Statistical Analysis Plan

Version 1

TITLE: ^{99m}Tc-rhAnnexin V-128 Imaging of Apoptosis and Cardiotoxicity in Relationship to Ventricular Function in Patients with Early Stage Breast Cancer Receiving Doxorubicin-Based Chemotherapy

PROTOCOL #: AAA-Annexin-05 v.7.0 dated 11 March 2018

NCT #: NCT02677714

PHASE: Proof of Concept and Phase II study

DATE: Final version 1 dated 22 March 2019

DESIGN: Single centre study.

INVESTIGATIONAL PRODUCT: Kit for the Preparation of Tc-99m Recombinant Human Annexin V-128 for Injection

APPROVAL/REVISION HISTORY

Autorship/Approval

Author:	[redacted], [redacted]	Date
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Revision history

Rev.	Name	Date	Note
1			

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01				

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2 List of abbreviations

AAA	Advanced Accelerator Applications
AC	Doxorubicin/Cyclophosphamide chemotherapy
AE	Adverse Event
ALAT	Alanine Aminotransferase
ALP	Alkanine Phosphatase
ALT	Alanine Transaminase
ANOVA	ANalysis Of VAriance
ASAT	Aspartate Aminotransferase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical classification system
AU	Absolute Uptake
BMI	Body Mass Index
BP	Blood Pressure
C.I.	Confidence Interval
CMRI	Cardiac Magnetic Resonance Imaging
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUR	Cardiac Uptake Ratio
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked ImmunoSorbent Assay
[redacted]	[redacted]
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase

Hb	Hemoglobin
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
ID/g	Injected Dose per gram
IP	Investigational Product
IQR	Interquartile Range
ITT	Intention To Treat
kVp	Peak Kilovoltage
LGE	Late gadolinium enhancement
LLT	Lowest Level Term
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MBq	Mega Becquerel
MCV	Mean Corpuscular Volume
MHLTC	Ministry of Health and Long Term Care
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NT-proBNP	N Terminal pro B-type Natriuretic Peptide
OHSN-REB	Ottawa Hospital Science Network Research Ethics Board
PoC	Proof of Concept
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cells
REB	Research Ethic Board
ROI	Region of Interest
[redacted]	[redacted]
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
S.D.	Standard Deviation
SOC	System Organ Class
SPECT	Single-Photon Emission Computed Tomography
SUV	Standardized Uptake Value
TE	Echo Time
TR	Repetition Time
UOHI	University of Ottawa Heart Institute
WBC	White Blood Cells

3 Protocol title and number

^{99m}Tc-rhAnnexin V-128 Imaging of Apoptosis and Cardiotoxicity in Relationship to Ventricular Function in Patients with Early Stage Breast Cancer Receiving Doxorubicin-Based Chemotherapy (Protocol Number AAA-Annexin-05 v.7.0 dated 11 March 2018).

4 INFORMATION TAKEN FROM THE PROTOCOL

4.1 Study objectives

4.1.1 Primary objective

The primary objective of this study is to investigate ^{99m}Tc-rhAnnexin V-128 imaging of apoptosis in the evaluation of doxorubicin-induced cardiotoxicity in patients with early stage breast cancer.

4.1.1.1 Primary hypothesis

Patients with early stage breast cancer undergoing doxorubicin-containing (neo) adjuvant chemotherapy will have increased uptake of ^{99m}Tc-rhAnnexin V-128 at the end of the 2nd and the 4th cycles of AC treatment, and 12 weeks after the last cycle of doxorubicin, compared to baseline uptake.

4.1.2 Secondary objective

The secondary objectives of this study are:

- To determine the timing and extent of ^{99m}Tc-rhAnnexin V-128 imaging of apoptosis (^{99m}Tc-rhAnnexin V-128 myocardial uptake).
- To determine the relationship between ^{99m}Tc-rhAnnexin V-128 myocardial uptake and the changes in left ventricular (LV) function measured by cardiac magnetic resonance imaging (CMRI) and the changes in the cardiotoxicity biomarkers.

4.1.2.1 Secondary hypotheses

- Patients with early stage breast cancer undergoing doxorubicin-containing (neo) adjuvant chemotherapy will have worsening of LV function measured with CMRI at the end of the 2nd and the 4th cycle of treatment and 12 weeks from the last dose of doxorubicin chemotherapy compared to baseline.
- The uptake of ^{99m}Tc-rhAnnexin V-128 (percentage of injected dose per gram, % ID/g) will correlate with changes in CMRI LV function parameters and changes in the cardiotoxicity biomarkers.

4.2 Study design

This is a single centre, Proof of Concept (PoC), Phase II study. Patients with histologically confirmed early stage (Stage I, II and III) HER-2 negative breast cancer and scheduled to receive (neo) adjuvant doxorubicin-based chemotherapy (A - 60 mg/m^2; C - 600 mg/m^2; every 2 or 3 weeks x 4 cycles) to be followed by paclitaxel or docetaxel as per clinical practice will be recruited from the Ottawa Hospital Cancer Centre. Participants will be scheduled for cardiac MRI and ^{99m}Tc-rhAnnexin V-128 imaging prior to initiating doxorubicin-based chemotherapy. Participants will also undergo ^{99m}Tc-rhAnnexin V-128 imaging and CMRI at the end of the 2nd and the 4th cycles of AC treatment and 12 weeks after the last cycle.

4.2.1 Study population

Approval for the study will be obtained from the Ottawa Hospital Science Network Research Ethics Board (OHSN-REB) and Health Canada. All participants will provide written informed consent prior to the initiation of any study procedures. It is foreseen to recruit thirty patients with early stage breast cancer.

4.2.1.1 Inclusion criteria

1. Females ≥ 18 years of age with histologically confirmed early stage (stage I, II or III) HER-2 negative breast cancer and planned to receive (neo) adjuvant doxorubicin-based (A - 60 mg/m^2; C - 600 mg/m^2; every 2 or 3 weeks x 4 cycles) chemotherapy.
2. Eastern Cooperative Oncology Group Status (ECOG) ≤ 2 (see Appendix II of study protocol).
3. Able and willing to comply with the study procedures.

4.2.1.2 Exclusion criteria

1. Pregnancy or lactation.
2. Moderate or severe valvular stenosis or regurgitation.
3. History of atrial fibrillation or flutter.
4. History of any disease or relevant physical or psychiatric condition which may interfere with the study objectives at the investigator judgment.
5. Known hypersensitivity to the investigational product or any of its components.
6. Prosthetic valve or pacemaker.
7. Claustrophobia or inability to lie still in a supine position.
8. Contraindication(s) to CMRI procedure.
9. Participation in another clinical trial within 4 weeks before study inclusion, except for patients who have participated or who are currently participating in a study without any study drug administration.
10. Unwillingness to provide consent.

4.2.2 Study exposure

The "Kit for preparation of ^{99m}Tc-rhAnnexin V-128 for injection" consists of 1 dose. Participants will receive 1 dose of 350 MBq ± 10% of ^{99m}Tc-rhAnnexin V-128 administered as a single intravenous bolus over 10-20 seconds at each of the four MRI scans (at screening, after the 2nd cycle, after the 4th cycle and 12 weeks after AC chemotherapy). Thus subjects will be exposed to a total of 4 ^{99m}Tc-rhAnnexin V-128 injections.

4.2.3 Termination of the study

Early termination of the study can occur in the following cases:

- When the visual review and analysis of the images of the first 10 participants by the DMC does not demonstrate the diagnostic potential of the study product in terms of quality or efficacy, the Sponsor may discontinue the clinical study by sending a written notice to the investigator and competent authorities.
- When the Sponsor is aware of new information on matters concerning the safety of the study product, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may discontinue the clinical study and send a written notice of the discontinuation to the investigator and competent authorities.
- If the investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor in written about the discontinuation and the reason for it.

- The study is stopped by a regulatory authority.

If none of the previous condition applies, the end of study is defined as the completion of all study procedures in the last enrolled participant (i.e. last visit, last participant).

The Sponsor reserves the right to discontinue the study at any time for any reason by sending a written notice of the discontinuation to the investigator and competent authorities.

4.3 Methods and procedures

4.3.1 Source of study population

Patients from the Ottawa Hospital Cancer Centre will be enrolled. The Ottawa Hospital Cancer Centre sees about 1,000 patients per year with breast cancer (Stage I to III) and it is estimated that 4 to 5 per month would meet the study inclusion criteria. We plan to recruit 30 patients over 18 to 24 months, or approximately 1 to 2 patients per month.

4.3.2 Participant study identification

A unique participant identification number (Participant ID) will be assigned at the start of the screening period to each participant who signs the informed consent form. This number will identify the participant throughout the study. Participant IDs will include the 2-digit protocol number (05), the 2-letter code (CA) and a 3-digit participant number (ex: 05-CA-001 for first participant in).

4.3.3 Study procedure

Voluntary written informed consent will be obtained prior to the initiation of any study-related procedures. Study conduct procedures will include a screening visit and the imaging visits.

4.3.3.1 Baseline assessments

- Each participant's date of birth (mm/yyyy), gender, ethnicity, medical history, and relevant baseline characteristics will be recorded.
- Inclusion and Exclusion criteria will be checked.
- Results from any standard of care testing related to the participant's condition will be collected and will include baseline echocardiography when available.
- Women of childbearing potential must have negative pregnancy test at screening.
- Height, weight, BMI and vital signs will be recorded.

4.3.3.2 Efficacy assessments

4.3.3.2.1 ^{99m}Tc-rhAnnexin V-128 Planar and SPECT imaging and image analysis

Administration of the ^{99m}Tc-rhAnnexin V-128 (350 MBq ± 10%) will be as a single bolus via an intravenous catheter in an antecubital vein followed by a saline flush. All images will be acquired with a dual head SPECT/CT gamma camera with low-energy high-resolution collimators. The energy acceptance window for the ^{99m}Tc photopeak will be 140 keV (± 10%). A low dose CT scan (helical, 120 kVp, 1 mA with 1.9 pitch) will be acquired of the thorax for attenuation correction.

Planar imaging will be performed in the anterior view with acquisition using a 256 x 256 matrix, an energy window set for Tc^{99m} at 140 keV +/- 10% and a low energy, high resolution (LEHR) collimator. The image will be acquired for 1200s at one and two hours post injection of radiotracer.

Reconstruction will be done using iterative reconstruction incorporating CT-based attenuation correction and dual-energy-window scatter correction. Planar and SPECT images of the thorax will be acquired at 1 and 2 hours post injection. Acquired images will be stored for off-line analysis using a Hermes Gold workstation (Hermes Medical Solutions). Myocardial uptake will be measured from regions of interest (ROIs) placed over the myocardium on the SPECT images co-registered with the corresponding CT images for anatomic delineation. Myocardial uptake will be expressed in absolute units (% injected dose/g) or as a standardized uptake value (SUV). As a secondary analysis, a simpler approach without attenuation and scatter corrections will also be used by determination of a cardiac uptake ratio (CUR) with a second group of ROIs placed over the axillary soft tissues to obtain a value representative of background.

$$\text{CUR} = \frac{\text{Myocardium (counts/pixel)} - \text{Soft tissue (counts/pixel)}}{\text{Soft tissue (counts/pixel)}}$$

Inter and intra-observer variability will be determined by repeated analysis of the images of all participants.

4.3.3.2.2 Cardiac magnetic resonance imaging

Cardiac MRI will be performed either with a 1.5-T scanner (Siemens, Erlangen, Germany) or a 3.0-T Scanner (Siemens, Erlangen, Germany). Transverse images will be acquired with an inversion recovery prepared dark blood HASTE sequence (repetition time [TR] 600 ms, echo time [TE] 26 ms, 6 mm slice thickness, 1.8 mm interslice gap, matrix 256x104). Cine bright-blood images in the 4- and 2-chamber and long-axis planes will be performed with a breath-hold balanced steady-state free precession sequence (true fast imaging with steady-state precession, TR 42 ms, TE 1.2 ms, flip

angle 70°, 6 mm slice thickness, matrix 192x174). Cine breath-hold balanced steady-state free precession short-axis images will be acquired for the entire LV from the base to the apex (stack of 10 sequential short-axis slices; TR 64 ms, TE 1 ms, flip angle 80°, 8 mm slice thickness, 1.6 mm interslice gap, matrix 192x132) to obtain measurements of left ventricular ejection fraction.

To evaluate for myocardial edema, dark blood T2-weighted turbo spin echo short-axis images will be obtained (TR 1,800 to 2,100 ms, TE 74 ms, 8 mm slice thickness, 4 mm interslice gap, matrix 256x175). At each imaging session, a single 5 mL blood sample will be withdrawn for measurement of the hematocrit, to be used in conjunction with the T1 measurements to ensure accurate estimation of extracellular volume. T1 maps in short-axis oblique and four chamber views using a modified Look-Locker inversion recovery, "MOLLI" will be acquired before the administration of contrast to obtain native T1 values. Late gadolinium enhancement (LGE) images will be obtained after 10 min of 0.2 mmol/kg injection of gadolinium (Gadovist®, Bayer Inc.) with a T1-weighted inversion recovery-prepared multislice true fast imaging with steady-state precession sequence with magnitude and phase-sensitive reconstruction. Images will be acquired sequentially in the short axis, followed by horizontal and vertical long-axis images (TR 700 ms, TE 1.0 ms, flip angle 40°, 8 mm slice thickness, 1.6 mm interslice gap, matrix 192x144). To quantify the myocardial mass of the LGE, the endocardial and epicardial borders of the short-axis view of the LV will be manually traced. The computer-assisted detection algorithm will be used to define LGE as any region with a signal intensity ± 2 SD above a reference remote myocardial region. The LGE mass will be expressed as a percentage of the LV mass. 15 minutes post injection, we will acquire post contrast T1 maps in short-axis oblique and four chamber views. All analysis including quantitative will be performed with dedicated computer software (CVI 42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada).

4.3.3.2.3 Cardiotoxicity biomarkers assessments

Blood samples (3 mL) for cardiotoxicity biomarkers assessments (troponin, NT-proBNP) will also be collected at screening and before each injection of ^{99m}Tc-rhAnnexin V-128.

4.3.3.3 Safety assessments

- Medical review, including the measurement of the weight and BMI, will be performed before each ^{99m}Tc-rhAnnexin V-128 administration.
- Measurement of vital signs (systolic and diastolic blood pressure and heart rate) will be performed 15 minutes before each ^{99m}Tc-rhAnnexin V-128 administration and at the end of the second imaging procedure.

- Women of childbearing potential must have negative pregnancy test at screening, before each IP administration and before each CMRI (in case the CMRI is not performed on the same day of IP administration).
- After signature of the ICF, any medical events defined as Adverse Events will be recorded and followed until the last study related procedure or until resolution.
- All medications taken from 2 weeks prior to the first administration date through the end of study will be recorded as concomitant medications.

4.3.3.3.1 Adverse events and other safety aspects

Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a participant and which does not necessarily have a causal relationship with the IP. An AE can therefore be any unfavorable and unintended sign (including an abnormal clinically significant laboratory finding), symptom, or disease, temporarily associated with the use of an IP, whether or not causally related to the IP.

AEs will be reported, if applicable, from the signing of the informed consent until the last study-related procedure. AE severity will be assessed according to the grading system of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) as included in Appendix III of study protocol.

Definition of Serious Adverse Events

A SAE is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
  Note: “life-threatening” refers to an event in which the participant is 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 was more severe;
- results in persistent or significant disability/incapacity;
- results in congenital anomaly or birth defect;
- requires in-participant hospitalization or leads to prolongation of hospitalization, with the exception of elective pre-planned hospitalizations.

Serious Adverse Events (SAE) will be defined according to ICH/GCP and Regulatory Standards. SAEs will be reported from the signing of the informed consent and followed until resolution or determined to be not clinically significant. The specific SAE Reporting Form should be used (Appendix IV of study protocol).

Procedure in Case of Pregnancy

Prior to clinical study enrolment, women of childbearing potential must be advised of the importance of avoiding pregnancy during clinical study participation and the potential risks for an unintentional pregnancy. During the clinical study, all women of childbearing potential should use of a reliable means of contraception, and should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g. missed or late menstrual period).

The investigator must report to the Sponsor any pregnancy associated with IP exposure including conceptions occurring until 30 days after the IP administration using the specific Pregnancy Form (Appendix V of study protocol). Appropriate pregnancy follow-up procedures will be considered if indicated. The Investigator should respond in accordance with the reporting procedure for SAEs including information regarding the outcome of pregnancy.

New Safety Information Affecting the Conduct of the Study

Any information or changes significantly affecting the conduct of the trial and/or increasing the risk to participants will be provided to all investigators, REB(s), and Regulatory Authorities. Depending on the nature of the information or the changes, the protocol and/or the participant information may necessitate an amendment.

Data Monitoring and Safety

The data collected for this study is observational in design and will not be used for clinical care or clinical decision making. No formal DSMB will be formed. However, the safety data will be part of the review and assessment by the DMC.

4.3.3.3.2 Laboratory assessments

Blood samples for hematology, blood chemistry and urinalysis will be obtained at baseline for screening, and 12 weeks after the end of chemotherapy and following any adverse effects attributed to the study procedures. Results from laboratory analysis conducted during the oncology treatment will be used for research analysis.

In the case of clinically significant abnormalities in baseline laboratory values, the participant will be declared as a screening failure.

Hematology	**Blood chemistry**	**Urinalysis**
• WBC with differential • RBC • Platelets • Hb • MCV • Hematocrit[2]	• Total bilirubin • ALP • AST/ASAT • ALT/ALAT • Gamma-GT • Creatinine[3]	• Dipstick test[1] • Pregnancy test (*at screening, before each injection of study product*

		and before each CMRI, if applicable)

[1] If any of the assessments of the dipstick test is positive, a microscopic analysis of the urine must be performed.
[2] An additional 5 mL blood sample will be collected at each CMRI visit for measurement of hematocrit to be used in conjunction with the T1 measurements to ensure accurate estimation of extracellular volume.
[3] Creatinine will be repeated for CMRI when required if not clinically available.

Laboratory Assessments, including cardiotoxicity biomarkers assessments, will be performed [redacted] at The Ottawa Hospital according to Ministry of Health and Long Term Care (MHLTC) standards.

4.3.3.3.3 Immunogenicity assessments

Anti-rhAnnexin V-128 IgG and IgM antibodies will be quantified in serum samples by ELISA. For this purpose 10 mL blood samples will be collected at screening and 12 weeks after the last dose of doxorubicin, before injection of ^{99m}Tc-rhAnnexin V-128. Serum will be prepared, divided into six aliquots and frozen (-80°C). Three out of six serum samples per time-point will be shipped to the central laboratory [redacted]. Remaining samples will be shipped only if required for analysis and destroyed at study end if not required.

4.3.3.3.4 Radiation risk assessment

Participants will receive radiation from ^{99m}Tc-rhAnnexin V-128 (350 MBq) for a dose of 3.0 mSv (8.1 ± 0.8 µSv/MBq and from the CT scan for attenuation correction for a dose of 0.4 mSv. Total dose for the ^{99m}Tc-rhAnnexin V-128 and CT will be 3.4 mSv for one imaging study and 13.6 mSv for the 4 administrations.

Since the annual background radiation dose at sea level in North America is 2.7 mSv, the total effect of dose for this study per patient radiation is equivalent to living 5 years in North America. This poses minimal risk to the participant and there are no expected consequences with this exposure.

4.3.3.4 Withdrawal/discontinuation

The withdrawal of a study participant is mandatory in the following cases:

- Pregnancy
- Protocol violation determined as critical

- Lost to follow-up
- Serious intercurrent illness or other safety reasons for which the Investigator considers it is in the best interest of the participant to withdraw from the study
- Screening failure
- Failure to complete prescribed cycle of anthracycline chemotherapy

A “screening failure” is a participant who has signed the informed consent, but who does not meet all selection criteria following the screening evaluations. For participants not considered eligible after the screening period, the reason for not being eligible must be documented. No additional assessments are needed. Participant information collected at the Screening visit will be entered in the eCRF and will be used in the study analysis.

A participant may withdraw from the study at any time. The primary reason for a participant’s withdrawal from the study should be determined if possible. The date and reason for discontinuation will be documented in the eCRF.

4.3.3.5 Prohibitions and restrictions

Patients who are pregnant will not be permitted to participate in the study. Pregnancy tests will be performed for all study participants (of childbearing potential) at baseline and prior to each IP administration.

All imaging will be performed in an ambulatory care setting. There are no specific precautions required for participants upon completion of Annexin and CMR imaging.

Any concomitant medication deemed necessary for the welfare of the participant during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the case report form, including any changes that have occurred during the study.

4.3.4 Schedule of assessments

Patients who have signed the informed consent and are eligible to participate in the study will undergo the following assessments:

- Screening will be conducted within 2 weeks prior to chemotherapy treatment initiation. Eligible and consenting patients will undergo a medical review (including measurement of the height, weight, and BMI), vital signs (systolic and diastolic blood pressure, heart rate), blood analysis and urinalysis. The following blood analysis will be conducted: cardiotoxicity biomarkers troponin and NT-proBNP (N terminal pro B-type natriuretic peptide), assessment

of anti-annexin V-128 antibodies (baseline value) and hematology/biochemistry as detailed in Section 4.3.3.3.2. Participants will undergo the first CMRI and SPECT/CT ^{99m}Tc-rhAnnexin V-128 scans.

- The planned chemotherapy treatment consists of doxorubicin 60 mg/m2 in combination with cyclophosphamide 600 mg/m2 IV (AC) every 2 or 3 weeks for 4 cycles to be followed by paclitaxel or docetaxel as per clinical practice, at the Ottawa General Hospital, with potential dose adjustments.
- After the 2nd cycle of doxorubicin and before the 3rd cycle, the participants will undergo a second series of study imaging procedures (CMRI, planar and SPECT/CT with ^{99m}Tc-rhAnnexin V-128). Blood sampling will be performed for the assessment of cardiotoxicity biomarkers (troponin, NT-proBNP).
- After the 4th cycle of doxorubicin and with 2 weeks after the 4th cycle, participants will undergo the third series of study imaging procedures (CMRI, planar and SPECT/CT with ^{99m}Tc-rhAnnexin V-128). Blood sampling will be performed for the assessment of cardiotoxicity biomarkers (troponin, NT-proBNP).
- At 12 weeks after the 4th cycle of doxorubicin, participants will undergo the fourth series of study imaging procedures (CMRI, planar and SPECT/CT with ^{99m}Tc-rhAnnexin V-128). Blood sampling will be performed for the assessment of cardiotoxicity biomarkers (troponin, NT-proBNP) and hematology/biochemistry as detailed in Section 4.3.3.3.2. Urinalysis will also be performed. Immunology blood sampling will be performed to rule out the development of anti-annexin V-128 antibodies.
- The imaging procedures will be conducted at the University of Ottawa Heart Institute (UOHI). Safety assessments will be done at each procedure. The CMRI and the SPECT/CT imaging will be done on the same day or within one week of each other.
- Relevant results (if available) from clinical laboratory assessments performed during the treatment period will be used for the study analysis.
- After completion of the last follow-up visit at 12 weeks following chemotherapy in the first 10 participants, the Data Monitoring Committee (DMC) will conduct a visual assessment of the scans and provide recommendations for the continuation or termination of the Phase II study.

The following table summarizes all the procedures and evaluations to be conducted during the study:

Study Procedures	First UOHI Evaluation (Screening within 2 weeks prior to the start of AC treatment)	Second UOHI Evaluation (After the 2nd cycle of doxorubicin and before te 3rd cycle)	Third UOHI Evaluation (After the 4thcycle of doxorubicin and within 2 weeks)	Fourth UOHI Evaluation (12 weeks after the 4th cycle of doxorubicin)
Written informed consent	X			
Inclusion/exclusion criteria	X			
Medical history/review	X	X	X	X
Concomitant medications	X	X	X	X
Height[1], weight, BMI	X	X	X	X
Vital signs (BP, HR)	X	X	X	X
Lab analysis[2]	X			X
Immunogenicity by ELISA[3]	X			X
Cardiotoxicity biomarkers (troponin and BNP)	X	X	X	X
Pregnancy test	X	X	X	X
Cardiac Magnetic Resonance Imaging	X	X	X	X
rhAnnexin V-128 administration and SPECT/CT and Planar imaging	X	X	X	X
Adverse Events	X	X	X	X

[1] The height will only be measured at screening.

[2] See Section 4.3.3.3.2. Additionally, results from laboratory analysis conducted during the oncology treatment will be used for research analysis.

[3] Anti-rhAnnexin V-128 IgG and IgM antibodies will be quantified in serum samples by ELISA. For this purpose, 10 mL blood samples will be collected at screening and 12 weeks after the last dose of 4 cycles of doxorubicin (before ^{99m}Tc-rhAnnexin V-128 administration). Serum will be prepared, divided into six aliquots and frozen (-80°C). Three out of six serum samples per time-point will be shipped to the central laboratory [redacted]

4.3.5 Planned sample size

Sample size was estimated for the comparison of ^{99m}Tc-rhAnnexin V-128 uptake in doxorubicin treated patients imaged after 2 cycles of doxorubicin versus normal baseline uptake using a 5% significance level and power of 95%. The measured heart uptake in 6 normal females (age 29.5 ± 4.6 years, mean ± SD) was 1.2 ± 0.2% ID/g in the phase I study. Sample size estimations were done

assuming results in the baseline studies of the patients will be similar to the normal females in the phase I study.

For the comparison of ^{99m}Tc-rhAnnexin V-128 uptake using a paired analysis and assuming a similar SD of 0.2%, a sample size of 26 patients will allow to detect a change of 0.15 %ID/g with a two-sided 5% significance level and a power of 95% (difference between two dependent means).

For the comparison of left ventricular ejection fraction (LVEF) measured with CMR, a sample size of 28 patients will detect an absolute difference of 5% LVEF units with a two-sided 5% significance level and a power of 95% using a paired analysis and assuming a SD of 7 (difference between two dependent means). Assumptions were based on representative CMR data for LVEF of 58 ± 7% from 53 participants with breast cancer, lymphoma, leukemia and myelodysplastic syndrome.

The final study population for recruitment size will be 30 patients, allowing for 5 to 10% patient attrition or incomplete imaging data.

5 SUBJECT POPULATIONS (ANALYSIS SETS)

5.1 Efficacy

5.1.1 Full analysis set (FAS)

In accordance with the Intention To Treat (ITT) principle the FAS population includes all subjects who received the study drug and completed at least one ^{99m}Tc-rhAnnexin V-128 imaging procedure.

5.1.2 Per Protocol population (PP)

All subjects in the FAS population for whom no major protocol violations/deviations occurred and have attended all the scheduled visits. The criteria defining the major protocol deviations will be established before the data base locking.

5.2 Safety set

The safety population is made up of all subjects who received at least one administration of ^{99m}Tc-rhAnnexin V-128.

5.3 Primary population

The primary and secondary efficacy analysis will be based on the FAS population.

The assessment of safety and tolerability will be based on the Safety population.

6 STATISTICAL METHODS

6.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with the principles of ICH E9 guideline and the guideline on clinical evaluation of diagnostic agents and they will be based on data from the study site, unless otherwise stated.

The statistical analysis will be performed by [redacted] – Italy.

6.1.1 Efficacy endpoint(s)

6.1.1.1 Primary endpoint of PoC

Image quality, imaging agent uptake and clinical relevance of apoptosis imaging in the evaluation of doxorubicin-induced cardiotoxicity in patients with early stage of breast cancer using ^{99m}Tc-rhAnnexin V-128 will be determined by the DMC (visual image review and consensus). Parameters used by DMC to assess primary endpoint of PoC will be appended to the CSR.

6.1.1.2 Primary endpoint of Phase II

Given the early discontinuation of the study, and the fact that only 2 patients were enrolled in the Phase II part of the study, the efficacy endpoints of the Phase II will not be addressed. Any efficacy data collected for these 2 patients will be provided in patients data listings in addition to the results from the PoC phase.

6.1.1.3 Secondary endpoints

The secondary efficacy endpoints will not be addressed for the same reason as the primary efficacy endpoint for the Phase II part of the study.

6.1.2 Safety endpoint(s)

Safety and tolerability will be primarily evaluated by the incidence of adverse events, clinical laboratory values (hematology, blood chemistry and urinalysis), development of anti-annexin V-128 antibodies, vital signs (blood pressure and heart rate), and physical examination findings.

All safety data will be included in the data listings and summary tables will be based on the safety population. The statistical analysis of safety data will be mainly descriptive in nature.

For continuous variables, descriptive summary statistics will include the number of non-missing values, number of missing values, mean, standard deviation, 95% 2-sided confidence interval, median, lower and upper quartile, minimum and maximum. Box plot graphs will also be presented when appropriate.

For categorical variables, descriptive summary statistics will include counts and percentages per category. Staked column graphs or pie graphs will also be computed if appropriate.

For analysis purposes, baseline for a given assessment will be defined as the last non-missing value prior to the administration of ^{99m}Tc-rhAnnexin V-128, unless stated otherwise.

6.1.2.1 Adverse events

All original AE/SAE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0.

Adverse events (AEs) will be listed on an individual basis, including relationship and severity, PT (Preferred Term) and verbatim term. Treatment Emergent Adverse Events (TEAEs) and Adverse Drug Reactions (ADRs) will be summarized by System Organ Class (SOC) and Preferred Term (PT). Patients with more than one adverse event within a particular SOC and PT will be counted only once for that SOC and PT reporting the highest level in severity. The incidence of TEAEs and ADRs will also be summarized by severity.

Listings and summaries of serious adverse events (SAEs), adverse events leading to withdrawal and listings of deaths will also be presented.

Treatment Emergent Adverse Events and Adverse Drug Reactions will be defined as below:

- Treatment Emergent Adverse Events: Events that emerge after the first ^{99m}Tc-rhAnnexin V-128 injection and up to 30 days after the last injection that were absent before it or worsen relative to the pre-treatment state.
- Adverse Drug Reactions: Treatment emergent adverse events possibly or probably related to study treatment.

6.1.2.2 Clinical laboratory values

Hematology and blood chemistry values are recorded at each imaging visit (4 visits) while urinalysis and immunogenicity values are recorded only at baseline, for screening, and after 12 weeks of the

last cycle of doxorubicin. Patients data listings of all laboratory data collected during the study will be provided. Any abnormal results (both clinically and non-clinically relevant) will also be flagged in the listings.

6.1.2.3 Vital signs and medical review

Medical review data are recorded once at each imaging visit (4 visits) while vital signs data are recorded twice at each imaging visit (4 visits), before the injection of ^{99m}Tc-rhAnnexin V-128 and at the end of last SPECT/CT procedure (within 2 hrs after ^{99m}Tc-rhAnnexin V-128 injection). Patients data listings of all vital signs collected during the study will be provided.

6.1.3 Missing data and outliers

6.1.3.1 Missing data

As stated in the protocol, missing data will not be replaced.

6.1.3.2 Missing or incomplete dates

Incomplete dates due to missing day will be recorded as full dates replacing the missing day with the first day of month (01). Incomplete dates due to missing day and month will be recorded as full dates replacing the missing day and month with the first day of month and first month of the year (01/January). The trial database will record the information about incomplete dates due to missing day or due to missing day and month.

Only the incomplete dates related to medical history (date of diagnosis and end date), concomitant medications (start and end date) and AEs (start and end date) will be replaced according to the above rule.

Calculation, sorting or assignation based on dates, in case of incomplete dates, will be performed using the related full dates defined by the above rule.

In all listings, missing dates will be missing and incomplete dates will be reported as full dates. In all listings will also be reported the information about incomplete dates according to the following coding: missing value = full date, Day = missing day, Day&Month = missing day and month.

6.1.3.3 Outliers

For categorical or score data, like adverse events, physical exam's findings and disease assessment parameters, outliers are not expected.

Demographic, vital signs, and clinical laboratory (hematology, blood chemistry and urinalysis) parameters will be checked for outliers according to data plausibility, normal ranges and the range between ± 2 S.D.

For each identified outlier, [redacted] will inform the Sponsor in order to assess any errors. If data cannot be verified or if relevant, the descriptive statistics of the related parameters will be reported with and without the outliers. If appropriate, outliers can also be specifically identified in the boxplots.

6.1.4 Subject disposition

A listing of dates of assessments (relative day) and their study exposure will be presented by subject.

A summary table and a flow chart will be presented for each subject population presenting the number of subjects at each assessment procedure and identifying the number of subjects who withdrew over time.

6.1.5 Withdrawals

Discontinued subjects will be listed and a summary table of the number and percentage of subjects who withdrew from the study and the reasons for withdrawal will be presented for all screened subjects.

6.1.6 Demographic and baseline characteristics

All demographic and baseline characteristics will be listed by subject. Summary statistics will be provided for demographic and baseline characteristics for FAS population.

6.1.7 Medical and surgical history

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0.

Medical and surgical history will be listed on an individual basis, including Preferred Term (PT) and verbatim term; the listings will be sorted by subject.

6.1.8 Subject compliance

After reconstitution and radiolabeling, ^{99m}Tc-rhAnnexin V-128 is administered as a single intravenous bolus of 350 MBq ± 10% at each imaging visit (4 visits). The administered dose recorded in the eCRF will not be the difference between the pre-injection dose and the post-injection residual dose but will be the decay corrected dose which takes into account the natural product half-life.

A listing will be presented for imaging product administration (dose, quality, date) by subject. Deviations from observed and scheduled times will be presented. Summary tables will be presented for all the continuous variables.

A listing will be presented for important concomitant medications.

All the protocol deviations will be also listed by subject.

6.1.9 Prior and concomitant therapies

Concomitant therapies will be coded using ATC Drug Dictionary Version 2016.

Listings will be presented for ATC name (third level) and verbatim text. The listings will be sorted by subject, chronological start date, ATC name, verbatim text and active substance.

6.1.10 Derived data

The derived data are variables which are calculated from the raw data in the eCRF and not included in the database (e.g.: Age, BMI). The formula used for derived data and the strategy for missing data are provided in Section 12.1.

6.1.11 Visit windows

The screening visit (Screening Visit Part 1) can occur anytime within 2 weeks before the injection day (Screening Visit Part 2 – First IP injection and CMRI).

The first follow-up visit (Visit 2) should occur within 24 to 48 hrs after 2nd doxorubicin cycle. The second follow-up visit (Visit 3) should occur within 24 to 48 hrs after 4th doxorubicin cycle. The third and last follow-up visit (Visit 4) should occur 12 weeks after 4th doxorubicin cycle.

6.1.12 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places.

The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

For summary statistics, the following will be presented: number of non-missing values (n), number of missing values, arithmetic mean, standard deviation, median, the IQR (first quartile, third quartile), the range (minimum, maximum) and, only if appropriate, 95% 2-sided confidence interval.

Mean, standard deviation, first quartile, median, third quartile and confidence interval values will be rounded to one more decimal place than the raw data whereas minimum and maximum will be reported with the same precision as the raw data.

Percentages will be reported to one decimal place. Percentages will be calculated using a denominator of all subjects in a specified population. The denominator will be specified in a footnote to the tables for clarification if necessary.

p-values will be reported to four decimal places (e.g.: p=0.0037), after rounding; p-values which are less than 0.0001 will be presented as “<0.0001”.

All text fields must be left justified and numeric or numeric with some text specification (e.g. not done, unknown, <4.5, …) must be decimal justified. Dates will be presented in the format [dd/mm/yyyy] and times in the format [hh:mm] using 24-hour clock scale.

6.1.13 Pooling of centres

Not applicable.

6.1.14 Interim analysis

No formal interim analysis will be done; however the DMC will review the images of the first 10 participants of the study to determine the feasibility of imaging apoptotic activity in the evaluation of doxorubicin-induced cardiotoxicity.

6.1.15 Role of independent data monitoring committee (DMC) / interim data review committee

The Data Monitoring Committee (DMC) consists of investigators and Sponsor representatives, as well as external persons such as independent experts, if deemed necessary by the Sponsor. The main function of the committee will be to review and evaluate the images of the first 10 participants in terms of image quality, visual efficacy (uptake) and clinical relevance of the study product, and determine if there is a significant evidence of inadequate technical performance in this study group. The DMC will also determine if there is an excess of adverse events.

The DMC will promptly give recommendations to continue or terminate the study. The DMC report will be prepared by the Sponsor and sent to the REB and regulatory authorities as required. Preliminary results can be used by the Sponsor for publication purpose, before the end of the main trial.

6.1.16 Covariates and analysis of subgroups

Not applicable.

6.1.17 Sensitivity analysis

Not applicable.

6.1.18 Multiplicity

As stated in the protocol, no adjustements will be made for multiplicity.

6.1.19 Significance testing and estimation

Not applicable.

7 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

7.1 Hardware

The statistical analysis will be performed using Dell personal computer with Windows 7 professional (64 bit) as operating system.

7.2 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS version 9.4. All output will be in Word format.

7.3 Validation programs

An Independent Statistician is responsible for reviewing each project program and output associated with the deliverable product. Program logs are reviewed for logical, syntax and fatal errors. The review in SAS includes, but is not limited to, all ERRORS, WARNINGS, NOTES, and variables check. Program logs are also reviewed for accurate and consistent variable and observation counts following each procedure and data step.

The Independent Statistician is also responsible for checking and reviewing the work produced using whatever method he/she feels is appropriate (e.g. SAS commands review, hand calculation, etc.) to reassure of the quality of the output.

Outputs are reviewed for typographical errors, misspellings and nonsensical values or results and to check the consistency with the reporting and analysis plan. Outputs are cross-checked against each other for accuracy and consistency. For statistical tables, listings, and figures, this procedure includes comparison of subject group numbers, counts of subjects at each observation point, and consistency of results for variables between outputs.

Findings of the quality control reviews are communicated to the party responsible for making necessary changes. The programs will be retested after modifications.

After final review, and when no further changes are required to produce the deliverable, the Independent Statistician needs to complete and sign the SAS Outputs, to indicate that he has successfully performed all of his responsibilities.

8 CHANGES FROM PROTOCOL

As per the sponsor decision, it was decided to close the study after the first 12 patients were enrolled. For this reason and due to the small number of patients included in the protocol, the efficacy analyses will be reduced to the analyses presented during the proof of concept meeting (10 patients) and the imaging data from the 2 additional patients will be presented in subjects data listings. In addition, summaries of demography, subject disposition and adverse events will be provided and any additional data will be presented in subjects data listings and the results described in a short close-out CSR.

9 REFERENCES

Not applicable.

10 DATA PRESENTATION

Data listings are presented for all screened subjects.

Footnotes should be used to clarify ambiguities (e.g.: the denominator used to calculate a percentage or notes for the programmer). If the number of footnotes is high, they could be presented only in the last page, with on each page the following footnote “See last page for listing notes”. The order of the footnotes for key symbols (*, ~) will be in the order that they appear in the listing.

10.1 Listings index

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued subjects

Listing 16.2.1.1: Subject Disposition – All Subjects

Listing 16.2.1.2: Subject Disposition – Study Withdrawals

Listing 16.2.1.3: Inclusion Criteria

Listing 16.2.1.4: Exclusion Criteria

Listing 16.2.1.5: Screening Failures

16.2.2 Protocol deviations

Listing 16.2.2: Protocol Deviations and Reasons for Exclusion from the Study Populations

16.2.3 Subjects excluded from the efficacy analysis

Not applicable

16.2.4 Demographic data

Listing 16.2.4.1: Demographics

Listing 16.2.4.2: Medical History and Associated Pathologies

Listing 16.2.4.3: Prior and Concomitant Medications

16.2.5 Compliance and/or drug concentration data

Listing 16.2.5.1: Study Drug Administration and Extent of Subject Exposure

Listing 16.2.5.2: Chemotherapy Treatment

16.2.6 Individual efficacy response data

Listing 16.2.6.1: Imaging Assessment

Listing 16.2.6.2: Cardiac Magnetic Resonance Imaging

Listing 16.2.6.3: Cardiotoxicity Biomarkers

16.2.7 Adverse event listings (each subject)

Listing 16.2.7.1: All Adverse Events

Listing 16.2.7.2: Serious Adverse Events

Listing 16.2.7.3: Adverse Events Leading to Withdrawal

Listing 16.2.7.4: Adverse Events with Outcome Death

16.2.8 Listing of individual laboratory measurements by subject

Listing 16.2.8.1: Hematology

Listing 16.2.8.2: Blood Chemistry

Listing 16.2.8.3: Urinalysis

Listing 16.2.8.4: Immunogenicity

16.2.9 Listing of other safety data

Listing 16.2.9.1: Pregnancy Test

Listing 16.2.9.2: Pregnancy Test (Before CMRI Procedure)

Listing 16.2.9.3: Medical Review

Listing 16.2.9.4: Vital Signs

10.2 Listing templates

Listing templates are provided in Appendix 11.1. The listings will be presented in landscape, in a fixed font (Arial) with a minimum size as 8.

10.3 Tables index

14. TABLES, FIGURES AND GRAPHS

14.1 DEMOGRAPHIC DATA

Table 14.1.1: Subject Disposition

Table 14.1.2: Analysis Populations

Table 14.1.3: Protocol Deviations

Table 14.1.4.1: Demographics – FAS Population

Table 14.1.4.2: Demographics – Safety Population

Table 14.1.5.1: Medical History and Associated Pathologies – Safety Population

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Table 14.3.2.1: Listing of Adverse Events with Outcome Death – Safety Population

Table 14.3.2.2: Listing of Serious Adverse Events – Safety Population

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Only raw narratives will be presented in this section if any.

14.3.4 Abnormal Laboratory Value Listing (each patient)

Only patients with clinically significant abnormal laboratory value(s) will be presented in this section if any.

Table 14.3.4: Abnormal Laboratory Value Listing (Each Patient) – Safety Population

14.3.5 Laboratory Measurements

Table 14.3.5.1: Hematology – Safety Population

Table 14.3.5.2: Blood Chemistry – Safety Population

Table 14.3.5.3: Urinalysis – Safety Population

Table 14.3.5.4: Immunogenicity – Safety Population

14.3.6 Other Safety Data

Table 14.3.6.1: Medical Review – Safety Population

Table 14.3.6.2: Vital Signs – Safety Population

10.4 Table templates

Table templates are provided for each unique table in Appendix 11.2. The tables will be presented in landscape, in a fixed font (arial) with a minimum size as 8.

All tables, in table number order, must be presented in a single Word file.

10.5 Figures index

14. TABLES, FIGURES AND GRAPHS

14.2 EFFICACY DATA

Figure 14.2.1.1: Cardiotoxicity Biomarkers – FAS Population

Figure 14.2.1.1: Primary Efficacy Endpoint – AU (%ID/g) – FAS Population

Figure 14.2.1.2: Primary Efficacy Endpoint – AU (%ID/g) – PP Population

10.6 Figure templates

Figure templates are provided for each unique figure in Appendix 0. The figures will be presented in landscape, in a fixed font (arial) with a minimum size as 8.

All figures, in figure number order, must be presented in a single Word file.

10.7 Statistical appendix

A Statistical Appendix for inclusion in the study report will be provided. All the methods used in checking the assumptions of the analyses and conclusions should be included and explained. Transformation of the data or other methods used for the statistical analysis other than the ones detailed in the SAP will be described and the change will be justified. All the SAS output will be included without reworking the data (raw output).

This output should contain the study number, the date, the number of pages printed by SAS and the table number to which it refers. Any other relevant information (e.g. statistical references…) will be added in the statistical appendix.

11 APPENDICES

11.1 Standard listings

All listings must contain examples of possible data and be presented in fixed font (arial) with a minimum size as 8.

Listing 16.2.1.1: Subject Disposition – All subjects

Subject ID	Informed consent date	Screening part 1 date	Screening part 2 date	Visit 2 date	Visit 3 date	Visit 4 date	Premature study discontinuation date	FAS	PP	Safety
PAT_PATNUMBER	PAT_INFCONS_DATE	PAT_FIRSTVISITDATE	PATV_VISITDATE	PATV_VISITDATE	PATV_VISITDATE	PATV_VISITDATE	SD_DATE	[Derived data]	[Derived data]	[Derived data]
05-CA-001	11/03/2011	11/03/2011	11/03/2011	11/04/2011	12/04/2011	11/05/2011		Yes	Yes	Yes
05-CA-002	09/04/2011	09/04/2011	09/04/2011	09/04/2011	10/04/2011	10/05/2011		Yes	Yes	Yes
05-CA-003	10/07/2011	10/07/2011	10/07/2011	15/07/2011	16/07/2011	NA	10/08/2011	Yes	No	Yes

Data Source Table: W_PATIENT, W_PATIENTVIS, W_SD.

Note: NA = Not Available for patient early withdrawal

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.1.2: Subject Disposition – Study Withdrawals

Subject ID	Informed consent date	Screening part 1 date	Premature study discontinuation date	Reason for withdrawal	Explanation	Notes	FAS	PP	Safety
PAT_PATNUMBER	PAT_INFCONS_DATE	PAT_FIRSTVISITDATE	SD_DATE	SD_OUTCOME	SD_OUTCOME_SP	SD_NOTES	[Derived data]	[Derived data]	[Derived data]
05-CA-001	11/03/2011	11/03/2011	10/05/2012	XXXXXX	XXXXXX	XXXXXX	Yes	No	Yes
05-CA-002	09/04/2011	09/04/2011	10/05/2012	XXXXXX	XXXXXX	XXXXXX	Yes	No	Yes
05-CA-003	10/07/2011	10/07/2011	10/05/2012	XXXXXX	XXXXXX	XXXXXX	Yes	No	Yes

Data Source Table: W_PATIENT, W_SD.

Note: NA = Not Available for patient early withdrawal

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.1.3: Inclusion Criteria

			Inclusion criteria		
Subject ID	Age	Screening part 1 date	First	Second	Third
PAT_PATNUMBER	PAT_AGEYEAR	PAT_FIRSTVISITDATE	IC_1	IC_2	IC_3
05-CA-001	54	11/03/2011	Yes	Yes	No
05-CA-002	68	09/04/2011	Yes	Yes	Yes
05-CA-003	59	10/07/2011	No	Yes	Yes

Data Source Table: W_PATIENT, W_PATIENTVIS, W_IEC.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.1.4: Exclusion Criteria

			Exclusion criteria									
Subject ID	Age	Screening part 1 date	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	Ninth	Tenth
PAT_PATNUMBER	PAT_AGEYEAR	PAT_FIRSTVISITDATE	EC_1	EC_2	EC_3	EC_4	EC_5	EC_6	EC_7	EC_8	EC_9	EC_10
05-CA-001	54	11/03/2011	No	No	No	No	No	No	No	No	No	No
05-CA-002	68	09/04/2011	No	Yes	No	No	No	No	No	No	No	No
05-CA-003	59	10/07/2011	Yes	No	No	No	No	No	No	No	No	No

Data Source Table: W_PATIENT, W_PATIENTVIS, W_IEC.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.1.5: Screening Failures

Subject ID	Screening failure	Reason for screen failure
PAT_PATNUMBER	[Derived data]	[Derived data]
05-CA-001	Yes	XXXXX
05-CA-002	No	XXXXX
05-CA-003	No	XXXXX

Data Source Table: W_PATIENT, W_PATIENTVIS, W_IEC, W_SD.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.2: Protocol Deviations and Reasons for Exclusion from the Study Populations

Subject ID	Screening part 1 date	FAS	PP	Safety	Deviation description	Reason for exclusion
PAT_PATNUMBER	PAT_FIRSTVISITDATE	[Derived data]	[Derived data]	[Derived data]	[Derived data]	[Derived data]
05-CA-001	11/03/2011	Yes	Yes	No	XXXXXX	XXXXXX
05-CA-002	09/04/2011	No	Yes	Yes	XXXXXX	XXXXXX
05-CA-003	10/07/2011	Yes	No	Yes	XXXXXX	XXXXXX

Data Source Table: W_PATIENT, W_PATIENTVIS, W_SD.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.4.1: Demographics

Subject ID	Screening part 1 date	Date of birth (month/year)	Age	Ethnicity	Specify other ethnicity
PAT_PATNUMBER	PAT_FIRSTVISITDATE	PAT_BIRTH_MONTH PAT_BIRTH_YEAR	PAT_AGEYEAR	PAT_ETHNIC	PAT_ETHNIC_SP
05-CA-001	11/03/2011	03/1959	54	Other	XXXXXXXX
05-CA-002	09/04/2011	09/1945	68	Caucasian	
05-CA-003	10/07/2011	02/1954	59	Asian	

Listing 16.2.4.2: Medical History and Associated Pathologies

Subject ID	Medical condition	Preferred term	Date of diagnosis	Partial date	Ongoing?	Currently treated?	Resolution date	Partial date
PAT_PATNUMBER	MH_MEDCOND	MEDDRA_PT	MH_DIAGN_DATE	MH_PARTIAL_START_DATE	MH_ONGOING_YN	MH_TREATED_YN	MH_END_DATE	MH_PARTIAL_END_DATE
05-CA-001	XXXXXX	XXXXXX	15/08/1990	Day	No		14/04/1994	
05-CA-002	XXXXXX	XXXXXX	31/12/2007		No		15/06/2008	Day&Month
05-CA-003	XXXXXX	XXXXXX	05/05/2005		Yes	Yes		

Data Source Table: W_PATIENT, W_MH.

Dictionary Name: MedDRA Version: 19.0

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.4.3/1: Prior and Concomitant Medications

Subject ID	Medication trade name	ATC description (third level)	Enrollment date	Start date (day)	Partial date	Ongoing?	End date	Partial date
PAT_PATNUMBER	CM_NAME	ATC_LV3_DESCR	PAT_FIRSTVISITDATE	CM_START_DATE	CM_PARTIAL_START_DATE	CM_ONGOING_YN	CM_END_DATE	CM_PARTIAL_END_DATE
05-CA-001	XXXXXXXX	XXXXXX	11/03/2011	15/08/1990 (xx)	Day	No	14/04/1994	Day
05-CA-002	XXXXXXXX	XXXXXX	09/04/2011	31/12/2007 (xx)	Day&Month	No	15/06/2008	Day&Month
05-CA-003	XXXXXXXX	XXXXXX	10/07/2011	05/05/2005 (xx)		Yes		

Data Source Table: W_PATIENT, W_CM.

Dictionary Name: ATC Version: 2016

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.4.3/2: Prior and Concomitant Medications

Subject ID	Medication trade name	ATC description (third level)	Total daily dose	Unit	Specify other unit	Frequency of administration	Specify other frequency	Route of administration	Specify other route
PAT_PATNUMBER	CM_NAME	ATC_LV3_DESCR	CM_DOSE	CM_DOSEU	CM_DOSEU_SP	CM_FREQ	CM_FREQ_SP	CM_ROUTE	CM_ROUTE_SP
05-CA-001	XXXXXXXX	XXXXXX	3	G		BID		Otherl	XXXXXX
05-CA-002	XXXXXXXX	XXXXXX	3	Other	XXXXXX	TID		Intramuscolar	
05-CA-003	XXXXXXXX	XXXXXX	12	Mg		Other	XXXXXX	Subcutaneous	

Data Source Table: W_PATIENT, W_CM.

Dictionary Name: ATC Version: 2016

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.5.1/1: Study Drug Administration and Extent of Subject Exposure

Subject ID	Visit	Visit date	Has the injection been performed?	Reason for not performing the injection	Injection date	Injection time	Batch of kit	Batch of ^{99m}Tc generator
PAT_PATNUMBER	VISIT_NAME	PATV_VISITDATE	ANN_YN	ANN_YN_SP	ANN_DATE	ANN_TIME	ANN_KIT	ANN_GEN
05-CA-001	Screening part 1	10/03/2011	Yes		11/03/2011	10:50	09101-110631	09101-110631
05-CA-002	Screening part 2	08/02/2011	Yes		03/03/2011	10:00	09101-110981	09101-110981
05-CA-002	Visit 1	08/03/2011	Yes		08/03/2011	11:00	09101-110981	09101-111012
05-CA-003	Screening part 2	01/04/2011	No	XXXXXXX				

Data Source Table: W_PATIENT, W_PATIENTVIS, W_ANN.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.5.1/2: Study Drug Administration and Extent of Subject Exposure

Subject ID	Visit	Visit date	Has the injection been performed?	Radiochemical purity	Pre injection total activity-dose in the syringe (MBq)	Post injection residual activity-dose in the syringe (MBq)	Actual dose injected (MBq)	Volume of administered solution (mL)
PAT_PATNUMBER	VISIT_NAME	PATV_VISITDATE	ANN_YN	ANN_TEST1	ANN_TEST2_PRE	ANN_TEST2_POST	ANN_TEST2_EFF	ANN_TEST2_VOL
05-CA-001	Screening part 1	10/03/2011	Yes	98.7%	123	123	123	123
05-CA-002	Screening part 2	08/02/2011	Yes	99.1%	456	456	456	456
05-CA-002	Visit 1	08/03/2011	Yes	99.1%	789	789	789	789
05-CA-003	Screening part 2	01/04/2011	No					

Data Source Table: W_PATIENT, W_PATIENTVIS, W_ANN.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.5.2: Chemotherapy Treatment

				First cycle		Second cycle		Third cycle		Fourth cycle		
Subject ID	Visit date	Has chemotherapy been started?	Chemotherapy start date	Doxorubicin dose (mg/m^2)	Cyclophosphamide dose (mg/m^2)	Doxorubicin dose (mg/m^2)	Cyclophosphamide dose (mg/m^2)	Doxorubicin dose (mg/m^2)	Cyclophosphamide dose (mg/m^2)	Doxorubicin dose (mg/m^2)	Cyclophosphamide dose (mg/m^2)	Number of cycles
PAT_PATNUMBER	PATV_VISITDATE	CT_YN	CT_DATE	CT_DOX1	CT_CYC1	CT_DOX2	CT_CYC2	CT_DOX1	CT_CYC1	CT_DOX2	CT_CYC2	CT_CT_N
05-CA-001	10/03/2011	Yes	11/03/2011	400	250	514	625	514	625	514	625	4
05-CA-002	08/02/2011	Yes	03/03/2011	350	400	654	258	654	258	654	258	4
05-CA-003	01/04/2011	No										

Data Source Table: W_PATIENT, W_PATIENTVIS, W_CT.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.6.1/1: Imaging Assessment

Subject ID	Visit	Visit date	Injection date	Imaging procedure	Time from IP injection (min)	Has the imaging been completed?	Reason for non completion	Date	Time	Have images been received and reviewed?
PAT_PATNUMBER	VISIT_NAME	PATV_VISITDATE	ANN_DATE	[Derived data]	[Derived data]	SP_YN SPCT_YN	SP_YN_SP SPCT_YN_SP	SP_DATE SPCT_DATE	SP_TIME SPCT_TIME	SP_REV_YN SPCT_REV_YN
05-CA-001	Screening part 2	10/03/2011	11/03/2011	SPECT	60	Yes		11/03/2011	10:50	Yes
05-CA-001	Screening part 2	10/03/2011	11/03/2011	SPECT/CT	120	Yes		11/03/2011	10:00	Yes
05-CA-002	Visit 1	08/03/2011	03/03/2011	SPECT	60	No	XXXXXXX			
05-CA-002	Visit 1	08/03/2011	03/03/2011	SPECT/CT	120	Yes		08/03/2011	15:00	Yes

Data Source Table: W_PATIENT, W_PATIENTVIS, W_SPECT_SPECTCT.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.6.1/2: Imaging Assessment

							Uptake			
Subject ID	Visit	Visit date	Injection date	Imaging procedure	Time from IP injection (min)	Has the imaging been completed?	AU (%ID/g)	SUV	CUR1	CUR2
PAT_PATNUMBER	VISIT_NAME	PATV_VISITDATE	ANN_DATE	[Derived data]	[Derived data]	SP_YN SPCT_YN	SP_RESULT _SPCT_RES ULT	SP_SUV SPCT_SUV	SP_CUR1 SPCT_CUR1	SP_CUR2 SPCT_CUR2
05-CA-001	Screening part 2	10/03/2011	11/03/2011	SPECT	60	Yes	49%	22,78	48,99	77,00
05-CA-001	Screening part 2	10/03/2011	11/03/2011	SPECT/CT	120	Yes	97%	35,28	07,31	64,69
05-CA-002	Visit 1	08/03/2011	03/03/2011	SPECT	60	No				
05-CA-002	Visit 1	08/03/2011	03/03/2011	SPECT/CT	120	Yes	98%	51,28	45,13	64,29

Data Source Table: W_PATIENT, W_PATIENTVIS, W_SPECT_SPECTCT.

Note: NA = Not Available; AU = Absolute Uptake, SUV = Standardized Uptake Value; CUR = Cardiac Uptake Ratio

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.6.2: Cardiac Magnetic Resonance Imaging

Subject ID	Visit	Visit date	Has CMRI been done?	Reason for non performance	CMRI date	CMRI time	LVEF (%)	Any clinically relevant finding?	First finding	Second finding	Third finding
PAT_PATNUMBER	VISIT_NAME	PATV_VISITDATE	CMRI_YN	CMRI_YN_SP	CMRI_DATE	CMRI_TIME	CMRI_LVEF	CMRI_REL_YN	CMRI_REL1	CMRI_REL2	CMRI_REL3
05-CA-001	Screening part 2	10/03/2011	Yes		11/03/2011	10:50	68.5	No			
05-CA-002	Screening part 2	08/02/2011	Yes		03/03/2011	10:00	72.3	No			
05-CA-003	Visit 1	08/03/2011	No	XXXXXXX			85.9	Yes	XXXXXXX	XXXXXX	XXXXXX

Data Source Table: W_PATIENT, W_PATIENTVIS, W_CMRI.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.6.3: Cardiotoxicity Biomarkers

							Troponin (µg/L)		NT-proBNP (ng/L)	
Subject ID	Visit	Visit date	Have blood tests been done?	Reason for non performance	Sample date	Sample time	Not done	Result	Not done	Result
PAT_PATNUMBER	VISIT_NAME	PATV_VISITDATE	CB_YN	CB_YN_SP	CB_DATE	CB_TIME	CB_TRO_ND	CB_TRO	CB_NTP_ND	CB_NTP
05-CA-001	Screening part 2	10/03/2011	Yes		11/03/2011	10:50	Yes			68.5
05-CA-002	Screening part 2	08/02/2011	Yes		03/03/2011	10:00		72.3	Yes	
05-CA-003	Visit 1	08/03/2011	No	XXXXXXX						

Data Source Table: W_PATIENT, W_PATIENTVIS, W_CB.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.1/1: All Adverse Events

Subject ID	Event ID	Event description	Primary system organ class	Preferred term	Study day of onset (days)§	Ongoing?	Duration (days)	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	MEDDRA_SOC	MEDDRA_PT	[Derived data]	AE_ONGOING_YN	[Derived data]	[Derived data]
05-CA-001	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	YY	No	≥2	Yes
05-CA-002	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	YY	No	15	Yes
05-CA-003	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	YY	Yes	≥30	Yes

Data Source Table: W_PATIENT, W_AE.

Dictionary Name: MedDRA Version: 19.0

Note: NA = Not Available

§ Study day of onset is defined as days from first Annexin injection

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.1/2: All Adverse Events

Subject ID	Event ID	Event description	AE caused premature withdrawal?	SAE	SAE seriousness	Maximal severity	Causal relationship with medication or procedure	Possible cause	Specify other possible cause	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_WITHD_YN	AE_SAE_YN	[Derived data]	AE_MAXSEV	AE_REL	AE_CAUSE	AE_CAUSE_SP	[Derived data]
05-CA-001	XXX	XXXXXXXX	Yes	Yes	XXXXXX / XXXXX	Grade 2 (Moderate)	Possible	Other	XXXXXXXXXX	Yes
05-CA-002	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX	Grade 1 (Mild)	Unlikely	Pre-existing/ underlying disease	XXXXXXXXXX	Yes
05-CA-003	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX	Grade 3 (Severe)	Unrelated	Other treatment	XXXXXXXXXX	Yes

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.1/3: All Adverse Events

Subject ID	Event ID	Event description	Action taken	Other action taken	Other action taken, specify	Outcome	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_ACT	[Derived data]	AE_ACT_OTH_SP	AE_OUTCOME	[Derived data]
05-CA-001	XXX	XXXXXXXX	No action	XXX/XXXXX/XXX		Resolved	Yes
05-CA-002	XXX	XXXXXXXX	Dose modification in next treatment	XXX/XXXXX	XXXXXX	Worsened	Yes
05-CA-003	XXX	XXXXXXXX	Unknown	XXX		Persisting	Yes

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.2/1: Serious Adverse Events

Subject ID	Event ID	Event description	Primary system organ class	Preferred term	Lowest level term	Study day of onset (days)§	Ongoing?	Duration (days)	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	MEDDRA_SOC	MEDDRA_PT	MEDDRA_LLT	[Derived data]	AE_ONGOING_YN	[Derived data]	[Derived data]
05-CA-001	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	No	≥2	Yes
05-CA-002	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	No	15	Yes
05-CA-003	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	Yes	≥30	Yes

Data Source Table: W_PATIENT, W_AE.

Dictionary Name: MedDRA Version: 19.0

Note: NA = Not Available

§ Study day of onset is defined as days from first Annexin injection

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.2/2: Serious Adverse Events

Subject ID	Event ID	Event description	AE caused premature withdrawal?	SAE	SAE seriousness	Maximal severity	Causal relationship with medication or procedure	Possible cause	Specify other possible cause	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_WITHD_YN	AE_SAE_YN	[Derived data]	AE_MAXSEV	AE_REL	AE_CAUSE	AE_CAUSE_SP	[Derived data]
05-CA-001	XXX	XXXXXXXX	Yes	Yes	XXXXXX / XXXXX	Grade 2 (Moderate)	Possible	Other	XXXXXXXXXX	Yes
05-CA-002	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX	Grade 1 (Mild)	Unlikely	Pre-existing/ underlying disease	XXXXXXXXXX	Yes
05-CA-003	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX	Grade 3 (Severe)	Unrelated	Other treatment	XXXXXXXXXX	Yes

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.2/3: Serious Adverse Events

Subject ID	Event ID	Event description	Action taken	Other action taken	Other action taken, specify	Outcome	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_ACT	[Derived data]	AE_ACT_OTH_SP	AE_OUTCOME	[Derived data]
05-CA-001	XXX	XXXXXXXX	No action	XXX/XXXXX/XXX		Resolved	Yes
05-CA-002	XXX	XXXXXXXX	Dose modification in next treatment	XXX/XXXXX	XXXXXX	Worsened	Yes
05-CA-003	XXX	XXXXXXXX	Unknown	XXX		Persisting	Yes

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.3/1: Adverse Events Leading to Withdrawal

Subject ID	Event ID	Event description	Primary system organ class	Preferred term	Study day of onset (days)§	Ongoing?	Duration (days)	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	MEDDRA_SOC	MEDDRA_PT	[Derived data]	AE_ONGOING_YN	[Derived data]	[Derived data]
05-CA-001	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	YY	No	≥2	Yes
05-CA-002	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	YY	No	15	Yes
05-CA-003	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	YY	Yes	≥30	Yes

Data Source Table: W_PATIENT, W_AE.

Dictionary Name: MedDRA Version: 19.0

Note: NA = Not Available

§ Study day of onset is defined as days from first Annexin injection

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.3/2: Adverse Events Leading to Withdrawal

Subject ID	Event ID	Event description	AE caused premature withdrawal?	SAE	SAE seriousness	Maximal severity	Causal relationship with medication or procedure	Possible cause	Specify other possible cause	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_WITHD_YN	AE_SAE_YN	[Derived data]	AE_MAXSEV	AE_REL	AE_CAUSE	AE_CAUSE_SP	[Derived data]
05-CA-001	XXX	XXXXXXXX	Yes	Yes	XXXXXX / XXXXX	Grade 2 (Moderate)	Possible	Other	XXXXXXXXXX	Yes
05-CA-002	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX	Grade 1 (Mild)	Unlikely	Pre-existing/ underlying disease	XXXXXXXXXX	Yes
05-CA-003	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX	Grade 3 (Severe)	Unrelated	Other treatment	XXXXXXXXXX	Yes

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.3/3: Adverse Events Leading to Withdrawal

Subject ID	Event ID	Event description	Action taken	Other action taken	Other action taken, specify	Outcome	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_ACT	[Derived data]	AE_ACT_OTH_SP	AE_OUTCOME	[Derived data]
05-CA-001	XXX	XXXXXXXX	No action	XXX/XXXXX/XXX		Resolved	Yes
05-CA-002	XXX	XXXXXXXX	Dose modification in next treatment	XXX/XXXXX	XXXXXX	Worsened	Yes
05-CA-003	XXX	XXXXXXXX	Unknown	XXX		Persisting	Yes

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.4/1: Adverse Events with Outcome Death

Subject ID	Event ID	Event description	Primary system organ class	Preferred term	Study day of onset (days)§	Duration (days)	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	MEDDRA_SOC	MEDDRA_PT	[Derived data]	[Derived data]	[Derived data]
05-CA-001	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	YY	≥2	Yes
05-CA-002	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	YY	15	Yes
05-CA-003	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	YY	≥30	Yes

Data Source Table: W_PATIENT, W_AE.

Dictionary Name: MedDRA Version: 19.0

Note: NA = Not Available

§ Study day of onset is defined as days from first Annexin injection

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.4/2: Adverse Events with Outcome Death

Subject ID	Event ID	Event description	AE caused premature withdrawal?	SAE	SAE seriousness	Maximal severity	Causal relationship with medication or procedure	Possible cause	Specify other possible cause	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_WITHD_YN	AE_SAE_YN	[Derived data]	AE_MAXSEV	AE_REL	AE_CAUSE	AE_CAUSE_SP	[Derived data]
05-CA-001	XXX	XXXXXXXX	Yes	Yes	XXXXXX / XXXXX	Grade 2 (Moderate)	Possible	Other	XXXXXXXXXX	Yes
05-CA-002	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX	Grade 1 (Mild)	Unlikely	Pre-existing/ underlying disease	XXXXXXXXXX	Yes
05-CA-003	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX	Grade 3 (Severe)	Unrelated	Other treatment	XXXXXXXXXX	Yes

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.7.4/3: Adverse Events with Outcome Death

Subject ID	Event ID	Event description	Action taken	Other action taken	Other action taken, specify	Outcome	TEAE^
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_ACT	[Derived data]	AE_ACT_OTH_SP	AE_OUTCOME	[Derived data]
05-CA-001	XXX	XXXXXXXX	No action	XXX/XXXXX/XXX		Resolved	Yes
05-CA-002	XXX	XXXXXXXX	Dose modification in next treatment	XXX/XXXXX	XXXXXX	Worsened	Yes
05-CA-003	XXX	XXXXXXXX	Unknown	XXX		Persisting	Yes

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

^ TEAE: Treatment Emegent Adverse Event as defined in paragraph 6.1.2.1

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.8.1/1: Hematology

Subject ID	Visit	Have hematology tests been done?	Sample collection date	Sample collection time	Parameter	Result	Unit	Abnormality
PAT_PATNUMBER	VISIT_NAME	HE_YN	HE_DATE	HE_TIME		HE_RBC		HE_RBC_ABN
05-CA-001	Screening part 1	Yes	11/03/2011	10:52	Red Blood Cells	99.99	10^{12}/L	Abnormal Non-Clinical Relevant
					Hematocrit	99.99	L/L	Abnormal Non-Clinical Relevant
05-CA-001	Visit 2	Yes	09/04/2011	15:00				
05-CA-002	Screening part 1	Yes	10/07/2011	Not done				
05-CA-003	Visit 4	No: XXXXX						

Listing 16.2.8.2/1: Blood Chemistry

Repeat listing 16.2.8.1 for chemistry parameters

Listing 16.2.8.3/1: Urinalysis

Repeat listing 16.2.8.1 for urinalysis parameters

Listing 16.2.8.4: Immunogenicity

Subject ID	Visit	Has venous sample been done?	Reason for non performance	Sample collection date	Sample collection time	Result
PAT_PATNUMBER	VISIT_NAME	IM_YN	IM_YN_SP	IM_DATE	IM_TIME	[Provided data]
05-CA-001	Screening part 1	Yes		11/03/2011	10:52	Negative
05-CA-001	Visit 4	Yes		09/04/2011	15:00	Positive
05-CA-002	Screening part 1	Yes		10/07/2011	09:38	Positive
05-CA-003	Visit 4	No	XXXXXXXXX			

Data Source Table: W_PATIENT, W_PATIENTVIS, W_IM. Other data source: database provided by Sponsor: XXXXXXXX.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.9.1: Pregnancy Test

Subject ID	Age	Visit	Has the pregnancy test been performed?	Reason for non performance	Specify reason	Pregnancy test date	Pregnancy test time	Pregnancy test result
PAT_PATNUMBER	PAT_AGEYEAR	VISIT_NAME	PT_YN	PT_NOTDONE	PT_NOTDONE_SP	PT_DATE	PT_TIME	PT_RESULT
05-CA-001	54	Screening part 1	Not applicable					
05-CA-001	54	Visit 2	Not applicable					
05-CA-002	38	Screening part 1	Yes			09/04/2011	12:00	Negative
05-CA-002	38	Visit 4	Yes			12/04/2011	10:00	Negative
05-CA-003	59	Visit 3	No	Menopause				

Data Source Table: W_PATIENT, W_PATIENTVIS, W_PT.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.9.3: Physical Examination

										Specify		
Subject ID	Visit	Has the physical examination been done?	Reason for non performance	Physical examination date	Physical examination time	Height (cm)	Weight (Kg)	BMI (Kg/m^2)	Any clinically relevant finding?	First finding	Second finding	Third finding
PAT_PATNUMBER	VISIT_NAME	MR_YN	MR_YN_SP	MR_DATE	MR_TIME	HEIGHT	WEIGHT	BMI	MR_RELFIND_YN	MR_RELFIND1	MR_RELFIND2	MR_RELFIND3
05-CA-001	Screening part 1	Yes		09/04/2011	12:00	180	68.5	23.8	No			
05-CA-002	Visit 2	No	XXXXXXXX									
05-CA-003	Screening part 1	Yes		06/05/2013	9:45	178	85.9	27.3	Yes	XXXXXXX	XXXXXXX	XXXXXXX

Data Source Table: W_PATIENT, W_PATIENTVIS, W_MR.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

Listing 16.2.9.4: Vital Signs

Subject ID	Visit	Evaluation period	Have vital signs been evaluated?	Reason for non evaluation	Vital signs evaluation date	Vital signs evaluation time	Height (cm)	Weight (kg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse rate (beats/min)
PAT_PATNUMBER	VISIT_NAME	[Derived data]	VS_PRE_YN VS_POST_YN	VS_PRE_YN_SP VS_POST_YN_SP	VS_PRE_DATE VS_POST_DATE	VS_PRE_TIME VS_POST_TIME			VS_PRE_SBP VS_POST_SBP	VS_PRE_DBP VS_POST_SBP	VS_PRE_HR VS_POST_HR
05-CA-001	Screening part 2	Before injection	Yes		09/04/2011	12:00	175	xx.x	165	99	77
05-CA-001	Screening part 2	After injection	Yes		12/04/2011	10:00			129	93	60
05-CA-002	Visit 1	Before injection	Yes		06/05/2013	9:45		xx.x	147	68	76
05-CA-002	Visit 1	After injection	No	XXXXXXXX							

Data Source Table: W_PATIENT, W_PATIENTVIS, W_VS.

Note: NA = Not Available

File directory: *path of directory status from study level downwards* /XXXXXX.sas

11.2 Standard Tables

Table 14.1.1: Subject disposition

POPULATION	STATISTIC	ALL SUBJECTS (N=xx)
Screened subjects	n (%)	99 (99.9)
Screen failures	n (%)	99 (99.9)
Reason 1	n (%)	99 (99.9)
…	n (%)	99 (99.9)
Reason m	n (%)	99 (99.9)
Enrolled subjects	n (%)	99 (99.9)
Dosed subjects	n (%)	99 (99.9)
Completed study subjects	n (%)	99 (99.9)
Discontinued study subjects	n (%)	99 (99.9)
Reason 1	n (%)	99 (99.9)
…	n (%)	99 (99.9)
Reason m	n (%)	99 (99.9)

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}*

Note: All percentages are based upon the number of screened subjects.

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Table 14.1.4.1: Demographics – FAS Population

PARAMETER		STATISTIC	FAS (N=xx)
Age (years)		n	99
		Missing	99
		Mean	99.9
		S.D.	99.9
		Median	99.9
		Q1, Q3	99.9, 99.9
		Min, Max	99, 99
Ethnicity	Asian	n (%)	99 (99.9)
	Black	n (%)	99 (99.9)
	Caucasian	n (%)	99 (99.9)
	Hispanic	n (%)	99 (99.9)
	Other	n (%)	99 (99.9)
	Missing	n (%)	99 (99.9)

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}*

Note: The denominator for the percentage is based on the number of subjects in the FAS population.

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Table 14.1.7.2/1: Study Drug Administration – Safety Population

QUALITY CONTROL ON THE FINAL PRODUCT	STATISTIC	SCREENING PART 2 (N=xx)	VISIT 2 (N=xx)	VISIT 3 (N=xx)	VISIT 4 (N=xx)
Radiochemical purity (%)	n	99	99	99	99
	Missing	99	99	99	99
	Mean	99.9	99.9	99.9	99.9
	S.D.	99.9	99.9	99.9	99.9
	Median	99.9	99.9	99.9	99.9
	Q1, Q3	99.9, 99.9	99.9, 99.9	99.9, 99.9	99.9, 99.9
	Min, Max	99, 99	99, 99	99, 99	99, 99

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}*

Notes: Acceptance criteria is radiochemical purity ≥ 90%.

N = total number of subjects in Safety population; n = number of subjects who received Annexin injection.

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Table 14.1.7.2/2: Study Drug Administration – Safety Population

QUALITY CONTROL ON THE FINAL PRODUCT	STATISTIC	SCREENING PART 2 (N=xx)	VISIT 2 (N=xx)	VISIT 3 (N=xx)	VISIT 4 (N=xx)
Pre-injection total activity-dose in the syringe (MBq)	n	99	99	99	99
	Missing	99	99	99	99
	Mean	99.9	99.9	99.9	99.9
	S.D.	99.9	99.9	99.9	99.9
	Median	99.9	99.9	99.9	99.9
	Q1, Q3	99.9, 99.9	99.9, 99.9	99.9, 99.9	99.9, 99.9
	Min, Max	99, 99	99, 99	99, 99	99, 99
Post-injection residual activity-dose in the syringe (MBq)	n	99	99	99	99
	Missing	99	99	99	99
	Mean	99.9	99.9	99.9	99.9
	S.D.	99.9	99.9	99.9	99.9
	Median	99.9	99.9	99.9	99.9
	Q1, Q3	99.9, 99.9	99.9, 99.9	99.9, 99.9	99.9, 99.9
	Min, Max	99, 99	99, 99	99, 99	99, 99

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}*

Note: N = total number of subjects in Safety population; n = number of subjects who received Annexin injection.

Program: <path of directory, study level downwards>/ xxxx.sas

Table 14.1.7.2/3: Study Drug Administration – Safety Population

QUALITY CONTROL ON THE FINAL PRODUCT	STATISTIC	SCREENING PART 2 (N=xx)	VISIT 2 (N=xx)	VISIT 3 (N=xx)	VISIT 4 (N=xx)
Actual dose in the syringe (MBq)	n	99	99	99	99
	Missing	99	99	99	99
	Mean	99.9	99.9	99.9	99.9
	S.D.	99.9	99.9	99.9	99.9
	Median	99.9	99.9	99.9	99.9
	Q1, Q3	99.9, 99.9	99.9, 99.9	99.9, 99.9	99.9, 99.9
	Min, Max	99, 99	99, 99	99, 99	99, 99
Volume of administered solution (mL)	n	99	99	99	99
	Missing	99	99	99	99
	Mean	99.9	99.9	99.9	99.9
	S.D.	99.9	99.9	99.9	99.9
	Median	99.9	99.9	99.9	99.9
	Q1, Q3	99.9, 99.9	99.9, 99.9	99.9, 99.9	99.9, 99.9
	Min, Max	99, 99	99, 99	99, 99	99, 99

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}*

Note: N = total number of subjects in Safety population; n = number of subjects who received Annexin injection.

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Table 14.3.1.1: Overall Summary of Adverse Events – Safety Population

ADVERSE EVENT CATEGORY	STATISTIC	SAFETY (N=xx)
Treatment emergent AEs	n (%) [n. events]	99 (99.9) [99]
Treatment emergent adverse drug reactions	n (%) [n. events]	99 (99.9) [99]
Treatment emergent SAEs	n (%) [n. events]	99 (99.9) [99]
Treatment emergent serious adverse drug reactions	n (%) [n. events]	99 (99.9) [99]
Treatment emergent AEs leading to withdrawal	n (%) [n. events]	99 (99.9) [99]
Treatment emergent AEs leading to death	n (%) [n. events]	99 (99.9) [99]

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}*

Note: Format is number of subjects (percent of subjects) [number of events].

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Table 14.3.1.2: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term – Safety Population

PRIMARY SYSTEM ORGAN CLASS PREFERRED TERM	STATISTIC	SAFETY (N=xx)
Any adverse events	n (%)	99 (99.9)
System organ class 1	n (%)	99 (99.9)
Preferred term 1	n (%)	99 (99.9)
…	n (%)	99 (99.9)
Preferred term m	n (%)	99 (99.9)
System organ class …	n (%)	99 (99.9)
Preferred term 1	n (%)	99 (99.9)
…	n (%)	99 (99.9)
Preferred term m	n (%)	99 (99.9)
System organ class m	n (%)	99 (99.9)
Preferred term 1	n (%)	99 (99.9)
…	n (%)	99 (99.9)
Preferred term m	n (%)	99 (99.9)

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}* Dictionary Name: MedDRA Version: 19.0

Notes: The denominator for the percentage is based on the number of subjects in the Safety population. Subjects with more than one event within a particular SOC and PT will be counted only once for that SOC and PT.

Program: <path of directory, study level downwards>/ xxxx.sas

Table 14.3.1.3: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Severity – Safety Population

PRIMARY SYSTEM ORGAN CLASS PREFERRED TERM	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Threatening/disabling)	Grade 5 (Death)	Missing	Total
Any adverse events	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class …	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}* Dictionary Name: MedDRA Version: 19.0

Notes: The denominator for the percentage is based on the number of subjects in the Safety population. Subjects with more than one event within a particular SOC and PT will be counted only once for that SOC and PT and the maximum CTC grade will be reported.

Program: <path of directory, study level downwards>/ xxxx.sas

Table 14.3.1.4: Number (%) of Subjects Reporting Treatment Emergent Adverse Drug Reactions by Severity – Safety Population

PRIMARY SYSTEM ORGAN CLASS PREFERRED TERM	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Threatening/disabling)	Grade 5 (Death)	Missing	Total
Any adverse drug reactions	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class …	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}* Dictionary Name: MedDRA Version: 19.0

Notes: The denominator for the percentage is based on the number of subjects in the Safety population. Subjects with more than one event within a particular SOC and PT will be counted only once for that SOC and PT and the maximum CTC grade will be reported.

Program: <path of directory, study level downwards>/ xxxx.sas

Table 14.3.1.5: Number (%) of Subjects Reporting Treatment Emergent Serious Adverse Events by Primary System Organ Class and Preferred Term – Safety Population

PRIMARY SYSTEM ORGAN CLASS PREFERRED TERM	STATISTIC	SAFETY (N=xx)
Any serious adverse events	n (%)	99 (99.9)
System organ class 1	n (%)	99 (99.9)
Preferred term 1	n (%)	99 (99.9)
…	n (%)	99 (99.9)
Preferred term m	n (%)	99 (99.9)
System organ class …	n (%)	99 (99.9)
Preferred term 1	n (%)	99 (99.9)
…	n (%)	99 (99.9)
Preferred term m	n (%)	99 (99.9)
System organ class m	n (%)	99 (99.9)
Preferred term 1	n (%)	99 (99.9)
…	n (%)	99 (99.9)
Preferred term m	n (%)	99 (99.9)

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}* Dictionary Name: MedDRA Version: 19.0

Notes: The denominator for the percentage is based on the number of subjects in the Safety population. Subjects with more than one event within a particular SOC and PT will be counted only once for that SOC and PT.

Program: <path of directory, study level downwards>/ xxxx.sas

Table 14.3.1.6: Number (%) of Subjects Reporting Treatment Emergent Serious Adverse Events by Severity – Safety Population

PRIMARY SYSTEM ORGAN CLASS PREFERRED TERM	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Threatening/disabling)	Grade 5 (Death)	Missing	Total
Any serious adverse events	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class …	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}* Dictionary Name: MedDRA Version: 19.0

Notes: The denominator for the percentage is based on the number of subjects in the Safety population. Subjects with more than one event within a particular SOC and PT will be counted only once for that SOC and PT and the maximum CTC grade will be reported.

Program: <path of directory, study level downwards>/ xxxx.sas

Table 14.3.1.7: Number (%) of Subjects Reporting Treatment Emergent Serious Adverse Drug Reactions by Severity – Safety Population

PRIMARY SYSTEM ORGAN CLASS PREFERRED TERM	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Threatening/disabling)	Grade 5 (Death)	Missing	Total
Any serious adverse drug reactions	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class …	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
System organ class m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term 1	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
…	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)
Preferred term m	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)	99 (99.9)

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}* Dictionary Name: MedDRA Version: 19.0

Notes: The denominator for the percentage is based on the number of subjects in the Safety population. Subjects with more than one event within a particular SOC and PT will be counted only once for that SOC and PT and the maximum CTC grade will be reported.

Program: <path of directory, study level downwards>/ xxxx.sas

Table 14.3.2.1: Listing of Adverse Events with Outcome Death – Safety Population

Subject ID	Age	Primary cause of death	Date of study drug latest injection	Time of study drug latest injection	Date of death	Time between study drug latest injection and death (days)	Relationship with study treatment
05-CA-001	82	Heart Attack	10/05/2012	11:30	17/05/2012	7	Probable
05-CA-002	88	Aneurysm	05/10/2012	12:38	08/10/2012	3	Possible
05-CA-003	71	Tuberculosis	15/07/2012	09:45	16/10/2012	1	Unlikely
…	…	…	…	…	…	…	…

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}*

Program: <path of directory, study level downwards>/ xxxx.sas

Table 14.3.2.2: Listing of Serious Adverse Events – Safety Population

Subject ID	Event description	Primary system organ class	Preferred term	SAE date	Study day of onset (days)[#]	Duration (days)	SAE criteria	Relationship with study treatment	Outcome
04-CA-001	Vertigo	Ear and labyrinth disorders	Vertigo	14/05/2012	1	<1	2, 3	Unlikely	Resolved
04-CA-002	Fainting	Nervous system disorders	Syncope	10/09/2012	15	<1	2	Unlikely	Resolved with sequelae
04-CA-003	Internal bleeding	Vascular disorders	Internal haemorrhage	16/11/2011	4	3	5	Probable	Improved
…	…	…	…	…	…	…	…	…	…

Source: Data listings *{Specify data listing number(s)}* Analysis dataset: *{Specify datasets}* Dictionary name: MedDRA Version XX.X

Note: SAE criteria: 1=Death, 2=Life-threatening, 3=Involved or prolonged hospitalization, 4=Congenital anomaly, 5=Persistent or significant disability or incapacity, 6=Significant from a medical standpoint.

[#] Study day of onset is days since first annexin administration.

Program: <path of directory, study level downwards>/ xxxx.sas

11.3 Standard Figures

The different lines on the figures should look different (e.g. dotted lines) rather than using different colours so that the lines can be distinguished when using a non-colour printer.

12 APPENDICES TO THE SAP TEMPLATE

12.1 Derived data

The following derived data will be calculated and included in the listings or in the tables:

(1) **Age**
Subject age (years) will be derived as (first visit date - birth date)/365.25 and truncated to the largest integer that is less than or equal to the calculated result. Since birth date is truncated (i.e. only month and year will be filled in the eCRF), it will be approximated using “01” as value for the day.

(2) **BMI**
BMI (kg/m^2) will be automatically derived as [WEIGHT] (kg)/([HEIGHT](cm)/100)^2 and rounded to the nearest decimal.

(3) **Time from injection**
Time from injection (min) will be derived as the difference between SPECT or SPECT/CT scan time and injection time [SP_TIME/SPCT_TIME - ANN_TIME].

(4) **Adverse event duration**
If the start and end dates of the adverse event are identical then “<1” day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration will be calculated as (end date/time - start date/time) and presented in days hh:mm. If at least one time is missing and if the duration is greater than 24 hours then it will be calculated as (end date - start date)+1 and presented in days. If the recorded end date is CONT. (for continuing), the end date will be listed as “ongoing” and the duration will be approximated as “≥(last attended visit date - start date)+1” day(s). If the start date or the end date are partial the duration will be presented as a superior inequality “≥ xx” day(s) (i.e. “≥2” where start date = 31JAN2004 and end date = FEB2004 or start date = JAN2004 and end date = 01FEB2004).

(5) **Study day of onset**
If the start date of the adverse event is identical to the date of injection, then “1” day will be presented with the time to onset in hh:mm recorded in the eCRF if it is available. If the date of onset is greater than the date of injection then it will be calculated as (start date - injection date+1) and presented in days. If the date of onset precedes the date of injection the study day will be calculated as (start date - injection date). If the start date is partial, the time since injection will be presented as a superior inequality (i.e. for an AE started in FEB2004 after the injection performed on 31JAN2004, the delay of onset will be “≥2” days).

12.2 SAS programs

This section provides the SAS programs related to the statistical tests specified in the statistical methods section 6. All computer output from SAS statistical programs used as a basis for extracted results should be retained for review by Responsible of statistical analysis.

1 Data manipulation

Proc Format

Proc Print

Proc Sort

Proc SQL

Proc Transpose

2 Descriptive statistics

Proc Corr

Proc Freq

Proc Means

Proc Tabulate

3 Test statistics

Proc GLM

Proc Mixed

Proc Ttest

Proc Univariate

4 Graphs

Proc Boxplot

Proc Sgplot