Statistical Analysis Plan

Version 1

TITLE: Phase II Study of ^{99m}Tc-rhAnnexin V-128 Radionuclide Imaging in Patients with Clinical Suspicion or Confirmed Diagnosis of Spondyloarthritis (SpA)

PROTOCOL #: AAA-Annexin-03

NCT #: NCT03232580

PHASE: Proof of Concept and Phase II study

DATE: Final version 1.0 dated 06 March 2019

DESIGN: Monocentric, open label, study.

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

APPROVAL/REVISION HISTORY

Autorship/Approval

Author:	[redacted] Statistician	Date
Reviewed by:	[redacted] Statistician	Date
Approved by:	Advanced Accelerator Application S.A. (Sponsor), [redacted]	Date

Revision history

Rev.	Name	Date	Note
1			

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01				

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2 List of abbreviations

AAA	Advanced Accelerator Applications
AE	Adverse Event
ADR	Adverse Drug Reaction
ALAT	Alanine Aminotransferase
ALP	Alkanine Phosphatase
ALT	Alanine Transaminase
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondylo-Arthritis Society
ASAT	Aspartate Aminotransferase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical classification system
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CRO	Clinical Research Organization
CRP	C-Reactive Protein
CT	Computed Tomography
DMARD	Disease Modifying Anti-Rheumatic Drug
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immuno-absorbent Assay

ANNEXIN 03

FAS	Full Analysis Set
GGT	Gamma-Glutamyl Transpeptidase
Hb	Hemoglobin
HR	Heart Rate
ICH	International Conference on Harmonization
ID	Identification
IEC	Indipendent Ethics Committee
INR	International Normalized Ratio
IP	Investigational Product
IQR	Interquartile Range
IRB	Institutional Review Board
ITT	Intention To Treat
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
MASES	Maastricht Ankylosing Spondylitis Enthesis Score
MBq	Mega Becquerel
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NSAID	Non-Steroidal Anti-Inflammatory Drug
PoC	Proof of Concept
PP	Per Protocol
PS	Phosphatidylserine
PT	Preferred Term
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell

ANNEXIN 03

ROI	Region Of Interest
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S.D.	Standard Deviation
SI	Sacro-Iliac
SMA-20	Sequential Multiple Analysis-20
SpA	Spondyloarthritis
SPECT	Single Photon Emission Computed Tomography
SOC	System Organ Class
TBR	Target to Background Ratio
TEAE	Treatment Emergent Adverse Event
US	United States
VOI	Volume Of Interest
WBC	White Blood Cell

3 Protocol title and number

Phase II Study of ^{99m}Tc-rhAnnexin V-128 Radionuclide Imaging in Patients with Clinical Suspicion or Confirmed Diagnosis of Spondyloarthritis (SpA) (Protocol Number AAA-Annexin-03).

4 INFORMATION TAKEN FROM THE PROTOCOL

4.1 Study objectives

4.1.1 Primary objective

The primary objective of this study is to determine the magnitude and dynamic range of ^{99m}Tc-rhAnnexin V-128 uptake in disease affected sacro-iliac or lumbar spine joints in patients with clinical suspicion or confirmed diagnosis of SpA.

4.1.2 Secondary objective

The secondary objectives of this study are:

- To determine clinical utility of ^{99m}Tc-rhAnnexin V-128 SPECT imaging in the identification of chronic osteoarthritic active sites of SpA patients compared with MRI in patients with disease-affected sacro-iliac or lumbar spine joints.
- To assess the presence of antibodies against rhAnnexin V-128 at baseline and post-treatment.
- To determine the localization pattern and magnitude of focal uptake of ^{99m}Tc-rhAnnexin V-128 within the abdomen in patients with clinical suspicion or confirmed diagnosis of Spondyloarthritis (SpA).

[redacted]

4.1.4 Study hypoteses and justification

It is hypothesized that ^{99m}Tc-rhAnnexin V-128, a second generation form of ^{99m}Tc radiolabeled annexin V with significantly higher PS binding affinity and improved in vivo localization properties, will be highly specific in imaging degenerative osteoarthritis particularly of the lumbosacral spine and sacroiliac joints as seen by SPECT/CT in patients with SpA. It is also hypothesized that ^{99m}Tc- rhAnnexin V-128 will be localized within the abdomen of SpA patients with active disease showing suspicious Crohn's disease.

At the completion of this study, there will be preliminary data on the expected magnitude and dynamic range and specificity of ^{99m}Tc-rhAnnexin V-128 uptake at sites of active disease in SpA patients at presentation.

4.2 Study design

This is a monocentric, open label, PoC, Phase II study. Patients who have signed the informed consent and are eligible for study participation according to the inclusion and exclusion criteria will receive a single intravenous bolus of ^{99m}Tc-rhAnnexin V-128 on Day 0 followed by SPECT/CT of the sacro-iliac joints, spine and abdomen at 60 min and 2 hrs after injection of the radiotracer within 14 days after screening in order to minimize the potential delay in changing NSAID therapy or non-biologic DMARD or the start of non-biologic DMARD or biologic DMARD (excepted for the first 5 enrolled patients who will not be eligible for the start of biologic DMARD). Patients will undergo also a whole body scan and spot views on specific areas at the same time-points (spot views may not be repeated at T+2 hrs). T1 and STIR without contrast MRI of the sacro-iliac joints and lumbar spine will also be performed within this same time window.

4.2.1 Study population

Approval for the study will be obtained from the local IRB of Cedars-Sinai Medical Center Office of Research of Compliance. All patients will provide written informed consent prior to the initiation of any study procedures. Up to twenty evaluable patients will be recruited.

4.2.1.1 Inclusion criteria

For the first 5 patients enrolled in the PoC part:

1. Patients with clinical suspicion or confirmed diagnosis of SpA, based on the ASAS criteria with active symptoms including back, hip or buttock pain prior to:
   - a change in NSAID therapy or
   - a change in non-biologic DMARD or
   - a start of non-biologic DMARD.

For the next 15 patients enrolled in the Phase II part:

1. Patients with clinical suspicion or confirmed diagnosis of SpA, based on the ASAS criteria with active symptoms including back, hip or buttock pain prior to:
   - a change in NSAIDs therapy or
   - a change in non-biologic DMARD or
   - a start of non-biologic DMARD or
   - a start of biologic DMARD.

For all patients:

2. Age over 18 years old.
3. Signed Informed Consent Form.

4.2.1.2 Exclusion criteria

1. Pregnancy or lactation.
2. Liver impairment (ALT, AST or Bilirubin > 2 ULN) at screening visit or baseline.
3. Kidney impairment (serum creatinine > 1.5 mg/dL).
4. History of any disease or relevant physical or psychiatric condition or abnormal physical finding which may interfere with the study objectives at the investigator judgment.
5. Known hypersensitivity to the investigational drug or any of its components.
6. Contraindication(s) to the MRI procedure (claustrophobia, prosthetic valve, pacemaker, inability to lie still in a supine position).

7. Participation to another clinical trial within 4 weeks before study inclusion except for patients who have participated or who are currently participating in an interventional study without any study drug administration.

4.2.2 Study exposure

The "Kit for preparation of ^{99m}Tc-rhAnnexin V-128 for injection" consists of 1 dose. Following the reconstitution and labelling of rhAnnexin V-128, the imaging product will be administered as a single intravenous bolus of 350 MBq ± 10% over 10-20 seconds at Day 0 for the purpose of SPECT/CT imaging.

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 5 patients by the DMC does not enable to demonstrate the potential of the study product in terms of quality or efficacy, the Sponsor may discontinue the clinical study by sending a written notice of the discontinuation along with the reasons to the investigator and applicable 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 along with the reasons to the investigator and applicable authorities.
- If the investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor of the discontinuation and the reason for it.

If none of the previous condition applies, the end of study is defined as the moment that the last enrolled patient has completed the planned assessments at Day 3; study duration is maximum 7 weeks (including the screening period) for each patient.

The Sponsor reserves the right to discontinue the study at any time for failure to meet expected enrolment goals.

4.3 Methods and procedures

4.3.1 Source of study population

Twenty evaluable patients with clinical suspicion or confirmed diagnosis of SpA due to ankylosing spondylitis, or associated with other known clinical conditions like inflammatory bowel disease, psoriatic arthritis, or undifferentiated spondyloarthropathy will be recruited at Cedars-Sinai Medical Center.

4.3.2 Participant study identification

Each patient will be anonymized and identified with a patient ID number. A unique patient identification number (Patient ID) will be assigned at the start of the screening period to each patient who signs the informed consent form until the study termination of the patient. This number will identify the subject throughout the study. Patient IDs will include the 2-digit protocol number (03), the 2-letter country code (US) and a 3-digit patient number (ex: 03-US-001 for first subject 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 screening, the imaging visit and follow-up visits.

4.3.3.1 Baseline assessments

- Each patient's demography, i.e. date of birth, gender, ethnicity, medical history and relevant baseline characteristics, will be recorded at Screening visit.
- Inclusion/exclusion criteria will be checked at Screening.
- Women of childbearing potential must have negative urine pregnancy test at Screening before the radiotracer administration and before MRI (in case the MRI is not performed on the same day of the screening visit).
- Vital signs will be taken at Screening.
- Physical examination will be conducted at Screening.
- BASDAI, BASFI, BASMI and MASES assessments will be performed.

4.3.3.2 Efficacy assessments

4.3.3.2.1 Imaging

Patients will be injected intravenously with 350 ± 10% MBq of ^{99m}Tc-rhAnnexin V-128 with an 18 gauge angiocath IV and saline TKO drip set up placed in the antecubital fossa.

Bone Lumbar Spine SPECT/CT, SI SPECT/CT and abdomen SPECT/CT will be performed 60 minutes and 2 hours after injection of radiotracer followed by a whole body scan and spot views on specific areas (spot views may not be repeated at T+2 hrs if deemed unnecessary).

The Infinia™ Hawkeye 4 SPECT/CT (GE Healthcare) scanner will be used for patients with the following parameters; start at 0°, 180° rotation/detector, 64 steps, 3° per step, 30 sec per step, overall ARC 360°, (scan time = 23 minutes) 128 x 128, multi-purpose collimator (Skylight) in 1x zoom mode. An attenuation and diagnostic CT scan will be performed on the lumbar spine using a 512 x 512 matrix, 140 keV, 2.5 mA, axial 1 sec, 5 mm slices.

Semi-quantitative assessment of inflammatory joints and abdomen will be performed in terms of TBR as well as by calculating the relative uptake in ROI/VOIs. ROI and VOI defined and used in the different scintigraphies will strictly have the same pixel size and localization and will be measured in counts.

In case a suspected anomaly is found at imaging, it would be reported to the rheumatologist and the patient's general practitioner.

A whole lumbar spine and sacro-iliac joint MRI will be performed within 14 days of ^{99m}Tc-rhAnnexin V-128 scanning using the following parameters: **SI Joint Sequences** / 3 plane localizer / Whole pelvis Coronal T1 / Whole pelvis Coronal T2 FS. Small FOV over SI Joints (~20 cm FOV): Sequences / Obl Axial T1. Obl Axial T2 FS (May use STIR or IDEAL for poor FS), Obl Coronal T1, Obl Coronal T2, FS (May use STIR or IDEAL for poor FS). Following pre/post sequences will be used to help assess for subtle sacroilitis: Obl Ax T1 FSE FS Pre / Obl Ax T1 FSE FS Post / Obl Cor T1 FSE FS Post. FOV notes: Small FOV width should be approximately from femoral head to femoral head; oblique axial and coronal are prescribed relative to the sacrum. **Protocol for Spine:** Sag T1, T2 FSE no fat sat, STIR, FOV 28 / Ax T1 and T2 FSE (no fat sat), FOV 20.

4.3.3.2.2 Clinical asessment

A clinical evaluation including the search for enthesopathy – using the Maastricht Score (MASES) – and assessments with BASDAI, BASFI and BASMI will be performed at Screening.

The clinical assessment will be completed by the measurement of biological markers of inflammation (CRP and CBC) at Screening and at Day 30.

4.3.3.3 Safety assessments

- Physical examination will be conducted at D30.
- Measurement of vital signs (systolic and diastolic blood pressure and heart rate) will be performed 15 minutes before the radiotracer administration and at the end of the last imaging procedure at Day 0.
- Women of childbearing potential must have negative urine pregnancy test before injection of the radiotracer at Day 0.
- All medications taken from 2 weeks prior to the administration date through the end of study are to be recorded as prior and concomitant medications, including therapies for SpA.
- Any adverse events occurring during the course of the study will be reported and recorded in the eCRF. 24 hours after treatment injection (at Day 1), each patient will be called in order to inquire if they experienced signs or symptoms such as edema, rash or have any clinical findings.

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 study medication. 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 a study medication, whether or not causally related to the study medication.

AEs will be reported, if applicable, from the signing of the informed consent onwards until the last study-related procedure. If the information of an untoward medical occurrence is collected before

starting the intake of study medication, this information will be listed as a pre-treatment AE during statistical analysis.

Throughout the study, the study staff will question the patient in a non-directive way as to the occurrence of AEs. The patient will also be instructed, when signing the informed consent, as from that moment, to contact the Investigator to report any study medication or non-study medication related adverse or unusual event that occurs during participation to the study.

The study staff will record all these events in the patient's medical records and eCRF, whether observed by the Investigator, the investigational staff, or spontaneously reported by the patient. The Investigator will provide a complete description of the event in standard medical terminology, the date of onset and termination, severity, relationship to the study medication, action taken regarding the study medication, any treatment given, the outcome, and whether or not the event is considered as a SAE. If known, the Investigator should report the underlying illness or disorder rather than the individual signs and symptoms.

All AEs occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized. An assessment should be made at the last study-related visit for each patient. Certain long-term AEs cannot be followed until resolution within the settings of the protocol. In these cases follow-up will be the responsibility of the treating physician.

Since it is unpredictable how long such a follow-up might take, data from this follow-up generated after the patient's last study-related visit will be recorded by the Investigator. Full details regarding this follow-up will be described in the Clinical Study Report, if necessary. If during AE follow-up the case has progressed to the level of "SAE", or if a new SAE whose relationship to the study medication could not be ruled out is observed, the situation must be reported immediately by the Investigator becoming aware of the information (considering that the "date of SAE onset" is the date of the first manifestations of that AE).

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-patient hospitalization or leads to prolongation of hospitalization.
  Hospitalization or prolongation of hospitalization will not be considered as SAE in the following cases:
  - Hospitalization planned before the patient inclusion,
  - Hospitalization les than 24 h
  - Hospitalization needed for the routine follow-up of the patient disease.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for severe allergic reactions that do not result in hospitalization.

The Investigator must report all SAEs by sending a completed SA Reporting Form (Appendix III of study protocol) to the Safety Officer designee within 24 h of becoming aware of the event. All SAEs must be addressed to Advanced Accelerator Applications pharmacovigilance department.

The minimum information required for immediate reporting is the event description, the patient ID, the study medication concerned and the identifiable reporter (Investigator or designee). Even if not all the facts are known, an initial report should be made. The Investigator must provide follow-up information as soon as possible. If requested by the delegated Safety Officer designee, documents relevant to the diagnosis, treatment, and course of the event must be submitted (e.g. technical

investigation reports, histology findings, hospital discharge documents). All documents must be anonymized with respect to the patient's personal identification data.

When the Investigator determines that there is not more information likely to be available, a final report should be provided. The Sponsor or delegated CRO will assume responsibility for appropriate reporting of AEs to the regulatory authorities and the Independent Ethics Committee(s)/Institutional Review Board(s) (IEC/IRB) according to local laws and regulations.

SAEs will be collected following the patient written consent to participate in the study. The collection of SAE information will continue to be reported by the Investigator for each patient until 30 days after the last study medication administration.

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 risk factors for an unintentional pregnancy. The Investigator must report any pregnancy associated with investigational product exposure including conceptions occurring until 30 days after the last injection of radiotracer. The report should be carried out within 24 hours of pregnancy confirmation by sending a completed Pregnancy Reporting Form to the Safety Officer designee.

Appropriate pregnancy follow-up procedures should be considered if indicated. The Investigator must report follow-ups within 24 hours of the receipt of any new information on the course of the pregnancy, including perinatal and neonatal outcome, by sending a completed Pregnancy Reporting Form to the Safety Officer designee (Appendix IV of study protocol).

4.3.3.3.2 Standard laboratory assessments

General laboratory analysis will be performed and blood samples will be collected at screening and at Day 30.

Blood samples will be drawn and urine will be collected as mentioned in the study chart. A total volume of 50 mL, including blood samples for immunogenicity assessments, will be collected during the study for each patient.

Hematology	Coagulation	Blood chemistry	Urinalysis
• WBC with differential • RBC • Platelets • Hb • MCV • Hematocrit	• PT • PTT • INR	• BUN • Serum creatinine • Uric acid • Albumin • Total bilirubin • Direct bilirubin • AP • AST/ASAT • ALT/ALAT • Gamma-GT • Sodium • Potassium	• Dipstick test[1] • Pregnancy test *(at screening and before injection of study product)*

[1] In case one of the assessments of the dipstick test is positive, a microscopic analysis of the urine must be performed.

4.3.3.3.3 Immunogenicity assessments

As rhAnnexin V-128 is an exogenous protein, development of antibodies against the protein must be assessed in order to evaluate the risk and consequences of such a development.

Assays for anti-rhAnnexin V-128 IgG and IgM antibodies will be performed in serum samples by ELISA at screening visit. An additional sample is required at Day 30.

For this purpose 10 mL blood samples will be collected at screening and Day 30. At each time-point, after centrifugation, serum will be divided into six aliquots and frozen (-80°C). Three out of six serum aliquots will be then shipped to the central laboratory at [redacted]. Remaining samples will be shipped only if required for analysis and destroyed at study end if not required. Blood Samples Handling will be detailed in the Laboratory Manual provided by [redacted].

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 what the Investigator considers it is in the best interest of the participant to withdraw from the study
- Screening failure

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

Patients who will not have received the study product will be replaced.

The patient is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. It is also possible that the Sponsor or the regulatory authorities request termination of the study if there are concerns about conduct or safety.

The primary reason for a patient’s withdrawal from the study should be determined as possible. The date and reason for discontinuation must be documented in the eCRF.

4.3.3.5 Prohibitions and restrictions

The most important required restriction for study patients is pregnancy. Pregnancy tests will be performed for all patients (of child bearing potential) at baseline and prior to the radiotracer administration.

Imaging is performed ambulatory. After imaging, patient may go back home or go back to work without particular precaution for him or his relatives.

Any concomitant medication deemed necessary for the welfare of the subject 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:

- At screening visit, eligible and consented patients who have clinical suspicion or confirmed diagnosis of SpA will undergo a physical examination, vital signs (systolic and diastolic blood pressure, heart rate), blood analysis, i.e. CBC with automated differential, general chemistry

panel (SMA-20) including CRP, PT/PTT, INR (international normalized ratio for PT values), assessment of anti-annexin V-128 antibodies, and urinalysis. In addition, disease activity score assessments (BASDAI, BASFI, BASMI and MASES) will also be performed. Screening laboratory assays, physical examination and vital signs will be performed 24 hours to 14 days before ^{99m}Tc-rhAnnexin V-128 imaging. Within 14 days of ^{99m}Tc-rhAnnexin V-128 scanning patients will undergo T1 and STIR without contrast Magnetic Resonance Imaging (MRI) of the sacro-iliac and lumbar spine joints.

- At Day 0 (the day of intravenous injection and imaging with ^{99m}Tc-rhAnnexin V-128), a dedicated lumbosacral spine and abdomen SPECT/CT starting 60 minutes after injection of tracer followed by a whole body planar scan and spot views on selected areas will be performed. The same SPECT/CT and whole body planar X^{4}scans will be repeated at 2 hrs after injection of tracer except the spot views unless they suggest to be repeated. Vital signs assessment will also start 15 minutes before and for 2 hours after injection of radiotracer.
- At Day 1 (one day after the administration of ^{99m}Tc-rhAnnexin V-128), 15\20 patients will be contacted over the phone for assessment of possible adverse events (e.g. allergic reaction such as rash, edema). 5 patients will return for an optional whole body planar scan at 24hrs post injection as well as spot views, if deemed appropriate by the investigator. Safety information will be collected at this time for these 5 patients.
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- At Day 30 ± 3 days, all patients will return to the clinic for a physical examination and a final blood sampling to rule out the development of anti-annexin V-128 antibodies and for the following blood analysis and urinalysis: CBC with automated differential, general chemistry panel (SMA-20) including CRP, PT/PTT, INR (international normalized ratio for PT values).
- Once the first 5 patients have been administered with ^{99m}Tc-rhAnnexin V-128 and have performed the imaging at Day 0, a DMC will review the images. The visual assessment of the scans in these first 5 patients may support the continuation or the termination of the Phase II study. In the first case, the enrollment of 15 additional patients will be required.

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

Study Procedures	Screening (within 14 days prior to Day 0)	Visit 1 (Day 0)	Visit 2 (Day 1 24 hours[1])	Visit 3 (Day 30)
Written informed consent	X			
Inclusion/exclusion criteria	X			
Medical history	X			
Concomitant medications	X	X	X	X
Disease assessment (BASDAI, BASFI, BASMI, MASES)	X			
Physical examination	X			X
Vital signs (BP, HR)	X	X		
Lab analysis (hematology, PT/PTT/INR, biochemistry, urine)	X			X
Immunogenicity by ELISA[2]	X			X
Pregnancy test	X	X		
MRI (within 14 days of rh-Annexin V-128 scanning)	X[3]			
^{99m}Tc-rhAnnexin V-128 administration and scan (SPECT/CT and planar imaging)		X[4]	X[4]	
Whole Body Planar Imaging + spots			X[4]	
High resolution spot images of hands, feet, any symptomatic joint group		X[4]	X[4]	
Adverse Events	X	X	X	X

[1] 24 hours after injection of ^{99m}Tc-rhAnnexin V-128, each patient will be called over the phone to assess if they experienced any adverse events such as allergic reactions (edema, rash).

[2] 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 Day 30 post administration of test agent. Serum will be prepared, divided into six aliquots and frozen (-80°C). Three out of six serum aliquots will then be shipped to the central laboratory at [redacted]. The 3 remaining aliquots will be sent to [redacted] with an additional shipment.

[3] A whole lumbar spine MRI must be performed prior to the enrolment date, or within 14 days of ^{99m}Tc-rhAnnexin V-128 scanning prior to changing NSAID therapy or non-biologic DMARD or starting non-biologic DMARD for the first 5 patients and prior to changing NSAID therapy or non-biologic DMARD or starting non-biologic DMARD or biologic DMARD for the next 15 patients.

[4] First five patients after which the process will be re-evaluated:

- All patients will have whole body planar imaging at 60 minutes post injection.
- At two hours post injection do a whole body scan and SPECT/CT with onboard isotope with no spot views unless initial views suggest otherwise. The whole body scan adds 15-20 minutes; each spot adds 5 minutes.
- The SPECT/CT and spot imaging will be done for first 5 patients after which the protocol will be re-adjusted.
- An optional whole body planar scan will be done at 24hrs post injection for 5 patients as well as spot views, if deemed appropriate by the investigator.

4.3.5 Planned sample size

The number of patients in this study is not based on statistical power considerations. The planned sample includes 20 patients which is the number believed to provide sufficient data to assess the potential of ^{99m}Tc-rhAnnexin V-128 to image disease severity in SpA patients and provide sufficient preliminary data to plan larger pivotal trials focusing on the confirmation of the benefit for this new imaging procedure for the early diagnosis of SpA.

At first, five patients will be recruited and analyzed as a Proof of Concept (PoC). In the PoC part of the study, medical images will be reviewed by the DMC in charge of assessing the imaging potential of ^{99m}Tc-rhAnnexin V-128 in terms of image quality, uptake and medical relevance. After reaching a consensus, the committee will decide if the clinical investigation should continue with the remaining 15 patients. The planned number of patients in the PoC study is not based on statistical considerations. However, this number of patients should provide sufficient relevant information for the evaluation of the images in terms of quality and medical relevance.

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 the ^{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. Deviations from the protocol including violations of the Inclusion/Exclusion criteria will be assessed as minor/major before the data base locking.

5.2 Safety set

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

5.3 Primary population

The primary, secondary [redacted] efficacy analysis will be based on the FAS population.

The primary efficacy analysis on the Primary endpoint of Phase II will be also performed on the PP population as confirmatory analysis. The analysis on the PP population will be performed if the size difference between this population and the FAS population exceeds 2 patients.

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].

6.1.1 Efficacy endpoint

Due to the premature stopping of the study, the efficacy endpoints will not be addressed. All available efficacy data will be provided in subjects data listings and described in a descriptive manner in an abbreviated CSR.

6.1.1.1 Primary endpoint of PoC

The PoC phase will assess the imaging potential of ^{99m}Tc-rhAnnexin V-128 in terms of imaging quality, disease-lesion radiotracer uptake and medical relevance to enable the decision-making to terminate or to continue the clinical investigation completing the enrollment with the remaining patients.

Parameters used by DMC to assess primary endpoint of PoC will be described in the DMC charter.

6.1.1.2 Primary endpoint of Phase II

The primary endpoint of Phase II is to determine the magnitude and dynamic range of ^{99m}Tc-rhAnnexin V-128 uptake in disease affected sacro-iliac or lumbar spine joints, in patients with clinical suspicion or confirmed diagnosis of Spondyloarthritis (SpA). SPECT/CT scans will be interpreted and graded by the P.I. and two independent experienced nuclear medicine physicians blinded from clinical data and other imagings modality results. Briefly, ^{99m}Tc-rhAnnexin V-128 uptake compared with background (e.g. physiological liver uptake) should be assessed for each affected area by nuclear medicine physicians using a 4-grade scoring system (0 = none, 1 = mild or present

but lower than background uptake; 2, moderate or equal to background uptake; 3, intense or greater than background uptake). The assessed uptake will be the score with more adjudications (two or more). In case of discrepancies among the three different readers, an adjudication process based on consensus should be put in place in order to obtain one final outcome for each area.

Imaging procedure result, SUV and uptake intensity grades for SPECT/CT of sacro-iliac and lumbar spine joints will be summarized in descriptive tables; furthermore, concordance between the raters will be assessed with Kendall's W. For both SPECT/CT, two separate analysis will be conducted: one based on values measured 60 min after IP injection and the other on values measured 120 min after IP injection.

6.1.1.3 Secondary endpoints

The secondary endpoints of Phase II and the related statistical analyses are:

a) Endpoint: to determine the clinical utility of ^{99m}Tc-rhAnnexin V-128 SPECT/CT imaging in the identification of chronic ostheoarthritic active sites of SpA compared with conventional imaging (MRI), in patients with disease affected sacro-iliac or lumbar spine joints.
Statistical analysis: for quantifying the radioactivity uptake after injection of ^{99m}Tc-rhAnnexin V-128, ROIs will be drawn manually on the earliest images, and the shapes and sizes (i.e. number of pixels) will be kept constant over all subsequent images. Correction for background counts will be performed using an appropriate background region by subtracting the mean counts per pixel in the background region from the mean counts per pixel in each ROI to yield net counts. For each ROI, the geometric mean of net counts, corrected for physical decay, of total anterior and posterior counts will be calculated. In order to compare SPECT/CT scans and MRI scans, diagnostic performances will be evaluated in terms of sensitivity (i.e. true positive rate), specificity (i.e. true negative rate), positive predictive value (i.e. proportion of positive values) and negative predictive value (i.e. proportion of negative values). This analysis will be performed for both region, sacro-iliac and lumbar spine joints To do this, physical examinations will be necessary to define sites of pain in patients with clinical suspicion or confirmed diagnosis of SpA. When sites of pain will match with abnormalities on diagnostic images, this will be regard as true positive. Furthermore, for all the performed statistics, a two sided 95% C.I. will be computed

b) Endpoint: to assess the presence of antibodies against rhAnnexin V-128 at baseline and post-treatment.

Statistical analysis: The determination of antibodies against rhAnnexin V-128 at baseline and post-treatment will be described as present or absent; these data, related to immunogenicity, will be described in contingency tables reporting frequencies and percentages.

c) Endpoint: to determine the localization pattern and magnitude of focal uptake of ^{99m}Tc-rhAnnexin V-128 within the abdomen in patients with clinical suspicion or confirmed diagnosis of Spondyloarthritis (SpA).

Statistical analysis: Imaging procedure result, SUV and uptake intensity grades for SPECT/CT of abdomen and of spot views, and imaging procedure result and uptake intensity grades for whole body planar imaging will be summarized in descriptive tables; furthermore, concordance between the raters will be assessed with Kendall's W. For each imaging assessment, two separate analysis will be conducted: one based on values measured 60 min after IP injection and the other on values measured 120 min after IP injection

[redacted]

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), 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.

Categorical data will be presented as frequencies, percentages and 95% confidence interval if relevant. For continuous data, N, missing, mean, standard deviation, median, quartiles, minimum, maximum and if relevant 95% confidence interval will be presented. Graphs such as box plots, circular diagrams or histograms can also be computed if relevant. Considering the small sample size planned in this study, non-parametric approach will be favored.

6.1.2.1 Adverse events

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

Adverse events will be listed on an individual basis, including relationship and severity, LLT, LLT code and verbatim term. Treatment Emergent Adverse Events (TEAEs) and Adverse Drug Reactions 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 and relationship to the investigational imaging product. In the case several patients have experienced more than one adverse event, detailed descriptive statistics may also be presented on patients with 2, 3 or more than 3 AEs, if relevant.

Adverse drug reactions (ADRs, i.e. all AEs at least possibly related to the study drug according to the investigator) will be summarised in a similar way to TEAEs. Listings of serious adverse events (SAE), 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 ^{99m}Tc-rhAnnexin V-128 injection and up to 30 days after the 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 treatment.

6.1.2.2 Clinical laboratory values

Hematology, blood chemistry, urinalysis and immunogenicity values are recorded at baseline for screening and 30 days post IP administration. Descriptive statistics will be tabulated by measuring time for raw data and changes from baseline; boxplots will be reported, if appropriate. Data listing will be ordered by subject and measuring time. A listing of all the abnormal values (clinically and non-clinically relevant) will be reported.

6.1.2.3 Vital signs and physical examination

Vital signs data are recorded once at screening visit and twice at imaging visit (Day 0), before the injection of ^{99m}Tc-rhAnnexin V-128 and after the last imaging procedure (within 2 hrs after ^{99m}Tc-rhAnnexin V-128 injection). Physical examination data are recorded at screening visit and at Day 30. Descriptive statistics will be tabulated by measuring time for raw data and changes from baseline (screening visit); boxplots will be reported, if appropriate. For day 0, post imaging procedures values will also be compared with pre injection counterparts (i.e. assessed on the same day). If appropriate, comparisons between different measuring times will be performed according to appropriate non-parametric paired inferential statistics. Data listing will be ordered by subject and measuring time.

6.1.3 Multiplicity

Due to the exploratory nature of the study no adjustements will be made for multiplicity.

6.1.4 Significance testing and estimation

All statistical tests will be two-sided at the 5% level of significance.

6.1.5 Missing data and outliers

6.1.5.1 Missing data

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

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

6.1.5.3 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 (haematology, 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.

6.1.6 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.

6.1.7 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.

6.1.8 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 the FAS and Safety population.

6.1.9 Disease assessments

Descriptive statistics will be reported for all the parameters related to disease assessments (scores of BASDAI, BASFI, BASMI and MASES, MRI results, presence of clinical pain, number of inflammatory joints and category of patient treatment) for FAS and Safety population.

6.1.10 Medical and surgical history

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

Medical and surgical history will be listed on an individual basis, including SOC, preferred term and verbatim. A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by primary SOC and preferred term for FAS and Safety population.

6.1.11 Subject compliance

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 and, eventually, boxplots will be presented for all the continuous variables.

A listing will be presented for important concomitant medication for any subject who has received medication which could have an impact on safety assesments.

All the Protocol deviations will be also listed by subject.

6.1.12 Prior and concomitant therapies

Concomitant therapies will be coded using ATC Drug Dictionary.

Listings will be presented for active substance, ATC code and verbatim text. The listings will be sorted by subject, chronological start date, active substance, ATC code and verbatim text.

A frequency table of the number and percentage of subjects will be provided for concomitant therapies by Anatomical Main Group and Chemical substance for Safety population. Two different tables will report Prior Therapies (the drug therapies taken prior to the ^{99m}Tc-rhAnnexin V-128 injection) and Concomitant Therapies (the drug therapies that started after the ^{99m}Tc-rhAnnexin V-128 injection or that were ongoing at the start of ^{99m}Tc-rhAnnexin V-128 injection).

6.1.13 Derived data

The derived data are variables which are calculated from the raw data in the eCRF and could not be included in the database (e.g.: Age, BMI, days from ^{99m}Tc-rhAnnexin V-128 injection). The formula used for derived data and the strategy for missing data are provided in Section 11.4.

6.1.14 Visit windows

The screening visit can occur anytime within 2 weeks before the injection day. Visit 1 is the day of ^{99m}Tc-rhAnnexin V-128 administration (Day 0). The first follow-up visit (phone call) should occur within 24 hours after the injection. The second follow-up visit should occur 30 days after the injection with a window of 3 days, i.e. the visit has to be performed between the 27th and the 33rd day from the ^{99m}Tc-rhAnnexin V-128 administration.

6.1.15 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 the title of 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.

6.1.16 Pooling of Centres

Not applicable.

6.1.17 Interim analysis

No formal interim analysis will be done; however the DMC will review the images of the first 5 participants of the study to determine the presence of inadequate technical performance to assess disease-lesion radiotracer uptake.

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

The DMC consists of representatives of investigators and Sponsor representatives and could include external person such as independent experts, if judged appropriate by the Sponsor. The main function of the committee will be to review the images of the first 5 patients and determine if there is a premature high evidence of the presence of inadequate technical performance in this patients group. The DMC will also determine if there is a high evidence of an excess of adverse events.

The DMC will promptly give recommendations to continue or terminate the study. The DMC report will be edited by the Sponsor and sent to the ethics committee as well as competent authorities.

Preliminary results can be used by the Sponsor for publication purpose, before the end of the main trial.

6.1.19 Covariates and analysis of subgroups

Not applicable.

6.1.20 Sensitivity analysis

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 outputs 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.

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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 sponsor decision, it has been decided to close the study after the first 5 patients were enrolled. For this reason and due to the small number of patients enrolled, only subjects data listings will be produced for this study 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

Listing 16.2.3: Subjects Excluded from the Efficacy Analysis

16.2.4 Demographic data

Listing 16.2.4.1: Demographics

Listing 16.2.4.2: Disease Assessment

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Listing 16.2.4.4: Concomitant Medications

16.2.5 Compliance and/or drug concentration data

Listing 16.2.5.1: Study Drug Administration and Extent of Subject Exposure

16.2.6 Individual efficacy response data

Listing 16.2.6.1: Whole Body Planar Imaging – 60 min After IP Injection

Listing 16.2.6.2: Whole Body Planar Imaging – 120 min After IP Injection

Listing 16.2.6.3: Abdomen SPECT/CT Imaging – 60 min After IP Injection

Listing 16.2.6.4: Abdomen SPECT/CT Imaging – 120 min After IP Injection

Listing 16.2.6.5: Lumbosacral SPECT/CT Imaging – 60 min After IP Injection

Listing 16.2.6.6: Lumbosacral SPECT/CT Imaging – 120 min After IP Injection

Listing 16.2.6.7: Sacroiliac SPECT/CT Imaging – 60 min After IP Injection

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Listing 16.2.6.9: Spot SPECT/CT Imagings – 60 min After IP Injection

Listing 16.2.6.10: Spot SPECT/CT Imagings – 120 min After IP Injection

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: Deaths

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: Physical Examination

Listing 16.2.9.3: Vital Signs – Before IP Administration

Listing 16.2.9.4: Vital Signs – After Last Imaging Procedure

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.

The page number of each listing shell (n of N) represent n=page number of the listing and N=total number of pages for that specific listing.

Each listing must be presented in an independent, separate Word file for each ICH heading (e.g. Listings 16.2.9.X combined in one file).

10.3 Tables index

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

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 Figure templates

Figure templates are provided for each unique figure in Appendix 11.3. The figures will be presented in landscape, in a fixed font (arial) with a minimum size as 8.

10.6 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.

ANNEXIN 03

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	Screening date	Informed consent date	Visit 1 date	Phone call 2 date	Visit 3 date	Premature study discontinuation date	FAS	PP	Safety
PAT_PATNUMBER	PAT_FIRSTVISITDATE	PAT_INFCONS_DATE	PATV_VISITDATE	PATV_VISITDATE	PATV_VISITDATE	SD_DATE	[Derived Data]	[Derived Data]	[Derived Data]
03-US-001	11/03/2011	11/03/2011	11/04/2011	12/04/2011	11/05/2011		Yes	Yes	Yes
03-US-002	09/04/2011	09/04/2011	09/04/2011	10/04/2011	10/05/2011		Yes	Yes	Yes
03-US-003	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	Screening date	Informed consent date	Premature study discontinuation date	Reason for withdrawal	Explanation	Notes	FAS	PP	Safety
PAT_PATNUMBER	PAT_FIRSTVISITDATE	PAT_INFCONS_DATE	SD_DATE	SD_OUTCOME	SD_OUTCOME_SP	SD_NOTES	[Derived Data]	[Derived Data]	[Derived Data]
03-US-001	11/03/2011	11/03/2011	10/05/2012	XXXXXX	XXXXXX	XXXXXX	Yes	No	Yes
03-US-002	09/04/2011	09/04/2011	10/05/2012	XXXXXX	XXXXXX	XXXXXX	Yes	No	Yes
03-US-003	10/07/2011	10/07/2011	10/05/2012	XXXXXX	XXXXXX	XXXXXX	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 16.2.1.3: Inclusion Criteria

				Inclusion criteria			
Subject ID	Sex	Age	Screening date	First (PoC phase)	First (Phase II study)	Second	Third
PAT_PATNUMBER	PAT_GENDER	PAT_AGEYEAR	PAT_FIRSTVISITDATE	IC_1A	IC_1B	IC_2	IC_3
03-US-001	Male	54	11/03/2011	Yes	Yes	No	Yes
03-US-002	Female	68	09/04/2011	Yes	Yes	Yes	Yes
03-US-003	Female	59	10/07/2011	No	Yes	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	Sex	Age	Screening date	First	Second	Third	Fourth	Fifth	Sixth	Seventh
PAT_PATNUMBER	PAT_GENDER	PAT_AGEYEAR	PAT_FIRSTVISITDATE	EC_1	EC_2	EC_3	EC_4	EC_5	EC_6	EC_7
03-US-001	Male	54	11/03/2011	Not applicable	No	No	No	No	No	No
03-US-002	Female	68	09/04/2011	No	Yes	Yes	No	No	No	No
03-US-003	Female	59	10/07/2011	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]
03-US-001	Yes	XXXXX
03-US-002	No	XXXXX
03-US-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

Subject ID	Screening date	Deviation description
PAT_PATNUMBER	PAT_FIRSTVISITDATE	[Derived Data]
03-US-001	11/03/2011	XXXXXX
03-US-002	09/04/2011	XXXXXX
03-US-003	10/07/2011	XXXXXX

Listing 16.2.3: Subjects Excluded from the Efficacy Analysis

Subject ID	Screening part 1 date	FAS	Reason for exclusion from the FAS	PP set	Reason for exclusion from the PP set
PAT_PATNUMBER	PAT_FIRSTVISITDATE	[Derived Data]	[Derived Data]	[Derived Data]	[Derived Data]
03-US-001	11/03/2011	Yes		Yes	
03-US-002	09/04/2011	No	XXXXXXXXX	No	XXXXXX
03-US-003	10/07/2011	Yes		Yes	

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 date	Sex	Date of birth	Partial date	Age	Ethnicity	Specify other ethnicity
PAT_PATNUMBER	PAT_FIRSTVISITDATE	PAT_GENDER	PAT_BIRTH_DATE	PAT_PARTIAL_BIRTH_DATE	PAT_AGEYEAR	PAT_ETHNIC	PAT_ETHNIC_SP
03-US-001	11/03/2011	Male	12/03/1959	Day	54	Other	XXXXXXXX
03-US-002	09/04/2011	Female	10/09/1945	Day & Month	68	Caucasian	
03-US-003	10/07/2011	Female	24/02/1954		59	Asian	

Listing 16.2.4.2/1: Disease Assessment

Subject ID	SpA diagnosis date	Partial date	Score of BASDAI	Score of BASFI	Score of BASMI	Score of MASES
PAT_PATNUMBER	DA_DATE	DA_PARTIAL_DATE	DA_BASDAI	DA_BASFI	DA_BASMI	DA_MASES
03-US-001	11/03/2011	Day	9.4	5.4	7.7	12
03-US-002	09/04/2011	Day & Month	5.2	6.7	0.5	10
03-US-003	10/07/2011		8.3	3.5	9.9	2

Listing 16.2.4.2/2: Disease Assessment

Subject ID	Was a MRI performed?	MRI date	Number of inflammatory joints	MRI results in		Clinical pain in		Category of patient treatment
				lumbar spine	sacroiliac joints	lumbar spine	sacroiliac joints	
PAT_PATNUMBER	DA_MRI_YN	DA_MRI_DATE	DA_MRI_NUM	DA_MRI_RES_LUM	DA_MRI_RES_SAC	DA_CLIN_PAIN_LUM	DA_CLIN_PAIN_SAC	DA_PAT_TRT
03-US-001	Yes	11/02/2011	2	Positive	Negative	No	Yes	Start of non-biologic DMARD
03-US-002	Yes	01/04/2011	3	Negative	Positive	Yes	No	Start of biologic DMARD
03-US-003	No	NA	NA	NA	NA	No	No	Change in NSAID therapy

Listing 16.2.4.3: Significant Medical History and Associated Pathologies

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

Listing 16.2.4.4/1: Prior and Concomitant Medications

Subject ID	Medication trade name	ATC description	Start date (day)	Partial date	Ongoing?	End date	Partial date
PAT_PATNUMBER	CM_NAME	ATC_DESCR	CM_START_DATE	CM_PARTIAL_START_DATE	CM_ONGOING_YN	CM_END_DATE	CM_PARTIAL_END_DATE
03-US-001	XXXXXXXX	XXXXXX	15/08/1990 (-1)	Day	No	14/04/1994	Day
03-US-002	XXXXXXXX	XXXXXX	31/12/2007 (2)	Day&Month	No	15/06/2008	Day&Month
03-US-003	XXXXXXXX	XXXXXX	05/05/2005 (X)		Yes	Resolution date	

Listing 16.2.4.4/2: Prior and Concomitant Medications

Subject ID	Medication trade name	Total daily dose	Unit	Specify other unit	Frequency of administration	Specify other frequency	Route of administration	Specify other route
PAT_PATNUMBER	CM_NAME	CM_DOSE	CM_DOSEU	CM_DOSEU_SP	CM_FREQ	CM_FREQ_SP	CM_ROUTE	CM_ROUTE_SP
03-US-001	XXXXXXXX	3	G		BID		Otherl	XXXXXX
03-US-002	XXXXXXXX	3	Other	XXXXXX	TID		Intramuscolar	
03-US-003	XXXXXXXX	12	Mg		Other	XXXXXX	Subcutaneous	

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

Subject ID	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	ANN_YN	ANN_YN_SP	ANN_DATE	ANN_TIME	ANN_KIT	ANN_GEN
03-US-001	Yes		11/03/2011	10:50	09101-110631	09101-110631
03-US-002	Yes		03/03/2011	10:00	09101-110981	09101-110981
03-US-003	No	XXXXXXX				

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

Subject ID	Has the injection been performed?	Reason for not performing the injection	Radiochemical purity	Pre injection total dose in the syringe	Post injection residual dose in the syringe	Actual dose injected	Volume of solution
PAT_PATNUMBER	ANN_YN	ANN_YN_SP	ANN_TEST1	ANN_TEST2_PRE	ANN_TEST2_POST	ANN_TEST2_EFF	ANN_TEST2_VOL
03-US-001	Yes		98.7%	123	123	123	123
03-US-002	Yes		99.1%	456	456	456	456
03-US-003	No	XXXXXXX					

Listing 16.2.6.1: Imaging Results

									Grade of uptake		
Subject ID	Region	Time point	Has the imaging been completed?	Reason for not performing the imaging	Date	Time	Has the image been reviewed?	Result	PI	Reviewer 1	Reviewer 2
03-US-001	Whole Body Planar	60 min	Yes		11/03/2011	10:50	Yes	Positive	0	0	1
		120 min	Yes		11/03/2011	11:50	Yes	Positive	0	0	1
	Spot SPECT/CT: XXXXX	60 min	Yes		11/03/2011	10:50	Yes	Positive	0	0	1
		120 min	Yes		11/03/2011	11:50	Yes	Positive	0	0	1
	Etc…										
03-US-002			Yes		03/03/2011	10:00	Yes		2	3	2
03-US-003			No	XXXXXXX			No				

Listing 16.2.7.1/1: All Adverse Events

Subject ID	Event ID	Event description	SOC	PT	LLT	Day of onset§ (day)	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]
03-US-001	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	[redacted]	[redacted]	[redacted]
03-US-002	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	[redacted]	[redacted]	[redacted]
03-US-003	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	[redacted]	[redacted]	[redacted]

Data Source Table: W_PATIENT, W_AE.

SOC: System Organ Class

PT: Preferred Term

LLT: Lowest Level Term Dictionary Name: MedDRA Version: XX.X

§ Start day of onset in regarding to the annexin injection

^TEAE: Treatment Emegent Adverse Event

Note: NA = Not Available

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]
03-US-001	XXX	XXXXXXXX	Yes	Yes	XXXXXX / XXXXX / XX	Grade 2 (Moderate)	Possible	Other	XXXXXXXXXX	Yes
03-US-002	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX / XX	Grade 1 (Mild)	Unlikely	Pre-existing/underlying disease	XXXXXXXXXX	Yes
03-US-003	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX / XX	Grade 3 (Severe)	Unrelated	Other treatment	XXXXXXXXXX	Yes

Data Source Table: W_PATIENT, W_AE.

^TEAE: Treatment Emegent Adverse Event

Note: NA = Not Available

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
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_ACT	[Derived Data]	AE_ACT_OTH_SP	AE_OUTCOME
03-US-001	XXX	XXXXXXXX	No action	XXX/XXXXX/XXX		Resolved
03-US-002	XXX	XXXXXXXX	Dose modification in next treatment	XXX/XXXXX	XXXXXX	Worsened
03-US-003	XXX	XXXXXXXX	Unknown	XXX		Persisting

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

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	SOC	PT	LLT	Delay 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]
03-US-001	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	No	≥2	Yes
03-US-002	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	No	15	Yes
03-US-003	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	Yes	≥30	Yes

Data Source Table: W_PATIENT, W_AE.

SOC: System Organ Class

PT: Preferred Term

LLT: Lowest Level Term Dictionary Name: MedDRA Version: XX.X

§Delay of onset is defined as days from Annexin injection

^TEAE: Treatment Emegent Adverse Event

Note: NA = Not Available

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]
03-US-001	XXX	XXXXXXXX	Yes	Yes	XXXXXX / XXXXX / XX	Grade 2 (Moderate)	Possible	Other	XXXXXXXXXX	Yes
03-US-002	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX / XX	Grade 1 (Mild)	Unlikely	Pre-existing/underlying disease	XXXXXXXXXX	Yes
03-US-003	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX / XX	Grade 3 (Severe)	Unrelated	Other treatment	XXXXXXXXXX	Yes

Data Source Table: W_PATIENT, W_AE.

^TEAE: Treatment Emegent Adverse Event

Note: NA = Not Available

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
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_ACT	[Derived Data]	AE_ACT_OTH_SP	AE_OUTCOME
03-US-001	XXX	XXXXXXXX	No action	XXX/XXXXX/XXX		Resolved
03-US-002	XXX	XXXXXXXX	Dose modification in next treatment	XXX/XXXXX	XXXXXX	Worsened
03-US-003	XXX	XXXXXXXX	Unknown	XXX		Persisting

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

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	SOC	PT	LLT	Delay 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]
03-US-001	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	No	≥2	Yes
03-US-002	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	No	15	Yes
03-US-003	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	Yes	≥30	Yes

Data Source Table: W_PATIENT, W_AE.

SOC: System Organ Class

PT: Preferred Term

LLT: Lowest Level Term Dictionary Name: MedDRA Version: XX.X

§Delay of onset is defined as days from Annexin injection

^TEAE: Treatment Emegent Adverse Event

Note: NA = Not Available

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]
03-US-001	XXX	XXXXXXXX	Yes	Yes	XXXXXX / XXXXX / XX	Grade 2 (Moderate)	Possible	Other	XXXXXXXXXX	Yes
03-US-002	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX / XX	Grade 1 (Mild)	Unlikely	Pre-existing/underlying disease	XXXXXXXXXX	Yes
03-US-003	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX / XX	Grade 3 (Severe)	Unrelated	Other treatment	XXXXXXXXXX	Yes

Data Source Table: W_PATIENT, W_AE.

^TEAE: Treatment Emegent Adverse Event

Note: NA = Not Available

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
PAT_PATNUMBER	ID_WEB	AE_NAME	AE_ACT	[Derived Data]	AE_ACT_OTH_SP	AE_OUTCOME
03-US-001	XXX	XXXXXXXX	No action	XXX/XXXXX/XXX		Resolved
03-US-002	XXX	XXXXXXXX	Dose modification in next treatment	XXX/XXXXX	XXXXXX	Worsened
03-US-003	XXX	XXXXXXXX	Unknown	XXX		Persisting

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

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

Listing 16.2.7.4/1: Adverse Events Leading to Deaths

Subject ID	Event ID	Event description	SOC	PT	LLT	Delay 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]
03-US-001	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	No	≥2	Yes
03-US-002	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	No	15	Yes
03-US-003	XXX	XXXXXXXX	XXXXXX	XXXXXXXX	XXXXXX	YY	Yes	≥30	Yes

Data Source Table: W_PATIENT, W_AE.

SOC: System Organ Class

PT: Preferred Term

LLT: Lowest Level Term Dictionary Name: MedDRA Version: XX.X

§Delay of onset is defined as days from Annexin injection

^TEAE: Treatment Emegent Adverse Event

Note: NA = Not Available

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

Listing 16.2.7.4/2: Adverse Events Leading to Deaths

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]
03-US-001	XXX	XXXXXXXX	Yes	Yes	XXXXXX / XXXXX / XX	Grade 2 (Moderate)	Possible	Other	XXXXXXXXXX	Yes
03-US-002	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX / XX	Grade 1 (Mild)	Unlikely	Pre-existing/underlying disease	XXXXXXXXXX	Yes
03-US-003	XXX	XXXXXXXX	No	No	XXXXXX / XXXXX / XX	Grade 3 (Severe)	Unrelated	Other treatment	XXXXXXXXXX	Yes

Data Source Table: W_PATIENT, W_AE.

^TEAE: Treatment Emegent Adverse Event

Note: NA = Not Available

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

Listing 16.2.7.4/3: Adverse Events Leading to Deaths

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

Data Source Table: W_PATIENT, W_AE.

Note: NA = Not Available

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

Listing 16.2.8.1/1: Hematology

Subject ID	Visit	Have tests been done?	Sample collection date	Sample collection time	Parameter	Result	Unit	Abnormality
03-US-001	Screening	Yes	11/03/2011	10:52	Red Blood Cells	10^6/uL	XX	Abnormal Non-Clinical Relevant
					Hematocrit	%	XX	Abnormal Non-Clinical Relevant
					Etc…			
	Visit 3	Yes	09/04/2011	15:00				
03-US-002	Screening	Yes	10/07/2011	09:38				
03-US-003	Visit 3	No: XXXXX						

Listing 16.2.8.2/1: Blood Chemistry

Subject ID	Visit	Have tests been done?	Sample collection date	Sample collection time	Parameter	Result	Unit	Abnormality
03-US-001	Screening	Yes	11/03/2011	10:52	ALT	U/L	XX	Abnormal Non-Clinical Relevant
					AST	U/L	XX	Abnormal Non-Clinical Relevant
					Etc…			
	Visit 3	Yes	09/04/2011	15:00				
03-US-002	Screening	Yes	10/07/2011	09:38				
03-US-003	Visit 3	No: XXXXX						

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Listing 16.2.8.3/1: Urinalysis

Subject ID	Visit	Have tests been done?	Sample collection date	Sample collection time	Parameter	Result	Unit	Abnormality
03-US-001	Screening	Yes	11/03/2011	10:52	Appearance	XX	XX	Abnormal Non-Clinical Relevant
					pH	XX	XX	Abnormal Non-Clinical Relevant
					Etc…			
	Visit 3	Yes	09/04/2011	15:00				
03-US-002	Screening	Yes	10/07/2011	09:38				
03-US-003	Visit 3	No: XXXXX						

Listing 16.2.8.4: Immunogenicity

						anti-rhAnnexin V-128	
Subject ID	Visit	Has venous sample been done?	Reason for non performance	Sample collection date	Sample collection time	IgG	IgM
PAT_PATNUMBER	VISIT_NAME	IM_YN	IM_YN_SP	IM_DATE	IM_TIME		
03-US-001	Screening	Yes		11/03/2011	10:52	Negative	Negative
03-US-001	Visit 3	Yes		09/04/2011	15:00		
03-US-002	Screening	Yes		10/07/2011	09:38		
03-US-003	Visit 3	No	XXXXXXXXX				

Listing 16.2.9.1: Pregnancy Test

Subject ID	Sex	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_GENDER	PAT_AGEYEAR	VISIT_NAME	PT_YN	PT_NOTDONE	PT_NOTDONE_SP	PT_DATE	PT_TIME	PT_RESULT
03-US-001	Male	54	Screening	Not applicable					
03-US-001	Male	54	Visit 1	Not applicable					
03-US-002	Female	38	Screening	Yes			09/04/2011	12:00	Negative
03-US-002	Female	38	Visit 1	Yes			12/04/2011	11:00	Negative
03-US-003	Female	59	Screening	No	Menopause				

Listing 16.2.9.2/1: Physical Examination

Subject ID	Visit	Has the physical examination been done?	Reason for non performance	Physical examination date	Physical examination time	Any clinically relevant finding?	Specify		
							First finding	Second finding	Third finding
PAT_PATNUMBER	VISIT_NAME	PE_YN	PE_YN_SP	PE_DATE	PE_TIME	PE_RELFIND_YN	PE_RELFIND1	PE_RELFIND2	PE_RELFIND3
03-US-001	Screening	Yes		09/04/2011	12:00	No			
03-US-001	Visit 3	Yes		09/05/2011	10:00	No			
03-US-002	Screening	Yes		06/05/2013	9:45	Yes	XXXXXXX	XXXXXX	XXXXXX

Listing 16.2.9.3: Vital Signs

Subject ID	Visit	Time point	Have vital signs been evaluated?	Reason for non evaluation	Vital signs evaluation date	Vital signs evaluation time	Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse rate (beats/min)
PAT_PATNUMBER	VISIT_NAME		VS_POST_YN	VS_POST_YN_SP	VS_POST_DATE	VS_POST_TIME	VS_POST_SBP	VS_POST_DBP	VS_POST_HR
03-US-001	Visit 1	Before IP admin	Yes		09/04/2011	12:00	165	99	77
		After Last Imaging Procedure	Yes		09/04/2011	12:00	165	99	77
03-US-002	Visit 1		Yes		12/04/2011	10:00	129	93	60
03-US-003	Visit 1		Yes		06/05/2013	9:45	147	68	76

11.2 Standard Tables

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.

APPENDICES TO THE SAP TEMPLATE

11.4 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 ([visit date] – [birth date])/365.25 and truncated to the largest integer that is less than or equal to the calculated result. If birth date is not a complete date then it will be approximated using “01” as value for the day and “01” as value for the month.

(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 each imaging assessment (i.e. whole body planar imaging, abdomen SPECT/CT, lumbosacral SPECT/CT, sacroiliac SPECT/CT and spot SPECT/CT) time and injection time [WBPI1_TIME / WBPI2_TIME / ABD1_TIME / ABD2_TIME / LUMB1_TIME / LUMB2_TIME / SACRO1_TIME / SACRO2_TIME / SPOT1_TIME / SPOT2_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) **Delay of onset**

Delay of onset will be reported as the difference in days from the day of Annexin injection. 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 time to onset is greater than 24 hours then it will be calculated as (start date - injection date) and presented in days. 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).

11.5 SAS Programs

This section provides the SAS programs related to the statistical tests specified in the statistical analysis section. 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 SQL
- Proc Transpose

2 Descriptive statistics

- Proc Freq
- Proc Means
- Proc Tabulate

3 Test statistics

- Proc GLM
- Proc Mixed
- Proc Ttest
- Proc Univariate
- SAS macro %MAGREE

4 Graphs

- Proc Boxplot