2. STUDY SUMMARY

Name of Sponsor/Company: Gene PreDiT SA **Name of finished product:** Perindopril Bluepharma 8 mg tablets **Name of active ingredient:** Perindopril	**Individual Study Table referring to Part ___ of Dossier** Volume: Page:	*(For authorities use only)*

Title of Study:	Influence of single nucleotide polymorphisms of carboxypeptidase D (CPD) gene on body weight and fat mass reduction by perindopril in obese subjects: A phase II, multicenter, double-blind study.
Coordinating Investigator:	Paula Freitas, MD, PhD Graduate Hospital Assistant at Centro Hospitalar São João EPE; Invited Assistant Professor at Faculdade de Medicina da Universidade do Porto
Study Centers:	The study was conducted at the following 13 clinical sites: Serviço de Nutrição e Atividade Física, Centro Hospitalar Cova da Beira (CHCB), EPE, Hospital da Covilhã; Serviço de Endocrinologia, Centro Hospitalar do Baixo Vouga (CHBV), EPE, Sede Aveiro; Serviço de Medicina, Centro Hospitalar Vila Nova de Gaia / Espinho (CHVNG/E); Unidade de Cuidados de Saúde Personalizados Carvalhido (Centro de Saúde Aldoar); Unidade de Saúde Familiar Arca d'Água (Centro de Saúde Paranhos); Unidade de Saúde Familiar Canelas (Centro de Saúde Arcozelo); Unidade de Saúde Familiar Escariz (Centro de Saúde Arouca); Unidade de Saúde Familiar Lethes (Centro de Saúde Ponte de Lima); Unidade de Saúde Familiar Nova Salus (Centro de Saúde Soares dos Reis/Oliveira do Douro - Unidade Soares dos Reis); Unidade de Saúde Familiar Santo André de Canidelo (Centro de Saúde Barão do Corvo); Serviço de Endocrinologia, Unidade Local de Saúde do Alto Minho (ULSAM), EPE, Hospital de Santa Luzia; Serviço de Endocrinologia, Centro Hospitalar de São João (CHSJ), EPE; Serviço de Endocrinologia, Centro Hospitalar Vila Nova de Gaia/Espinho (CHVNG/E).
Publications:	None.
Times of Clinical Part:	02MAR2016 (first enrolment) to 27APR2017 (last completion). ***Note: After an interim analysis showed no evidence of efficacy, the study was prematurely terminated at Sponsor's decision, and this abridged report was prepared.***
Phase of development:	Phase II (therapeutic exploratory)

Study Objectives:	Primary: To evaluate CPD genotyping as a predictive biomarker of body weight and/or fat mass reduction in obese patients treated with perindopril. Secondary: To assess the association between CPD genotypes/single nucleotide polymorphisms (SNPs) and response to perindopril; to evaluate the effect of perindopril in waist circumference, waist/hip ratio, and BMI; to evaluate the tolerability and safety of perindopril in the study population; to evaluate CPD genotyping as a predictive biomarker of body weight and/or fat mass reduction as per regulatory requirements in obese patients treated with perindopril.
Methodology:	A multicenter, double-blind study in obese subjects. The study consisted of 2 periods and 4 visits (V): a run-in period of at least 4 weeks (V1 to V2) and a 12-week perindopril treatment period (V2 to V4). After written informed consent, patients underwent screening evaluations (V1). Patients who met the selection criteria entered a run-in period of 4 weeks where they were given dietary and exercise counseling as standardized non-drug therapy. After the run-in period (V2), patients started the pharmacological therapy period where they received perindopril 8 mg, once daily, for 12 weeks, concomitantly with the previously established standardized non-drug therapy. During the 12-week pharmacological treatment, patients attended an intermediate study visit (V3) at approximately 6 weeks and a final visit (V4) for efficacy and safety assessments. Body weight, body mass index (BMI), waist and hip circumference, and body fat mass estimation were assessed at every study visit.
Number of Subjects (Planned and Analyzed):	Planned: 160 subjects enrolled and at least 120 subjects evaluable. Actual: analyzed for safety = 140 subjects; intention-to-treat (ITT) population = 134; per protocol (PP) population = 106 subjects.
Diagnosis and Main Selection Criteria:	Obese male and female patients, with age ≥18, body mass index (BMI) between 30.0 to 40.0 kg/m^2 were selected according to the inclusion and exclusion criteria. Patients' health status was evaluated by pre-study medical history, physical examination, vital signs, and clinical laboratory tests (hematology and plasma biochemistry). If a woman, a pregnancy test was negative. The enrolled patients did not present any clinical condition that makes their participation in this study unfeasible.
CPD genotyping:	CPD SNPs genotyping was carried out using a validated TaqMan® genotyping assay.
Investigational Product, Dose and	Name: Perindopril 8 mg tablets Dosage form/Route of administration: tablets/oral

Mode of Administration, Batch Number:	Regimen: 1x 8 mg tablet, once daily, for 12 weeks, concomitantly with the previously established standardized non-pharmacological therapy. Batch no.: 02142950 (Expire date: AUG2016)
Criteria for Evaluation	
Efficacy:	Primary efficacy endpoint was: response rate, defined as the proportion of patients who lost at least 3% of body weight and/or at least 3% of fat mass from end of the run-in period to the end of the perindopril treatment period. Secondary efficacy endpoints were: End vs start of treatment relative change in body weight; end vs start of treatment relative change in fat mass; end vs start of treatment relative change in waist circumference; end vs start of treatment relative change in hip circumference; end vs start of treatment relative change in fasting lipid profile; response rate, defined as the proportion of patients who lost at least 5% of body weight and/or at least 5% of fat mass from end of the run-in period to the end of the perindopril treatment period.
Safety:	Secondary safety endpoint was: Frequency and type of adverse events.
Statistical Methods:	For efficacy endpoints: The primary efficacy analysis compared the response rate in the group of subjects with the SNPs of interest and the group of the remaining subjects. A logistic regression model was used to assess the group differences. Weight and fat mass at the start of the perindopril treatment period and gender was used as covariates. All the secondary efficacy endpoints were assessed using analysis of covariance (ANCOVA). In general, the principles applied for the primary efficacy analysis were replicated for the secondary efficacy analysis. For evaluation of safety: For safety analyses, adverse events are tabulated and summarized according to system organ class (SOC) and preferred term (PT).
Summary – Conclusions	
Efficacy Results:	According to the clinical study protocol (CSP), a blinded analysis of the CPD SNPs genotypes was performed to confirm the prevalence of the SNPs of interest assumed in the sample size estimation. Such analysis showed no significant effect of perindopril in any of the efficacy endpoints. Thus, the study was terminated, at Sponsor's decision, and INFARMED and CEIC were notified accordingly.
Safety Results:	During the study, a total of 170 treatment-emergent (TEAEs) were reported by 87 (62.1%) subjects who were administered at least one dose of investigational product. The most commonly reported TEAEs were "cough" (20 TEAEs reported by 18 subjects), "dyslipidemia" (9 TEAEs reported by 9 subjects),

	"headache" (8 TEAEs reported by 8 subjects) and "dizziness" (8 TEAEs reported by 8 subjects). There were 13 TEAEs leading to treatment discontinuation ("drug withdrawn") of 9 subjects. There was a serious adverse event (SAE), a "pregnancy", that led to premature study discontinuation.
Conclusion:	This exploratory study did not confirm CPD genotyping as a predictive biomarker of body weight and/or fat mass reduction in obese patients treated with perindopril. The tolerability and safety results are consistent with the known profile of perindopril.
Date of Report:	25JUL2017