7.3 Study Rationale

Armaron has identified there is a need for additional therapies in the immediate post-MI period. Armaron has developed NP202 for the treatment of cardiac remodelling based on the pharmacological evidence of a beneficial effect in several in vitro assays and in response to oral administration in a relevant animal model, and on the available safety pharmacology and toxicology data that indicate a broad safety profile for this novel therapeutic. NP202 has a novel mechanism of action, with potential to have additive benefits over ACE and ARB inhibitors.

Based on the available clinical and nonclinical data, this Phase 2 proof-of-concept study was conducted to further evaluate the safety and efficacy of NP202 in post-MI patients. Patients selected to take part in the study had suffered an ST elevation MI (STEMI) in the previous 5 days and were randomised to receive daily oral administration of NP202 for 90 days at a dose level of no more than 1000 mg/day or placebo.

8 STUDY OBJECTIVES

The primary objective of the study was to:

- Evaluate the efficacy of NP202 compared to placebo, when administered once daily for 3 months, in attenuating pathological LV remodelling in patients post MI.

The secondary objectives of the study were to:

- Assess the safety and tolerability of NP202 compared to placebo, when administered once daily for 3 months to patients post MI;

- Determine the pharmacokinetics (PK) of multiple doses of NP202 in a subset of patients post MI.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

The study was designed as a multi-centre, randomised, double blind, placebo-controlled study to assess the efficacy, safety, and PK of NP202.

It was planned to conduct this study at centres in multiple countries, in up to 180 adults who had an anterior STEMI in the 5 days prior to enrolment.

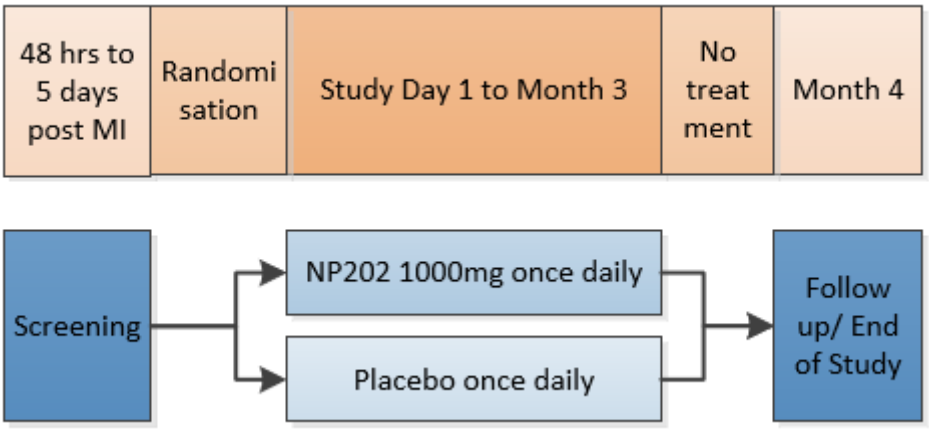
Subjects were screened post STEMI, with the screening echocardiogram and the baseline MRI conducted no earlier than 48 hours post-STEMI. Eligible subjects were randomised and administered their first dose of investigational product (IP) on Study Day 1 (3 to 5 calendar days post STEMI). Subjects were randomised to receive either NP202 1000 mg or placebo, in a 1:1 ratio.

Subjects were required to take their IP dose once a day for 3 months (90 days). During this treatment period they were required returned to the site for study visits at week 2, and months 1, 2, and 3. Month 3 was the end of the treatment period. Subjects returned for follow up and the final study visit at Month 4.

An independent Data Monitoring Committee (DMC) reviewed safety data at agreed recruitment and progression milestones throughout the study, as agreed and documented in the DMC Charter. The DMC could recommend continuation of the study with no changes or recommend cessation of dosing in a subject or all subjects, early termination of the study or changes to the protocol. Armaron had the final decision on acceptance of any DMC recommendations.

A Clinical Endpoints Committee (CEC) reviewed major cardiac and cerebrovascular events (MACCE) on an ongoing basis through the study.

Figure 1: Study Design



Abbreviations: MI=myocardial infarction

9.2 Discussion of Study Design, Including the Choice of Control Groups

Choice of design: A randomized, double blind, placebo-controlled design was selected. The study was blinded so that the subjects, study site staff administering study medication (NP202 or placebo) and study site staff conducting study assessments did not know which treatment the subject received in order to avoid any bias in the study assessments. The use of a placebo group lessens the risk that events due to chance are falsely attributed to NP202.

Choice of subjects: With the favourable safety and tolerability results obtained from Phase 1 study in healthy male adults, this Phase 2 study was conducted in patients who had experienced MI. This was to enable the efficacy of NP202 to be evaluated. To be included in this study, patients were required to have suffered a STEMI in the 5 days prior to anticipated first dose of IP.

Choice of endpoints: The efficacy endpoints selected for this study was appropriate to the proposed mechanism of action of NP202 as identified in the nonclinical testing. Safety and tolerability endpoints are appropriate for Phase 2 studies and this patient population. Pharmacokinetic endpoints provide supportive data for NP202 clinical development in this patient population.

Choice of duration of treatment period: Treatment duration of 3 months was selected as this is the duration of pre-clinical trials in animal data with supportive efficacy, safety and tolerability data.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

A subject was considered eligible for inclusion in this study if all of the following criteria were met:

1. Aged 18 to 80 years, inclusive;
2. Had a confirmed anterior STEMI in the previous 5 days, which met all of the following criteria;
   - ≥ 0.2 mV ST elevation in 2 or more V1 – V6 leads with presentation in a maximum of 12 hours of onset of symptoms;
   - Troponin levels >10 x upper limit of normal (ULN, local laboratory);
   - Successful revascularisation by percutaneous coronary intervention (PCI);
3. Had VL dysfunction post STEMI as evidenced by left ventricular ejection fraction (LVEF) ≤45% confirmed by echocardiogram at screening;
4. Was receiving guideline-directed medical therapy for acute MI and post-MI LV dysfunction according to national cardiology society/heart association guidelines;
5. Agreed to use contraception for the duration of the study, or were of non- child bearing potential;
6. Were able to provide written informed consent.

9.3.2 Exclusion Criteria

A subject who met any of the following criteria was not eligible for participation in this study:

1. Pregnant or breastfeeding females;
2. Known cardiomyopathy or heart failure prior to MI;
3. Cardiogenic shock and/or systolic blood pressure < 85 mmHg at screening;
4. Clinical history of ejection fraction ≤ 45% prior to MI, or multiple prior MIs;
5. Daily use of non-steroidal anti-inflammatory drugs (NSAIDs) and/or cyclooxygenase-2 (COX-2) inhibitors in the past month;
6. Prior coronary artery bypass graft to culprit vessel;
7. Presence of device/hardware incompatible with MRI imaging;
8. Estimated glomerular filtration rate < 30 mL/min;
9. Liver function tests 3 x ULN due to non-cardiac disease;
10. Receipt of any investigational research agent within 30 days or 5 half-lives (whichever was longer) prior to the first dose of IP;
11. History of severe or life-threatening drug allergy and/or known drug hypersensitivity;
12. Current malignancy or previous malignancy that was likely to recur during the period of the study (with the exception of a past history of basal or squamous cell carcinomas);

13. Human immunodeficiency virus, hepatitis B or hepatitis C;
14. Other than the current STEMI, history of or current clinically significant gastrointestinal, hepatic, renal, cardiovascular, respiratory, endocrine, oncological, immunodeficiency, neurological, metabolic, haematological, autoimmune or psychological disorder that, in the investigator's opinion, would compromise subject safety or protocol compliance;
15. Clinical signs of active infection and/or a temperature of >38.0°C at the time of screening.

9.3.3 Removal of Subjects from Therapy or Assessment

Subjects could terminate their study participation at any time and without giving a reason, and without prejudice to further treatment. Subjects who discontinued from the study were asked about the reason(s) for their discontinuation or about the presence of any AEs. If possible, they were seen and assessed by an investigator and asked to complete an early termination visit. Adverse events were followed up until resolved or stable and determined to be chronic.

The investigator or the medical monitor could exclude a subject from continuing in the study. Possible reasons for discontinuing a subject could include:

- Subject withdrawal of consent;
- Any unacceptable AEs, in the judgement of the investigator;
- Subject's non-compliance with the protocol;
- Armaron terminated the study for administrative, financial, or other reasons.

9.4 Treatments

9.4.1 Treatments Administered

Subjects were randomly assigned to one of the following treatment arms:

- 1000 mg of oral NP202 once per day for 3 months (90 days);
- Oral placebo once per day for 3 months (90 days).

Subjects were instructed to take 2 capsules orally once per day during the treatment period.

9.4.2 Identity of Investigational Product(s)

9.4.2.1 *NP202*

The NP202 drug substance was manufactured under GMP by Piramal Healthcare, 110 Industrial Parkway North, Aurora, Ontario L4G 3H4, Canada.

The active product for use in the clinical trial was manufactured by Pharmaceutical Packaging Professionals (PPP), Port Melbourne, Australia. The product was labelled by PPP, in accordance with all applicable regulatory requirements.

NP202 was encapsulated into hard gelatine capsules containing 500 mg of NP202 and microcellulose. Batch Number: PPP.15.574.

NP202 was packaged in high density polyethylene (HDPE) bottles and was supplied to the study sites after receipt of required documents in accordance with all applicable regulatory requirements. Each bottle contained capsules for 30 days plus sufficient overage.

9.4.2.2 *Placebo/Comparator/Control*

The placebo product for use in the clinical trial was manufactured by PPP, Port Melbourne, Australia. The product was labelled by PPP, in accordance with all applicable regulatory requirements.

Matching placebo capsules were filled with microcrystalline cellulose, an inert material extensively utilised in tablets and capsules. Batch Number: PPP.15.573.

Placebo was packaged in HDPE bottles and was supplied to the study sites after receipt of required documents in accordance with all applicable regulatory requirements. Each bottle contained capsules for 30 days plus sufficient overage.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subject eligibility was established before randomisation. Eligible subjects were assigned to either NP202 or placebo in a 1:1 ratio according to the randomisation schedule. Randomisation was stratified by LVEF (<35% versus ≥35%) as determined by echocardiogram at screening.

At each site, a subject identification (ID) number was allocated to each subject who provided informed consent, so that subjects could be identified without making assumptions about their subsequent eligibility for the main trial. Subjects were allocated to sequential, ascending 3-digit numbers (001, 002, 003 *etc.*), which, together with the 2-digit site number, provided a unique identifier. The subject retained the same ID number for the duration of the study.

Treatment allocation per subject is provided in Appendix 16.1.1.

9.4.4 Selection of Doses in the Study

In determining the dose level to be evaluated in this Phase 2 study, consideration was given to the available clinical and nonclinical data for NP202.

Preliminary data from the Phase 1 clinical trial support the safety and tolerability of NP202 when administered at oral dose levels of up to 1000 mg/day for 14 days. Preliminary PK data from the MAD cohorts show that steady state plasma concentrations of NP202 and NP201 conjugates appear to have been achieved after approximately 3 to 4 days of dosing. Mean plasma trough concentrations of NP202-related species were approximately 3.5 μM in the 400 mg/day cohort and approximately 6 μM in the 1000 mg/day cohort.

The nonclinical data from 90-day repeat-dose toxicity studies support the safety of NP202 when administered at oral dose levels of up to 1000 mg/kg body weight/day in rats and 300 mg/kg body weight/day in dogs (the no observed adverse effect levels [NOAELs] in the respective studies). These dose levels are equivalent to 161 and 167 mg/kg body weight/day in humans, respectively by the United States Food and Drug Administration, 2005. Notably, the PK profile and metabolic pathways for NP202 appear to be similar in rats, dogs, and humans, with NP202 being absorbed in a dose-dependent manner following oral administration and undergoing metabolism to form NP201 and various conjugated forms of

NP202 and NP201 that contribute to overall plasma exposure.

Based on the following considerations, a dose level of 1000 mg/day (equivalent to 16.7 mg/kg body weight/day for a 60 kg individual) was used to support the proof-of-concept Phase 2 study in post-MI patients:

- Safety
  - 1000 mg/day was the highest dose level evaluated in Phase 1 MAD cohorts;
  - 1000 mg/day was approximately10-fold less than the human equivalent dose (HED) values of 161 and 167 mg/kg body weight/day that were calculated from the NOAEL values from 90-day repeat-dose toxicity studies in rats and dogs, respectively.
- Efficacy
  - 1000 mg/day was anticipated to demonstrate positive signs of activity based on the observation of efficacy at a dose level with a lower HED of 3.2 mg/kg body weight/day (equivalent to 192 mg/day for a 60 kg individual) in a rat model of cardiac remodelling post- infarction;
  - 1000 mg/day was anticipated to provide similar maximum observed plasma concentration and the average plasma concentration over 24 hours, and considerably higher trough levels, as the efficacious dose in a rat model of cardiac remodelling post-infarction.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects were randomly assigned to one of the following treatment arms:

- 1000 mg of oral NP202 (x 2 500 mg NP202 and microcellulose gel capsules once per day for 3 months (90 days) plus 1 month follow up;
- 1000 mg of oral placebo (x 2 500 mg placebo and microcellulose gel capsules once per day for 3 months (90 days) plus 1 month follow up.

There were no requirements for the timing of dose administration, nor for the relation of dosing to meals. No specific instructions to subjects about when or how to take the dose(s) was provided.

9.4.6 Blinding

At each study drug dispensing visit, subjects were allocated a bottle number by an interactive web or voice response system (IW/VRS). The subject, site, sponsor and monitoring personnel were blinded as to whether the subject was receiving NP202 or placebo.

Due to the colour change that NP202 causes in semen, it was possible that subjects or study staff may be unblinded. However, as the study efficacy endpoints were objective and were assessed by blinded reviewers, this did not compromise the study objectives.

The IW/VRS provided the option for an investigator to break the blind. Sites were instructed to break the blind only in situations in which the investigator determined that adequate medical care could not be provided without knowing the treatment assignments. If a code break was to occur, the investigator or designee was to contact the study medical monitor

before unblinding. If the code was broken for a subject, the IW/VRS would immediately notify Armaron or their delegate. If the blind was broken, the investigator was to document the date and the reason the blind was broken in the subject's notes and case report form (CRF).

9.4.7 Prior and Concomitant Therapy

Prior therapy with daily use of NSAIDs and/or COX-2 inhibitors in the past month was prohibited.

Prior therapy with any investigational research agent within 30 days or 5 half-lives (whichever was longer) prior to the first dose of IP was prohibited.

Any medications taken other than the IP were to be documented in the subject notes and the CRF.

Any use of concomitant medications taken in the 7 days prior to Day 1 was recorded on the prior medication CRF. Any use of medications for the treatment of pre-existing conditions or AEs were recorded on the concomitant medication CRF.

9.4.8 Treatment Compliance

Subject compliance was assessed at each study visit by capsule count. Subjects were considered compliant if they took ±10% of scheduled doses. Subjects who are non-compliant were reminded of the dosing requirements and advised that they could be withdrawn from the study if compliance did not improve.

9.5 Efficacy, Safety and Pharmacokinetic Variables Measurements Assessed and Flow Chart

The schedule of study procedures and assessments for all study visits is presented in Table 3.

Table 3: Schedule of Study Assessments

Visit / Assessment	Screening	Baseline	Treatment period				End of study
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[3]	
	Up to 5 days post MI	Day 1 (48h to 5d post MI)	Day 14±2	Day 30±2	Day 60±2	Day 90±7	Day 120±7
Consent	X						
Inclusion/exclusion criteria	X	X					
Demographics	X						
Medical history (MI symptoms, treatment and intervention)	X						
(Abbreviated) PE	X	(X)	(X)	(X)	(X)	X	X
Vital signs	X	X	X	X	X	X	X
12 lead ECG	X	X	X	X	X	X	X
Biochemistry	X[1]	X	X	X	X	X	X

Visit / Assessment	Screening	Baseline	Treatment period				End of study
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[3]	
	Up to 5 days post MI	Day 1 (48h to 5d post MI)	Day 14±2	Day 30±2	Day 60±2	Day 90±7	Day 120±7
Haematology	X[1]	X	X	X	X	X	X
PSA (male participants)		X				X	
Coagulation studies	X[1]	X	X	X	X	X	X
Urinalysis	X[1]	X	X	X	X	X	X
Serum pregnancy test for WOCBP	X			X	X	X	X
Serum biomarker samples		X	X	X	X	X	X
Exploratory biomarker serum sample		X	X	X	X	X	X
Echocardiogram	X						
Killip classification		X					
NYHA classification			X			X	X
Cardiac MRI		X[2]				X	
Randomisation		X					
Dispense IP		X		X	X		
Trough PK samples		X	X	X	X	X	
AE assessment		X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X	X	X
IP accountability			X	X	X	X	

Abbreviations: AE = adverse event, ECG = electrocardiogram, IP = investigational product, MI = myocardial infarction, MRI = magnetic resonance imaging, NYHA = New York Heart Association, PE = physical examination, PK = pharmacokinetic, PSA = prostate specific antigen, WOCBP = woman of child-bearing potential.

1 Laboratory tests performed any time post PCI were used as screening results, if relevant (i.e. it was not required to repeat tests specifically for study screening if the tests were already done and the entry criteria met).

2 Cardiac MRI was performed during the screening period once a subject was known to be eligible.

3 Visit 5 procedures were performed as an early termination visit if applicable.

9.5.1 Efficacy Variables

9.5.1.1 *Cardiac Volumes and Structure*

Cardiac volume and structure were assessed by cardiac MRI at baseline and at Month 3. Images were sent to a central imaging centre and read in a blinded fashion.

A detailed imaging manual was provided to the sites. This specified the study requirement including site training and infrastructure, quality control, subject preparation, imaging sequences and acquisition, and submission to the imaging laboratory.

An additional manual detailed the imaging laboratory processes and procedures for image receipt, reading, quality assurance, reporting and archiving.

9.5.1.2 *Cardiac Biomarkers*

Blood samples were taken throughout the course of the study for biomarker tests. The following specific tests were performed at the central laboratory: Troponin I and T, high sensitivity C-reactive protein (hsCRP) and brain natriuretic peptide type B (NT pro-BNP).

An additional blood sample was taken at each study visit for exploratory biomarkers. This blood sample was stored until the study results were available, after which it was tested for additional biomarkers related to cardiac disease. Samples were not stored for longer than 2 years after study completion.

9.5.2 Safety and Tolerability Variables

Safety was assessed by recording of AEs, MACCE, vital signs, laboratory parameters, 12-lead ECGs, and physical examinations (PE).

9.5.2.1 *Physical Examinations*

Physical examinations during the study included: height (at screening only) and weight; assessment of skin, head, neck, lymphatic, eyes, ears, nose and throat, abdomen, and respiratory; cardiovascular/peripheral vascular, endocrine, central nervous, genitourinary and musculoskeletal systems, as appropriate to determine general condition. New or worsening clinically significant abnormalities were reported as an AE. An abbreviated PE was conducted at some visits based on prior findings and symptoms.

9.5.2.2 *Major Adverse Cardiac and Cerebrovascular Events*

Major adverse cardiac and cerebrovascular events were reviewed during the study by the CEC.

9.5.2.3 *Clinical Laboratory Safety Assessments*

Blood and urine samples were taken throughout the course of the study for safety assessments. The following specific tests were performed at the site's local pathology laboratory:

- Haematology, including haemoglobin, haematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count;
- Serum chemistry including sodium, potassium, blood urea nitrogen, serum albumin, total protein, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, cholesterol, glucose, creatine phosphokinase, lactate dehydrogenase, and creatinine (calculated creatinine clearance using the Cockcroft and Gault formula);
- Coagulation was analysed via partial thromboplastin time, prothrombin time, thrombin time;
- Urinalysis including a dipstick for specific gravity, pH, glucose, protein, blood, ketones, urobilinogen, nitrite, and leukocyte esterase. If protein, nitrite and leukocyte esterase were positive, microscopic examination of urine sediment was performed (RBC, WBC, epithelial cells, crystals, casts, bacteria);

- All males were tested for Prostate Specific Antigen.

9.5.2.4 *Vital signs*

Vital signs were measured after the subject was supine for 5 minutes and included blood pressure on the same arm (if possible) throughout the study, pulse rate, respiratory rate and temperature.

9.5.2.5 *12-lead Electrocardiograms*

At each visit, 12-lead ECGs were performed. The RR, PR, QRS, QT and QTc intervals were measured. The site investigator reviewed the ECG report, and any new or worsening clinically significant abnormalities were followed up with the subject and reported as an AE.

9.5.2.6 *Adverse Events*

It was the responsibility of the Investigator to ensure that AEs which occurred in the context of the study were reported and documented.

An AE was defined as any untoward medical occurrence in a subject administered IP and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IP whether or not related to the IP.

Laboratory reference ranges were defined by upper and lower limits of parameters by the laboratory. The Investigator was to ensure that each parameter out of the normal range was assessed for clinical significance and potential for being an AE. It was at the discretion of the Investigator to document any change in laboratory result as an AE if he considered the change to be clinically significant, even if the absolute value was within the alert limit or reference range.

Assessment of Severity: The Investigator (or medically qualified delegate) made an assessment of intensity for each AE and SAE reported during the study. The assessment was based on the Investigator's clinical judgment. The severity of each AE and SAE was described using one of the following categories:

- Severe events were those AEs which made normal daily routine impossible.
- Moderate events were those that impacted normal daily routine.
- Mild events were those that did not impact normal daily routine.

Assessment of Relationship: The Investigator assigned causality to each AE and SAE in relation to NP202 based on the following categories:

- Not related: events for which there was evidence of another explanation, e.g. the event was obviously explained by the subject's disease(s), is in accordance with the known effect of a concomitant medication or had occurred prior to first administration of NP202.

- Unlikely related: an event with a time to NP202 administration that made a relationship improbable (but not impossible), and disease or other drugs provide plausible explanations

- Possibly related: an event with a reasonable time relationship to NP202 administration, but which could also be explained by disease or other drugs. Information on NP202 withdrawal may be lacking or unclear

- Probably related: an event with reasonable time relationship to NP202 administration that is unlikely to be attributed to disease or other drugs. Response to NP202 withdrawal was clinically reasonable. Re-challenge was not required

- Definitely related: an event with a plausible time relationship to NP202 administration which could not be explained by disease or other drugs. Response to NP202 withdrawal was plausible (pharmacologically, pathologically), and event was definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon). Re-challenge, if performed/necessary, was satisfactory.

All AEs were to be documented by the Investigator, regardless of causality.

Serious Adverse Event: An AE was to be classified as serious if it:

- Resulted in death;

- Was life-threatening. Life threatening in the definition of serious referred to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe;

- Required in-patient hospitalisation or prolongation of existing hospitalisation. Hospitalisation was defined as in-patient admission or care regardless of duration. Out-patient treatment in an emergency room was not in itself an SAE, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Elective surgery, hospitalisation for social reasons (with no causal AE), or hospital admissions and/or surgical operations planned before or during this study were not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study;

- Resulted in persistent or significant disability/incapacity;

- Was a congenital anomaly/birth defect;

- Was an important medical event. This included events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above.

Recording of Adverse Events and Serious Adverse Events: Adverse events were captured from the time of informed consent until the final study visit. Subjects were asked at each visit whether they had experienced any AEs. SAEs possibly related to NP202 occurring to a study subject after the AE reporting period were to be reported to the sponsor if the Investigator becomes aware of them.

Adverse events were to be reported as diagnoses where possible, rather than individual signs and symptoms. The AE description, start and stop dates, intensity, causality and outcome were to be recorded, as well as any actions taken. Unless a diagnosis was made, or signs and symptoms were present, laboratory values or vital signs abnormalities were only to be reported as AEs if they caused the subject to discontinue from the trial, the investigator felt it was clinically significant, or they meet a criterion for a SAE.

Investigators and other site personnel were to report SAEs to Armaron or designee within 24 hours of becoming aware of the SAE, regardless of causality. Follow-up information on SAEs was also reported by the investigational site within the same time frame.

All AEs and all SAEs were followed by the Investigator until resolution, until the AE stabilised or was recognised as a permanent condition by the Investigator, or until the subject was lost to follow up, whichever comes first. Follow-up investigations were to be performed according to the Investigator's medical judgement.

9.5.3 Drug Concentration Measurements

Blood samples for plasma PK were taken throughout the course of the study, from a subset of 30 subjects. Samples were shipped to a central laboratory for determination of NP201 levels. NP201 is the active metabolite of NP202. Samples were stored frozen and analysed in batches.

Trough PK plasma samples (ie pre-dose) were collected at Baseline (Day 1), Day 14, Day 30, Day 60 and Day 90. No protocol mandated restrictions were provided for time of PK sampling to ingestion of food, posture, concomitant medication/alcohol/caffeine/nicotine.

Validated assays were used for drug concentration measurements (Appendix 16.1.10).

9.5.4 Appropriateness of Measurements

All procedures used to measure the efficacy, safety and tolerability of NP202 in this study were considered by the Sponsor and Investigator to be appropriate and necessary to obtain the required efficacy and safety information. The assessments are widely used and recognized as reliable and accurate to meet the objectives of this Phase 2 study.

A validated assay was used to measure plasma NP201 concentrations for the samples collected from subjects in the PK population.

9.6 Data Quality Assurance

9.6.1 Study Monitoring

Study monitoring was performed in accordance with applicable regulations, ICH GCP, and study site, Armaron and designee Standard Operating Procedures (SOPs).

Before the start of the trial, a representative of Armaron or designee contacted the investigational site to ensure facilities were adequate and discussed the responsibilities with the site staff with regards to following the protocol and regulatory and ethical requirements.

During the trial, a clinical research associate (CRA) from Armaron or its designee regularly visited the site to monitor and confirm protocol, regulatory and ethical adherence, confirm

data accuracy and provide information and support as needed.

The investigator agreed to allow the CRA direct access to all relevant documents, including electronic medical records, and to allocate their time and the time of their staff to the CRA to discuss findings and any relevant issues.

Site staff were provided with the CRA contact details in the event of any queries or the need for assistance.

9.6.2 Training of Staff

Each individual involved in conducting the trial was qualified by education, training, and were experienced to perform his or her respective tasks.

Site staff were trained for this study at the initiation visit by Armaron, or their designees.

The investigator maintained records of all individuals involved in the trial at their site. The investigator ensured that appropriate training relevant to the trial was given to all staff, and that staff received any new information relevant to the performance of the trial in a timely manner.

9.6.3 Audits and Inspections

An audit is a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, Armaron and study site SOPs and those of Armaron designees, GCP, and the applicable regulatory requirements.

Authorised representatives of Armaron, its designee, a regulatory authority, or the IEC could perform audits or inspections. The investigator was to contact Armaron or designee immediately if they were contacted by a regulatory agency about an inspection at their centre. If an audit or inspection occurred, the investigator and institution agreed to allow the auditor/inspector direct access to all relevant documents and allocated their time and the time of their staff to the auditor/inspector to discuss findings and any relevant issues.

9.6.4 Clinical Endpoints Committee

A CEC was established, consisting of individuals independent of the Sponsor, the DMC, the SC, the clinical study sites and the trial investigators. The CEC consisted of 3 cardiologists with prior experience with adjudication of cardiac events in clinical trials. No CEC member will be present during any study procedures, and all CEC members were blinded to the subject treatment assignments.

The CEC performed a blinded adjudication of all MACCE. The CEC also reviewed cardiac events not considered MACCE. Definitions and events are described in the CEC charter.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

The statistical and analytical plan (SAP) dated 09 Jul 2018 (v1.0) is provided in Appendix 16.1.9. Full details of the statistical analyses are presented in the SAP.

9.7.2 Data Analysis Considerations

All efficacy and safety data were listed and summarised using descriptive statistics by treatment group and nominal time. The descriptive summary for the categorical variables included counts and percentages. The descriptive summary for the continuous variables included means, medians, standard deviations (SDs) and minimum and maximum values. Where possible, data from subjects who withdraw prematurely from the study were included in any analysis.

All statements of statistical significance were based on a two-sided test at the 5% level of significance, unless stated otherwise.

The baseline value for each clinic assessment was the last pre-dose value obtained.

9.7.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics were listed and summarised by treatment arm.

9.7.4 Analysis of Efficacy

9.7.4.1 *Primary Efficacy Endpoint*

The primary endpoint of change from baseline in LV end systolic volume index (LVESVi) as assessed by MRI at 3 months (Day 90), was derived by subtracting the pre-dose LVESVi value at Day 1 from the LVESVi value at 3 months. The primary analysis was performed in the modified Intent to Treat (mITT) set using an Analysis of Covariance (ANCOVA) of the primary endpoint with terms for treatment, baseline LVESVi, and the randomisation stratification factor (LVEF<35% versus LVEF≥35%). The F-test was used to test for a treatment difference in the primary endpoint at the 5% alpha level. Descriptive statistics for LVESVi were summarised at baseline and at 3 months. Change from baseline was summarised at 3 months. The Least Squares Mean (LS Mean) estimate for change from baseline in LVESVi at 3 months, its standard error and 95% confidence interval (CI) was tabulated by treatment arm and for the difference between treatment arms (NP202 versus placebo). Model residuals were calculated to graphically check the model assumptions of homoscedasticity and normality for the primary analysis. If, upon visual inspection, the model assumptions of homoscedasticity and normality were not met, then the primary analysis could be repeated after making an appropriate transformation of the data and/or tested using non-parametric methods. If the equal slope assumption is violated, then an interaction term between the baseline value of LVESVi and treatment was to be added to the model and LS Means was to be tested and reported at the 25th, 50th, and 75th percentile for baseline LVESVi. These analyses were considered secondary and supportive of the primary analysis.

Sensitivity analyses of the primary endpoint was performed in the full analysis set (FAS) to assess the impact of missing data on the robustness of the primary analysis. The primary analysis will also be repeated in the per population (PP) set.

9.7.4.2 *Secondary Efficacy Endpoints*

The following secondary endpoints were analysed and summarised using the methods described for the primary endpoint:

- Change from baseline in left ventricular end diastolic volume index (LVEDVi) as assessed by MRI at 3 months;
- Change from baseline in LVEF as assessed by MRI at 3 months;
- Change from baseline in LV diastolic function based on LV peak filling rate as assessed by MRI at 3 months;
- Change from baseline in relative infarct size as assessed by MRI at 3 months.

9.7.5 Analysis of Safety and Tolerability

9.7.5.1 *Extent of Exposure*

The duration of exposure and number of subjects exposed to study treatment was summarised by treatment received.

9.7.5.2 *Adverse Events*

Adverse event data was listed individually, and incidence of AEs summarised by system organ class (SOC) and preferred terms (PT) within a SOC for each treatment group. When calculating the incidence of AEs, each AE, based on preferred terminology defined by Medical Dictionary for Regulatory Activities (MedDRA; Version 13.1, or later), was counted only once for a given subject. A summary of the number and percent of subjects with the following treatment emergent AEs was displayed by treatment groups:

- All AEs;
- Drug-related AEs;
- Severe AEs;
- Serious AEs;
- Adverse events leading to permanent discontinuation of NP202.

9.7.5.3 *MACCE analysis*

Major cardiac and cerebrovascular events was defined as the occurrence of any one of the following individual events: non-fatal MI, non-fatal stroke, cardiac hospitalisation due to heart failure, and cardiovascular death. The number and percent of subjects with MACCE, overall and by each individual event were tabulated by treatment arm. Ninety-five (95%) CI for the MACCE event rate was summarised by treatment arm. Survival analysis techniques was also used to summarise and analyse time to the first occurrence of a MACCE. Right censoring was applied to non-cardiovascular deaths, early terminations, and study completion. Kaplan Meier estimates of MACCE were tabulated over time by treatment arm. The treatment difference for time to MACCE was assessed using the log-rank test.

9.7.5.4 *Clinical Laboratory Evaluations*

Summary statistics were presented by treatment group for each laboratory value and change from baseline in each laboratory value at every assessment.

Each laboratory value was flagged to show whether it is a value within, below, or above the normal range.

9.7.5.5 *Other Safety Measures*

Continuous variables were summarised along with the change from baseline at each time point by treatment group. Other variables were summarised as appropriate to the data.

9.7.6 Pharmacokinetic Data

Multiple dose PK trough concentration-time profile of the NP202 active metabolite (NP201) was obtained from a subset of 30 subjects.

9.7.7 Cardiac Biomarker Data

Summary statistics were presented by treatment group for each biomarker, along with the change from baseline, at each time point. Point estimates and corresponding 95% CI were constructed for the differences between the treatment means (NP202 minus Placebo).

9.7.8 Interim Analysis

After approximately 50 subjects had completed an evaluable MRI at baseline and at 3 months (Day 90), a blinded interim analysis to estimate the pooled SD of the primary efficacy endpoint was reviewed by the DMC. If the estimated SD was larger than 11 mL/m^2 or if the proportion of subjects with a large infarct was less than 0.80, then the sample size required to detect a treatment difference of 6.6 mL/m^2 among all subjects was to be re-estimated. Additionally, the sample size required to detect a treatment difference of 8.25 mL/m^2 among subjects with a large infarct was to be calculated. Based on the observed enrolment rates (% of evaluable subjects and % of evaluable subjects with large infarcts) and sample size calculations based on updated assumptions, the sample size could be increased, and/or the primary analysis could be restricted to evaluable subjects with a large infarct at baseline. The identities of the treatment groups remained blinded and no information concerning the estimated treatment difference was used by personnel making these adaptations to the study. Refer to Appendix 16.1.9 for the minutes of DMC meetings held.

9.7.9 Determination of Sample Size

The study was designed to detect a treatment difference of at least 6.6 mL/m^2 in the primary efficacy endpoint among subjects with an evaluable MRI at baseline and at 3 months (Day 90). Since the treatment difference of the primary endpoint was expected to be negligible among subjects with a small infarct (less than 20% of LV mass), a treatment difference of 6.6 mL/m^2 among all subjects required a treatment difference of approximately 6.6/p mL/m^2 among subjects with a large infarct, where p is the proportion of subjects with a large infarct. When p is 0.80, the corresponding treatment difference among subjects with a large infarct is 8.25 mL/m^2.

To meet these requirements, a sample size of at least 90 subjects was needed to provide 80%

power to detect a treatment difference of at least 6.6 mL/m^2 in the primary efficacy endpoint. Power was calculated for a two-sided t-test with a 5% Type I error rate. The SD of the primary endpoint was assumed to be at most 11 mL/m^2. [8-10] A total of at least 120 randomised subjects were required to ensure at least 90 subjects with an evaluable MRI at baseline and at 3 months (Day 90) were enrolled. Sample size calculations were performed using SAS® software, Version 9.3.

Based on the results of the interim analysis described below, which showed a SD of 15 mL/m^2, recruitment continued up to a maximum of 180 subjects.

After approximately 50 subjects completed an evaluable MRI at baseline and at 3 months (Day 90), a blinded interim analysis to estimate the pooled SD of the primary efficacy endpoint was reviewed by the DMC. If the estimated SD was larger than 11 mL/m^2 or if the proportion of subjects with a large infarct was less than 0.80, then the sample size required to detect a treatment difference of 6.6 mL/m^2 among all subjects was re-estimated. Additionally, the sample size required to detect a treatment difference of 8.25 mL/m^2 among subjects with a large infarct was calculated. Based on the observed enrolment rates (% of evaluable subjects and % of evaluable subjects with large infarcts) and sample size calculations based on updated assumptions, the sample size was increased, and/or the primary analysis restricted to evaluable subjects with a large infarct at baseline. The identities of the treatment groups remained blinded, and no information concerning the estimated treatment difference was used by personnel making these adaptations to the study.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

The IEC approved protocol V1.1, dated 01 Jun 2015.

Protocol V2.0, dated 06 May 2016 was prepared and approved, which included the following changes:

- Left ventricular ejection fraction cut-off (inclusion criterion 3) was increased to ≤45%;
- The upper age limit (inclusion criterion 1) was amended to 80 years inclusive;
- An interim analysis was added and described in new Protocol Section 10.2.2;
- Administrative changes for clarity and consistency.

Protocol V3.0, dated 23 Feb 2018 was prepared and approved following the results of the interim analysis, which included the following change: The sample size was increased up to a maximum of 180 randomised subjects.

9.8.2 Changes in the Planned Analyses

There were no changes to the planned analyses.