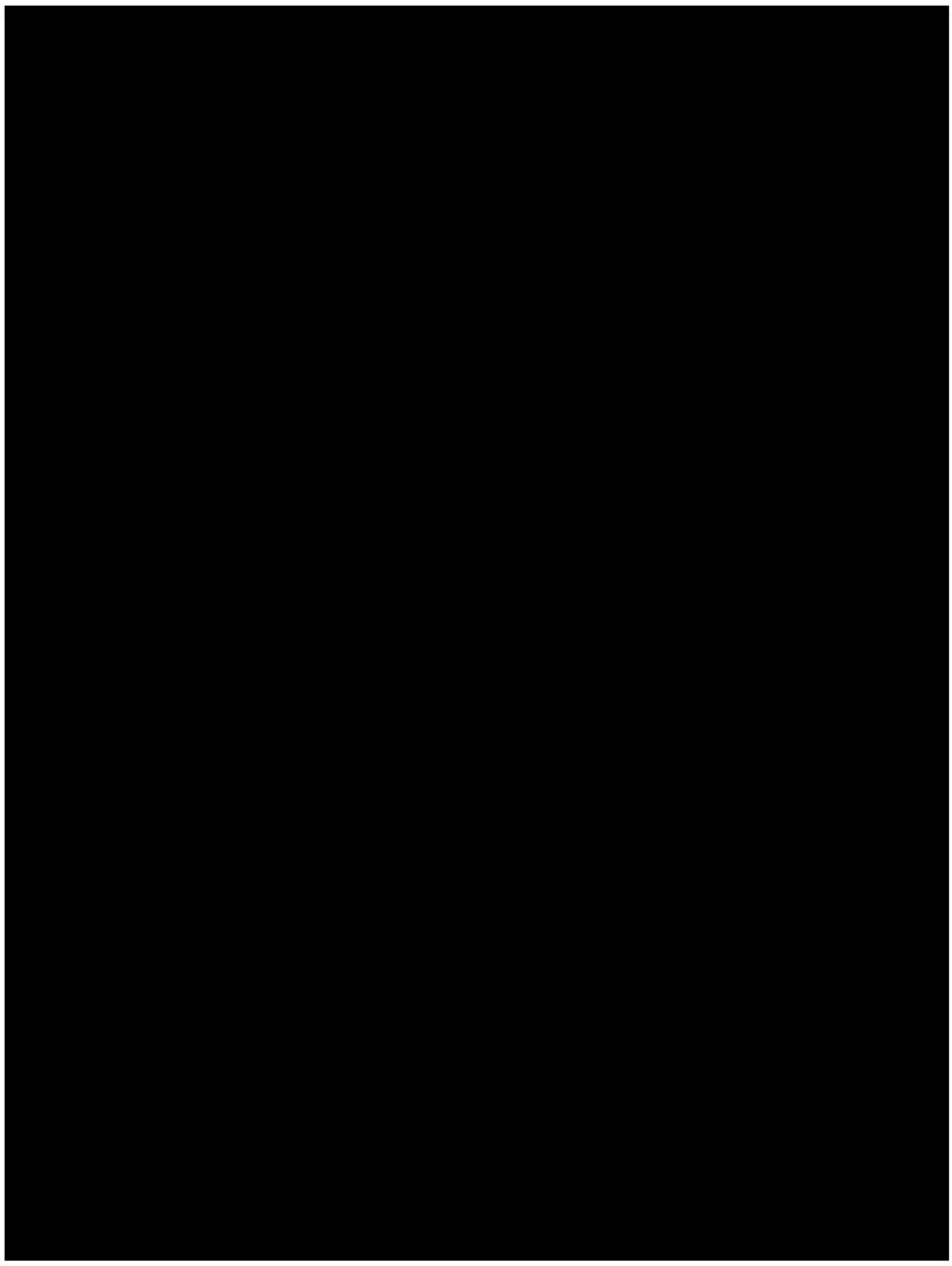
University of Toronto Atrial Fibrillation Severity Scale: Revised Jan 21, 2000 1

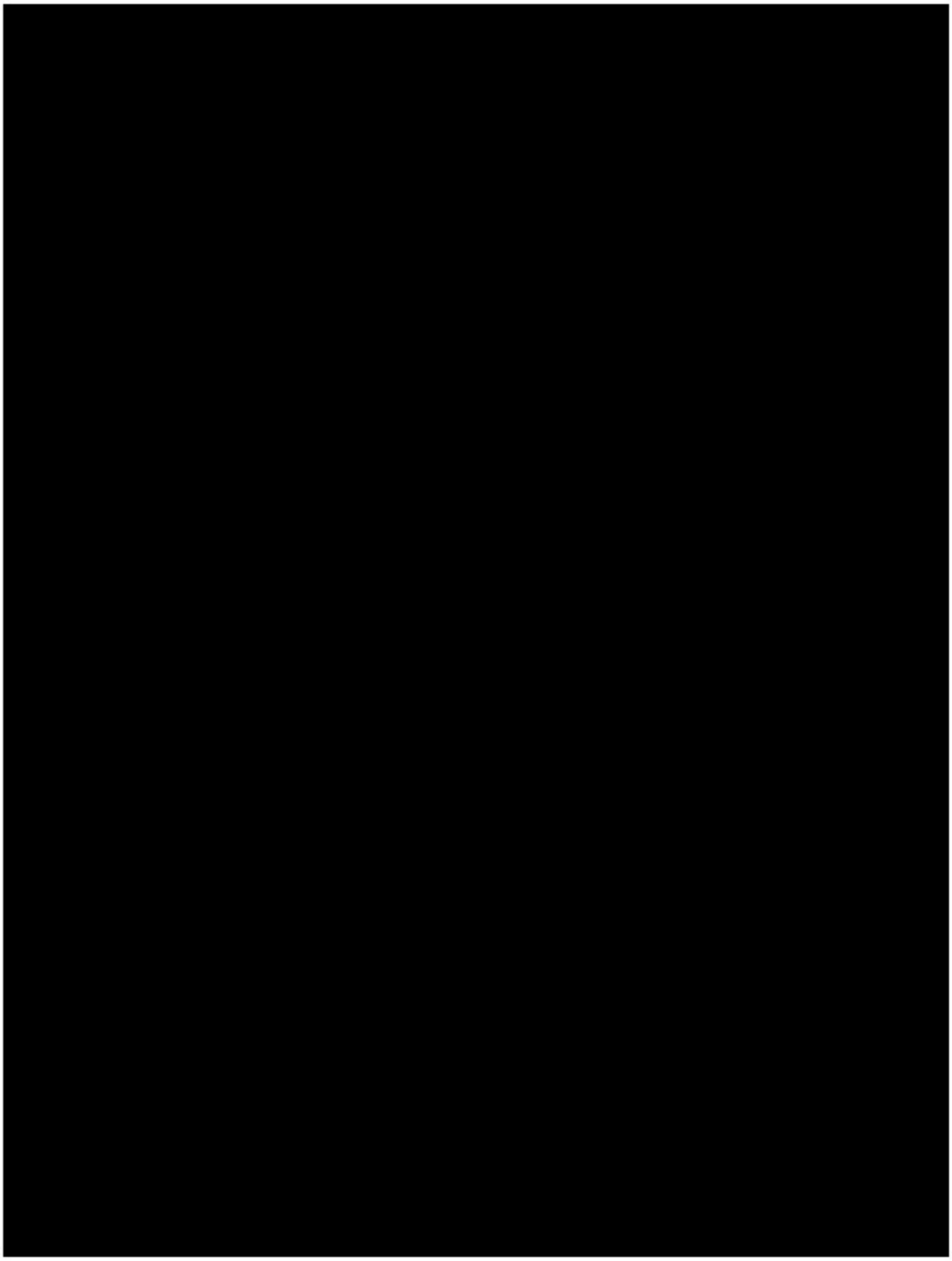


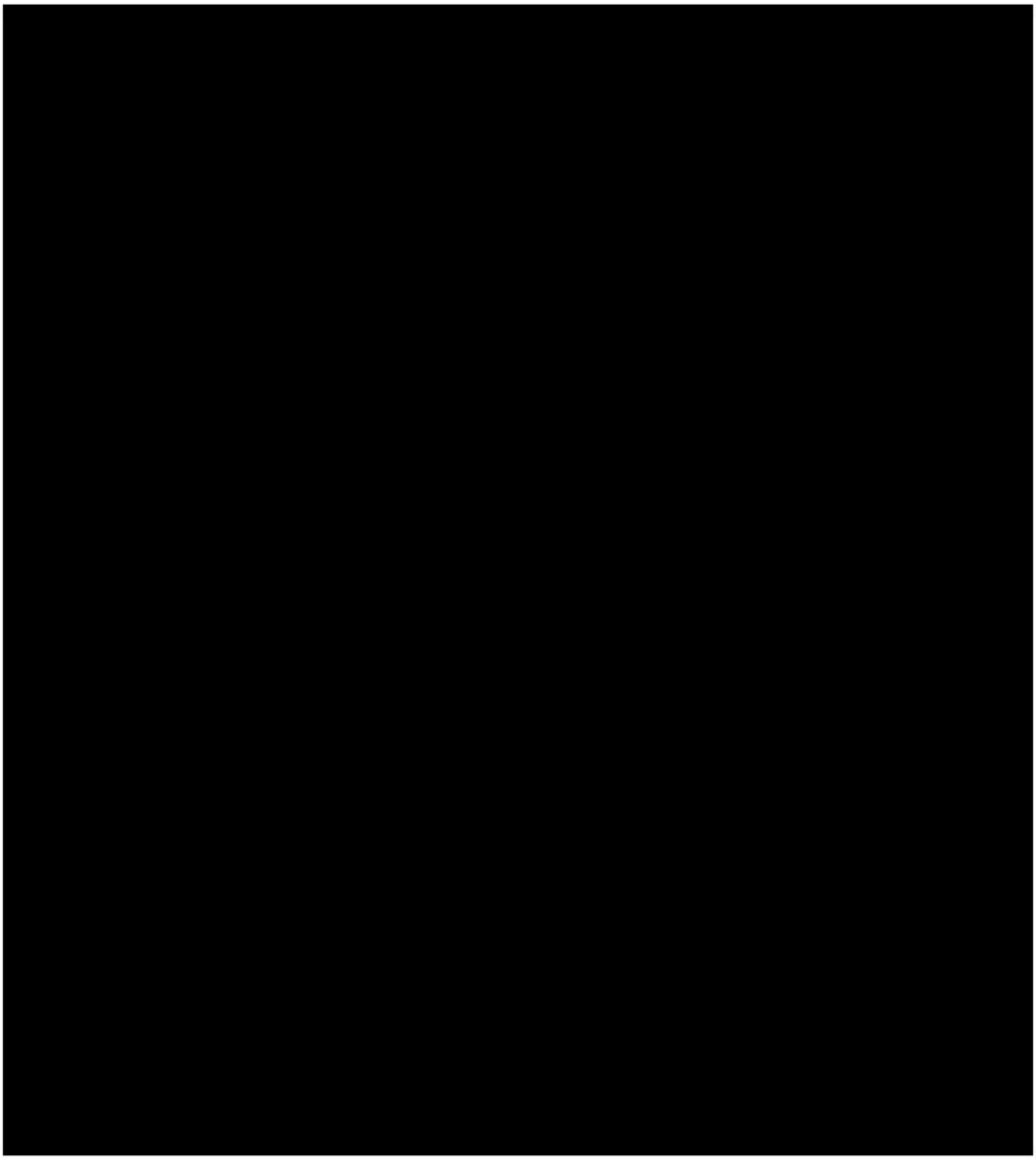


10.10. Appendix 10: Short Form-12 Health Survey

Sample survey.

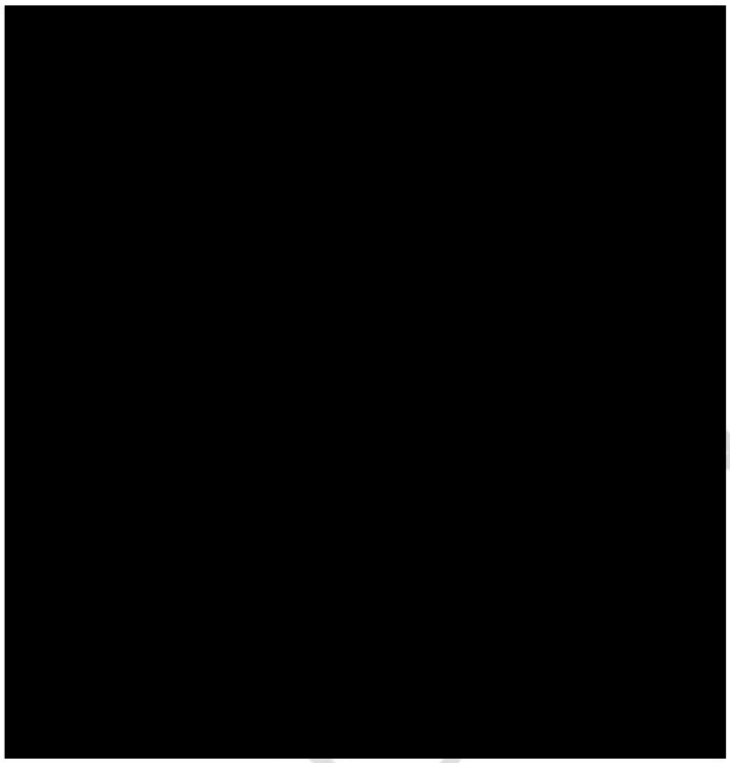


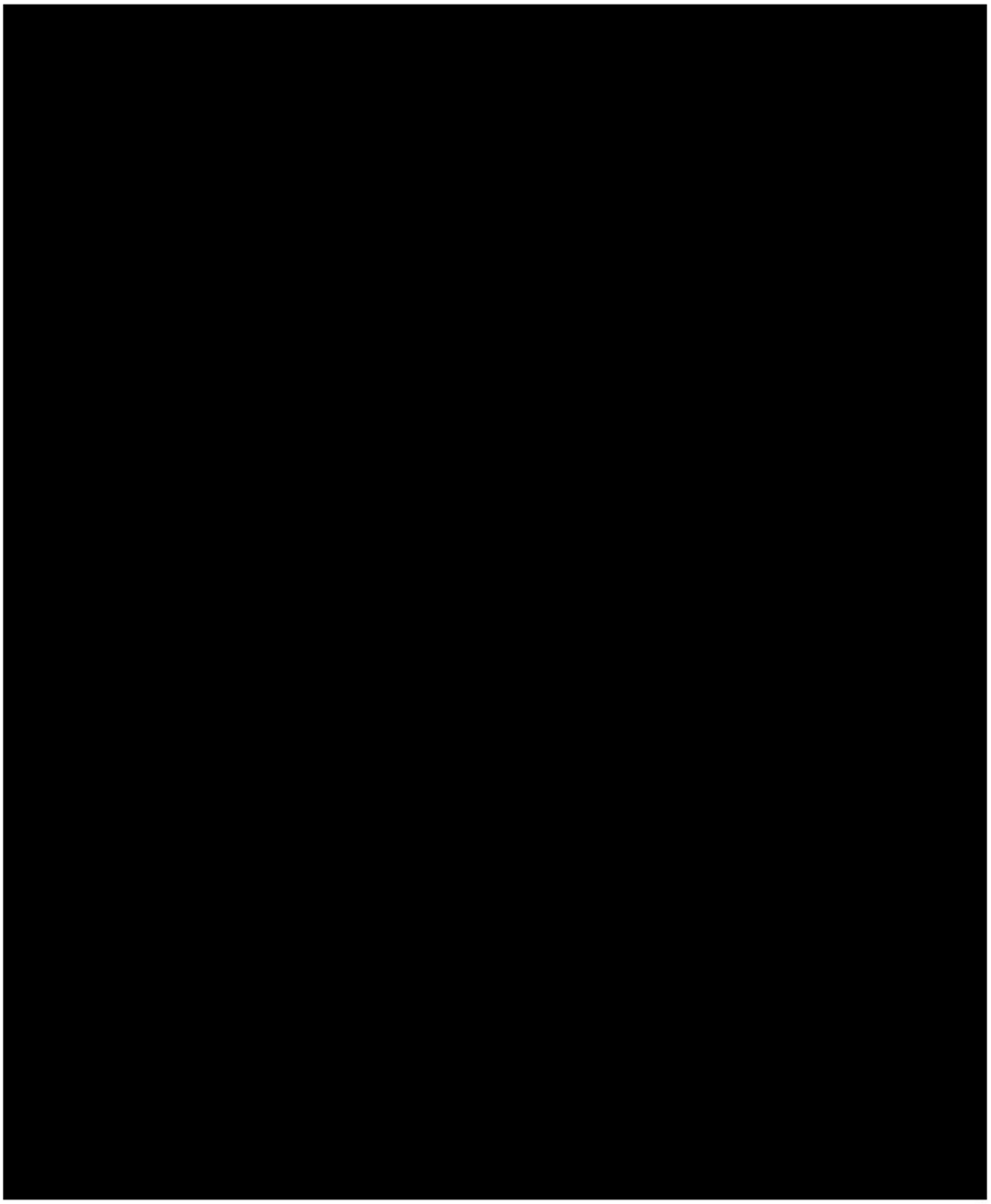




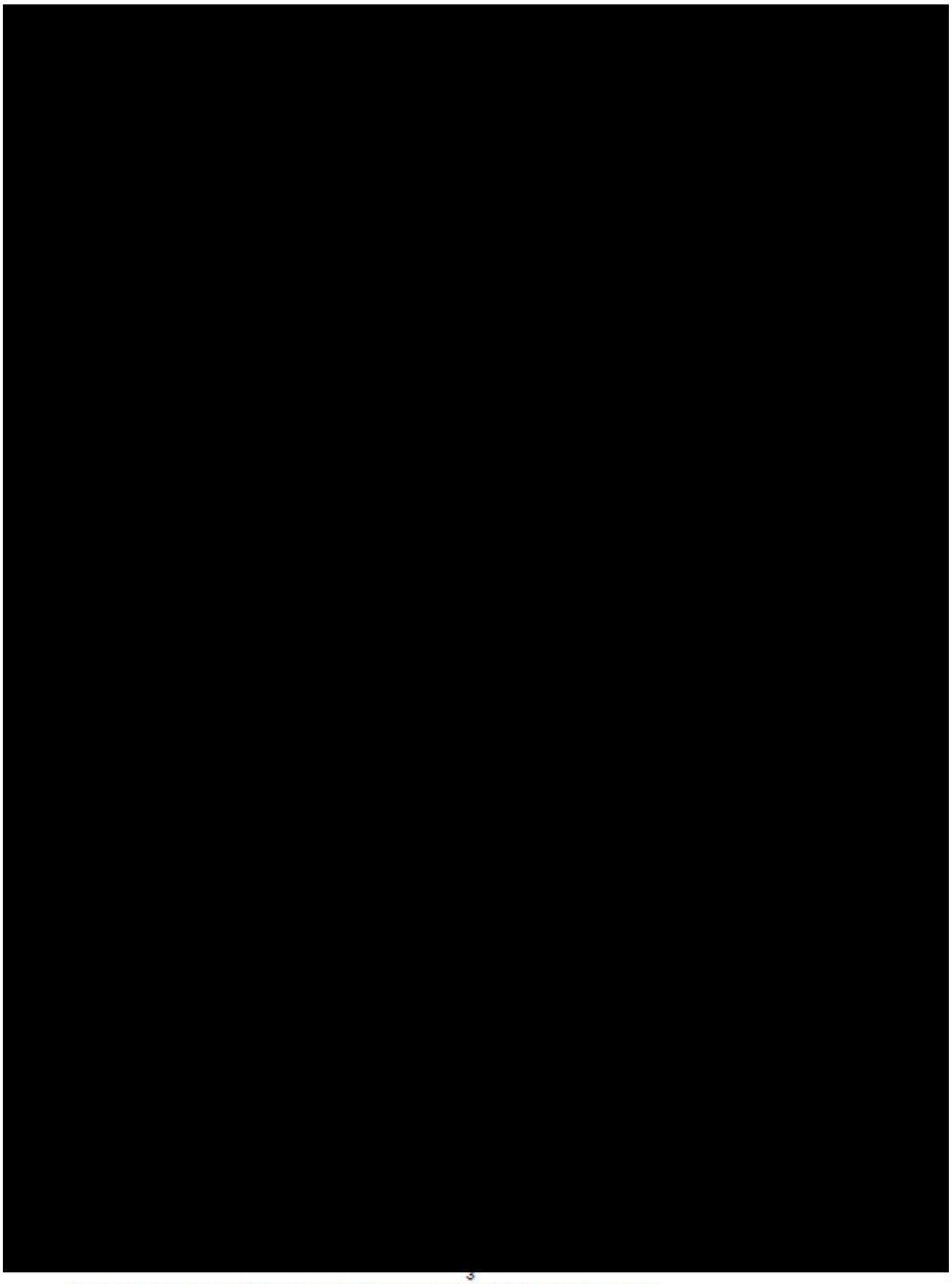
10.11. Appendix 11: EQ 5D-5L

Sample questionnaire.



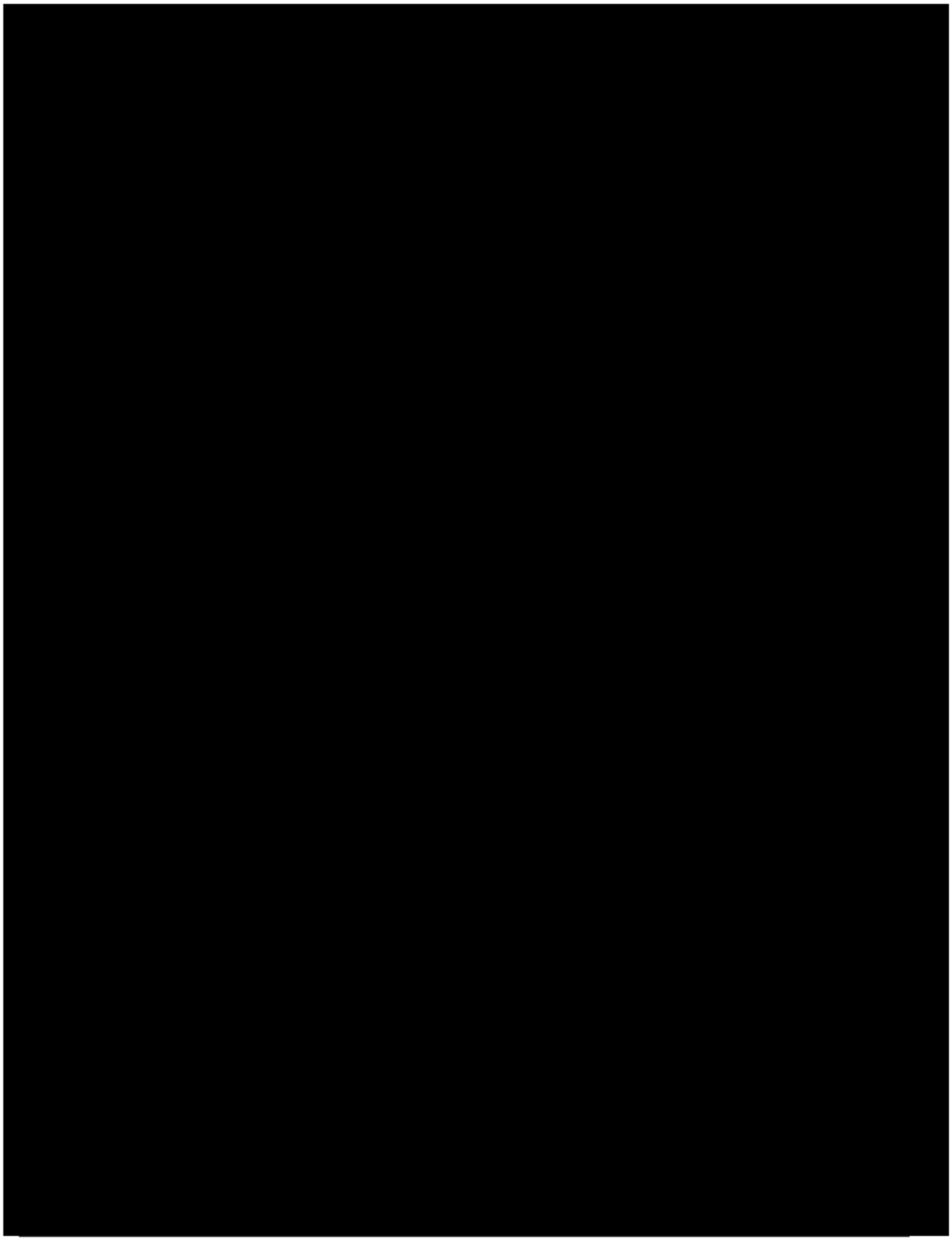


2

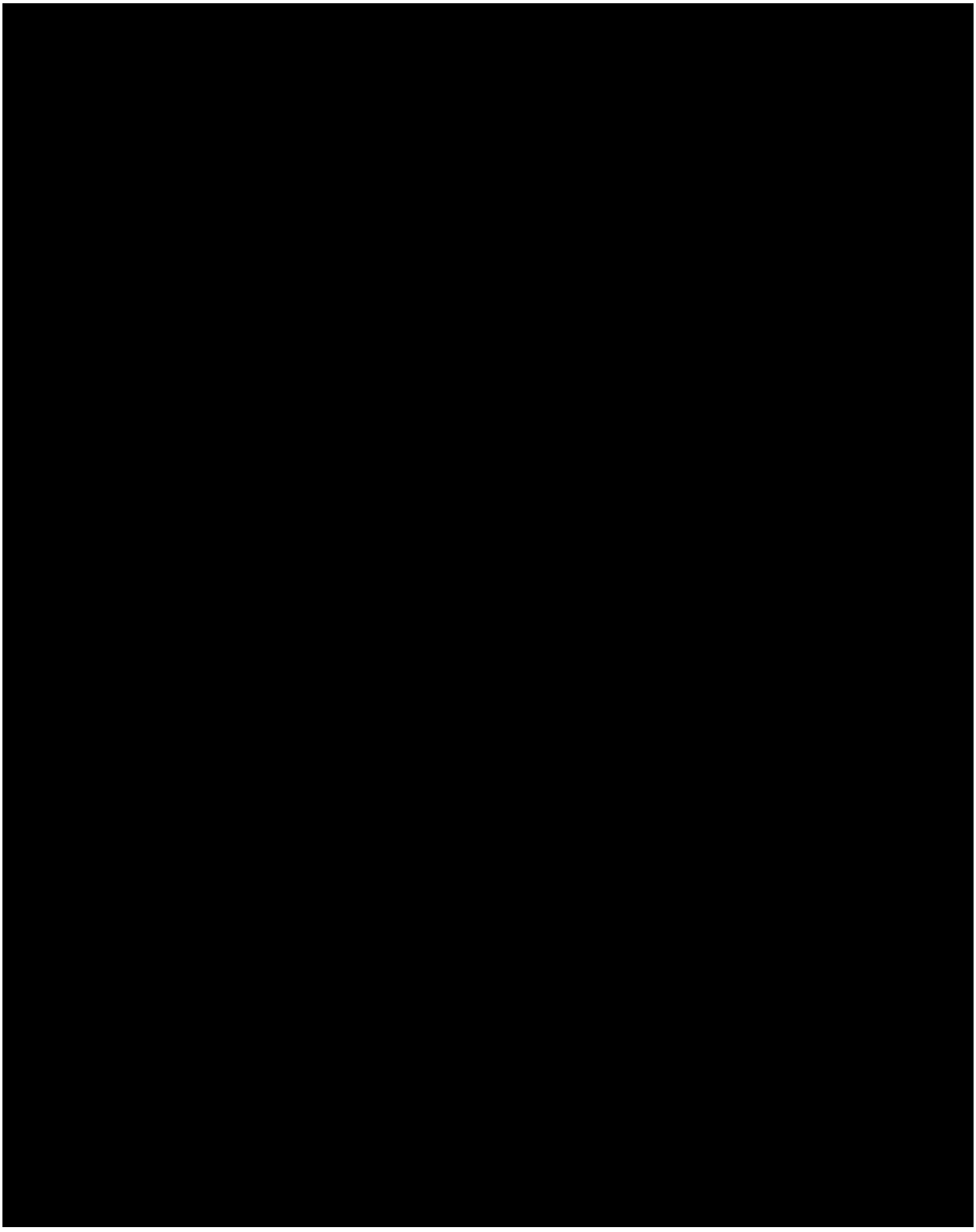


10.12. Appendix 12: Duke Activity Status Index

Sample index.



m:/mah/misc/DASI Notes-4-06



11. References

Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, Whitlock RP. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev. 2013;1:CD003611.

Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, et al. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. N Engl J Med. 2016;374:1911-1921.

Hintze J, 2008; PASS 2008, NCSS, LLC. Kaysville, Utah, USA. www.ncss.com

January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014-AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1-76.

Katritsis DG, Giazitzoglou E, Zografos T, Pokushalov E, Po SS, Camm AJ. Rapid pulmonary vein isolation combined with autonomic ganglia modification: a randomized study. Heart Rhythm. 2011;8:672-678.

Katritsis DG, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J Am Coll Cardiol. 2013;62:2318-2325.

Kertai MD, Li YW, Li YJ, Shah SH, Kraus WE, Fontes ML, et al. G protein-coupled receptor kinase 5 gene polymorphisms are associated with postoperative atrial fibrillation after coronary artery bypass grafting in patients receiving β-blockers. Circ Cardiovasc Genet. 2014;7:625-633.

LaPar DJ, Speir AM, Crosby IK, Fonner E Jr, Brown M, Rich JB, et al. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. Ann Thorac Surg. 2014;98:527-533.

Lo LW, Chang HY, Scherlag BJ, Lin YJ, Chou YH, Lin WL, et al. Temporary suppression of cardiac ganglionated plexi leads to long-term suppression of atrial fibrillation: evidence of early autonomic intervention to break the vicious cycle of "AF begets AF". J Am Heart Assoc. 2016;5:e003309.

Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA. 2004;291:1720-1729.

Mostafa A, El-Haddad MA, Shenoy M, Tuliani T. Atrial fibrillation post cardiac bypass surgery. Avicenna J Med. 2012;2:65-70.

Oh S, Choi EK, Choi YS. Short-term autonomic denervation of the atria using botulinum toxin. Korean Circ J. 2010;40:387-390.

Oh S, Choi EK, Zhang Y, Mazgalev TN. Botulinum toxin injection in epicardial autonomic ganglia temporarily suppresses vagally mediated atrial fibrillation. Circ Arrhythm Electrophysiol. 2011;4:560-565.

Pokushalov E, Romanov A, Katritsis DG, Artyomenko S, Shirokova N, Karaskov A, et al. Ganglionated plexus ablation vs linear ablation in patients undergoing pulmonary vein isolation for persistent/long-standing persistent atrial fibrillation: a randomized comparison. Heart Rhythm. 2013;10:1280-1286.

Pokushalov E, Kozlov B, Romanov A, Strelnikov A, Bayramova S, Sergeevichev D, et al. Long-term suppression of atrial fibrillation by botulinum toxin injection into epicardial fat pads in patients undergoing cardiac surgery: one-year follow-up of a randomized pilot study. Circ Arrhythm Electrophysiol. 2015;8:1334-1341.

Romanov A, Pokushalov E, Ponomarev D, Bayramova S, Shabanov V, Losik D. Long-term suppression of atrial fibrillation by botulinum toxin injection into epicardial fat pads in patients undergoing cardiac surgery: Three-year follow-up of a randomized study. Heart Rhythm. 2019 Feb;16(2):172-177.

Tsuboi M, Furukawa Y, Kurogouchi F, Nakajima K, Hirose M, Chiba S. Botulinum neurotoxin A blocks cholinergic ganglionic neurotransmission in the dog heart. Jpn J Pharmacol. 2002;89:249-254.

Waldron NH, Cooter M, Haney JC, Schroder JN, Gaca JG, Lin SS. Temporary autonomic modulation with botulinum toxin type A to reduce atrial fibrillation after cardiac surgery. Heart Rhythm. 2019 Feb;16(2):178-184.