1. SYNOPSIS

<table>
<tr><td colspan="2">Title of Study: Triiodothyronine for repair of left ventricular dysfunction and Remodeling in STEMI Patients (The Thy-REPAIR study)

Sponsor: UNI-PHARMA KLEON TSETIS Pharmaceutical Laboratories S.A.</td></tr>
<tr><td colspan="2">Investigational Medicinal Product: T3® Solution for injection 10μg/ml</td></tr>
<tr><td colspan="2">Active Ingredient : Triiodothyronine or Liothyronine</td></tr>
<tr><td colspan="2">Investigators Dr.Athanasios Trikas, Dr.Evangelos Pissimisis</td></tr>
<tr><td colspan="2">Study Centres 1. Cardiology Department, ELPIS General Hospital of Athens, Greece
2. Cardiology Department of Tzaneio General Hospital of Athens, Greece</td></tr>
<tr><td colspan="2">Publication ---------</td></tr>
<tr><td>Studied period: 4years
Date of first enrolment: 13 November 2016
Date of last completed subject: 12 November 2020</td><td>Phase of development: IIa</td></tr>
<tr><td colspan="2">Objectives: This randomized, double blind, placebo-controlled study explored the effects of acute triiodothyronine treatment on LV function and infarct healing in patients with anterior myocardial infarction undergoing primary angioplasty.</td></tr>
<tr><td colspan="2">Methodology: Coronary angiography and revascularization was performed using standard techniques.Participants had standard laboratory assessment and standard physical examination parameters. Cardiac Magnetic Resonance was performed at discharge and at 6 months followup. Echocardiographic analysis was performed at 48 hours, discharge, 3months and 6 months follow-up. The safety criteria were assessed throughout the study.High sensitive (hs) Troponin I was evaluated on admission, as well as at 6, 12 24, 48, 72 hours and on discharge.</td></tr>
<tr><td colspan="2">Number of patients: The investigators aimed to detect a minimum difference of 7 units in ejection fraction at 6 months between the groups (in favour of treatment group).For a statistical power of 96% and a probability of a type I error of 0.05 using a two-sided test, the sample size was estimated to 50 subjects (25 per group). Finally, the study enrolled 52 patients and 37 patients were included in the final analysis with complete CMR data.</td></tr>
<tr><td colspan="2">Diagnosis and main criteria for Inclusion: Patients (18 <Age≤75 years old) with anterior or anterolateral ST-Elevation Myocardial Infarctionwho presented within 12 hours after the onset of chest pain and were subjected to successful primary PCI.</td></tr>
<tr><td colspan="2">Test product, dose and mode of administration: T3® Solution for injection 10 μg/ml, each vial contains 150μg of T3 in a total volume of 15ml. The dose administered was 0.8μg/kg intravenously bolus starting at reperfusion followed by an infusion of 0.113μg./kg/h intravenously for 48 hours.</td></tr>
<tr><td colspan="2">Duration of treatment: 48 hours</td></tr>
<tr><td colspan="2">Reference therapy, dose and mode of adminsistration: Placebo with composition identical apart from the active substance. Dose identical as test product administered intravenously</td></tr>
</table>

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Criteria for Evaluation

Efficacy**:** Ejection fraction assessed by CMR wasused as a primary end-point to determine cardiac function. LV end-diastolic and end-systolic volume index was used to determine cardiac remodeling. Gadolinium late enhancement CMR was used to identify and characterize infarcted volume of LV myocardium and viability. Sequential measurements ofechocardiographyat 48hours, discharge, 3months and 6 months were usedas a secondaryend-pointto assess systolic and diastolic LV function and RV function.High sensitive cardiac troponin I was used to assess the extent of myocardial injury.

Safety**:** The following safety criteria were assessed throughout the study: cardiac and non-cardiac death, myocardial infarction, stroke, acute pulmonary edema, decompensated heart failure, angina, coronary revascularization, hospital re-admissions, episodes of arrhythmias (paroxysmal supraventricular tachycardia, atrial fibrillation, sustained ventricular tachycardia). Episodes of bleeding were recorded according to the TIMI classification. Vital signs (Heart rate, blood pressure and oxygen saturation) and standard laboratorytestswere assessed at 24h, 48h, 72h, discharge, 3 months and 6 months.

Statistical Methods: For baseline variables, categorical data are expressed as numbers and percentages, whereas continuous variables are expressed as means±SDs. Categorical data were compared by using Chi-square and the Fisher's exact test. Normal distribution of variables was estimated with Shapiro-Wilk test of normality. Normally distributed data were compared using an independent t-test. Skewed data (total ischemic time, area at risk, LVEDVI and LVESVI at 6 months) were analyzed non-parametrically using Mann-Whitney U test. Serial measurements of Ejection Fraction assessed by echocardiography were compared by mixed, repeated measures analysis of variance (mixed ANOVA). Simple linear regression analysis was used to assess the correlation between infarct size at discharge and left ventricular ejection fraction (LVEF) at 6 months in both groups.All reported *P* values are 2-sided and a value less than 0.05 was deemed as indicative of statistical significance.Analyses were performed using the statistical software package SPSS version 23 (IBM).

SUMMARY – CONCLUSIONS

Efficacy Results**:** LV ejection fraction assessed by CMR at 6 months was increased in T3 group but not at a statistical significant level compared to placebo (53.6±9.5% vs 48.6±11, respectively p=0.15). LV ejection fraction at discharge also showed a clear trend to increase in T3 group compared to placebo (49.1±8.4 vs 44.2±10.2, respectively,p=0.12). Interestingly, LV end-diastolic and end-systolic volume indices from CMR at discharge were found to be significantly reduced in T3 group compared to placebo indicating a favorable effect of T3 on cardiac remodeling (92.2±16.8 ml/m^2 and 47.5±13.9ml/m^2 vs 107.5±22.2 and 61.3±21.7, respectively, p<0.05). This effect was also evident at 6-month follow up at a marginal statistical significant level (94.7±17and 44.9±15.3 vs 110±32and 59±31.6, respectively, p=0.09and p=0.08. Although infarct volume at discharge was similar between the two groups in accordance with troponin measurements (27.9±11.1 ml for T3 vs 32.6±13 for placebo, p=n.s.), infarct size at 6 months was significantly lower in the T3 group (18.7±9.5ml vs 25.9±11.7, p=0.05). LV ejection fraction was assessed by echocardiography was similar between the two groups at 48 hours (43±5.7% for T3 group vs 41±8.2% for placebo, p=0.4). Interestingly, LVEF% was significantly increased in T3 group

compared to placebo at discharge, 3-month and 6-month follow up (47.5±5.7%, 50.8±6.3%,50.1±5.4% for T3 group vs 40±9.2%, 43.8±9.2% and 44.9±9.7% for placebo, respectively, $p<0.05$).

Safety Results**:** Serious safety issues related to T3 treatment were not reported in this study. Vital signs (blood pressure and oxygen saturation) were similar between the groups. During the first 72 hours there was a small increase in heart rate in T3 treated patients without causing any other complication. Duration of QTc as assessed by ECG at day 1, 2, 3 and discharge was similar between the two groups. In addition, duration of QRS was even decreased in T3 treated patients. A trend for increased rate of atrial fibrillation (AF) was found in T3 group during the first 48 hours (19% for T3 group vs 5% for placebo, $p=0.13$). All cases of AF in T3 group resolved either spontaneously with beta-blocker treatment or with electrical cardioversion. Treatment was continued in patients despite AF. Patient A09 was the only patient that received amiodarone at 24 hours and the infusion of T3 was stopped. Serious ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation) were not recorded during hospitalization in both groups. Serious ventricular arrhythmias were not recorded during hospitalization in both groups. Rates of other adverse events recorded during hospitalization, such as LV thrombus formation, minor hemorrhage and pericarditis were similar between the two groups. An episode of high temperature (>37.8°C) was reported in 30% of patients in T3 group and resolved with paracetamol administration. Standard biochemical tests concerning hemoglobin, hepatic and renal function, glucose, total protein and electrolytes were similar between the groups during the study (tables). A small transient increase was only recorded in gamma-GT in T3 treated group at 48h and 72h but without any clinical significance. No death was recorded during drug administration and till day 9. Two patients died after discharge in T3 group due to re-occlusion of the culprit lesion and rupture of the LV free wall. One patient died after discharge in placebo group due to sudden death (arrhythmic death).

CONCLUSION**:** Acute, high dose T3 administration in patients with anterior or anterolateral STEMI undergoing primary PCI resulted in favorable effects on recovery of cardiac function, cardiac remodeling and infarct healing without major side effects.

Date of report 17 March 2021