SYNOPSIS

Title of the study:	A randomized double-blind placebo-controlled parallel group study of the efficacy and safety of 4 administrations of XRP0038/NV1FGF 4 mg at 2–week intervals on amputation or any death in critical limb ischemia patients with skin lesions (EFC6145-TAMARIS-Long Term Safety Survey)
Investigator:	[redacted]
Study centers:	200 centers in 32 countries (Argentina, Australia, Austria, Belarus, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Italy, Japan, Republic of Korea, Mexico, Poland, Russian Federation, Singapore, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom, United States of America).
Publications (reference):	Belch J, Hiatt WR, Baumgartner I, Driver IV, Nikol S, Norgren L, et al. Effect of fibroblast growth factor NV1FGF on amputation and death: a randomised placebo-controlled trial of gene therapy in critical limb ischaemia. The Lancet. 2011;377(9781):1929-37.
Study period:	
Date first patient enrolled:	22 November 2007
Date last patient completed:	08 August 2012
Phase of development:	3

Objectives:

Main study

Primary objective: To demonstrate the superiority of 4 administrations of riferminogene pecaplasmid (XRP0038/NV1FGF) 4mg at 2-week intervals over placebo in the prevention of major amputation above the ankle of the treated leg or of death from any cause, whichever came first, in critical limb ischemia (CLI) patients with skin lesions.

Secondary objectives: To evaluate:

- The efficacy of riferminogene pecaplasmid versus placebo for delaying the time to major amputation.
- The efficacy of riferminogene pecaplasmid versus placebo for delaying the time to death.
- The safety of riferminogene pecaplasmid in the study population.

Four substudies were conducted for exploratory purposes in subgroups of patients randomized in the main study EFC6145, with the following objectives:

$TcPO_2$ substudy: To assess the effect of riferminogene pecaplasmid administration versus placebo on the skin oxygenation as measured by the transcutaneous pressure of oxygen ($TcPO_2$), in CLI patients with skin lesions.

Wound substudy: To assess the effect of 4 administrations of riferminogene pecaplasmid 4 mg at 2-week intervals versus placebo on wound healing in CLI patients with skin lesions.

Japan substudy: To perform an exploratory assessment of the efficacy of riferminogene pecaplasmid administration in alleviating ischemia through stimulation of vascularization in Japanese patients by examining skin perfusion pressure (SPP) and intra-arterial digital subtraction angiography (IA-DSA) imaging tests, in CLI patients with skin lesions; to perform specific safety assessment by the Data Monitoring Committee to reinforce safety assessment in Japanese patients.

German substudy: To assess all German patients for the immunogenicity of riferminogene pecaplasmid versus placebo and to perform complementary safety assessments as per the German Health Authorities request.

Long Term Safety Survey: To evaluate long term safety of riferminogene pecaplasmid and the potential for delayed adverse events.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel group, multinational, multicenter study, evaluating the effects of 4 administrations of riferminogene pecaplasmid 4 mg at 2-week intervals versus placebo, in CLI patients with skin lesions (ie, patients with severe peripheral artery disease [PAD] Fontaine stage IV, ie, with pain at rest and loss of tissue integrity), unsuitable for revascularization. In addition to a blinded Steering Committee responsible for the design and the good conduct of the study, a blinded Events Adjudication Committee adjudicated the unsuitability for revascularization, the cause of death and the justification of major amputation, as well as the acute ischemic events, and an independent Data Monitoring Committee periodically monitored patient safety (including specific safety assessments in Japanese patients). A long term safety survey (LTSS; study amendment 3) of an additional 18 months was planned at the end of the 6-month exploratory follow-up visit/contact (total safety follow-up: 36 months for the LTSS population). The safety of riferminogene pecaplasmid in the study population was reported during 3 periods: 0-12 months (TAMARIS clinical study report [CSR] on 03 December 2010), 12-18 months, and 18-36 months (in the present CSR).

Number of patients (main study):

Planned: 490	Randomized: 525	Treated: 523		
Evaluated (main study):	Efficacy: 525	Safety: 523		
Evaluated (substudies)	$TcPo_2$: 81	Wound: 29	Japan: 14	German: 37

All patients in the substudies were randomized in the main study.

Number of patients (LTSS):

Planned: All randomized patients alive at the end of the 12 months TAMARIS study (440 patients)

Consented to LTSS: 311 LTSS population: 309 LTSS safety population: 309

Diagnosis and criteria for inclusion:

The study was designed to include male and female patients, who had signed an informed consent, aged >50 years, and:

- having CLI with skin lesions (either ulcer(s) stable over the last 2-week interval or gangrene, ie, major tissue loss)
- with objective evidence of CLI such as ankle systolic pressure less than 70 mmHg, and/or toe systolic pressure less than 50 mmHg, or $TcPO_2$ less than 30 mmHg, and patent femoral inflow assessed preferably by angiography, magnetic resonance or computed tomography angiography (or by Doppler ultrasonography if the documentation of an older angiography technique was available), in the 6 months prior to first investigational medicinal product (IMP) administration
- unsuitable for standard revascularization of his/her PAD
- with negative screening for cancer

Patients included in a substudy had to also sign an informed consent specific to the substudy (for the German substudy, patients signed a single informed consent including the main study and the substudy procedures) and to fulfill additional specific selection criteria.

Patients were asked for their informed consent to a LTSS of an additional 18 months at the end of the 6-month exploratory follow-up visit/contact.

Study treatments

Investigational medicinal product(s): Riferminogene pecaplasmid

Formulation: 5 ml glass vials containing 2,5 ml riferminogene pecaplasmid

Route of administration: 8 intramuscular (IM) injections of 2.5 mL (0.5 mg) in the ischemic leg to be treated: 4 in the calf muscle covering the anterior and posterior area, and 4 in the thigh muscle

Dose regimen: Total dose of 16 mg, administered as 8 injections of 0.5 mg (ie, 4 mg) on each of Days 1, 15, 29, and 43

Batch numbers: [redacted]

Noninvestigational medicinal product(s): Placebo

Formulation: 5 ml glass vials containing 2,5 ml placebo for riferminogene pecaplasmid

Route of administration: 8 IM injections of 2.5 mL in the ischemic leg to be treated: 4 in the calf muscle covering the anterior and posterior area, and 4 in the thigh muscle.

Dose regimen: 0 mg

Batch numbers: [redacted]

Duration of treatment: 43 days corresponding to 4 administrations (IM injections) every 2 weeks on Days 1, 15, 29, and 43).

Duration of observation: 18 months for the randomized population (12 months and 6-month exploratory follow-up) and 36 months in total for the LTSS population (12 months, 6-month exploratory follow-up, and an additional 18-month follow-up period as per protocol amendment 3)

Criteria for evaluation: The current report is an abbreviated report of the 6-month exploratory follow-up and the LTSS and as such, only the safety results are being presented in full. The main efficacy findings have been presented in the TAMARIS CSR. In the LTSS, the safety criteria that were evaluated and analyzed using descriptive statistics were all adverse events (AEs)/serious adverse events (SAEs) reported. These events included but were not limited to cancers, cardiovascular events, active/proliferative retinopathy or revascularization, renal failure, and immunologic disorders. In the LTSS, suspected ischemic events were collected but not adjudicated.

Statistical methods: The frequency of patients with post-treatment-emergent adverse events (post-TEAEs; ie, AEs arising between 12 and 36 months), serious post-TEAEs, post-TEAEs leading to death, and post-TEAEs leading to treatment discontinuation was summarized by treatment group, primary system organ class (SOC), and preferred term (PT).

Post-TEAEs of special interest were defined based on the potential risks associated with gene therapy/growth factors (such as malignant neoplasms, retinal disorders (including but not limited to proliferative retinopathy and severe macular edema), acute ischemic events (including ischemic heart disease events, ischemic cerebrovascular condition events, and acute ischemic colitis), immunological disorders, renal impairment) as well as based on previously identified potential risks (cardiac failure events, injection site disorders, and peripheral leg edema) and other potential risks systematically considered (Torsades de Pointes/QT prolongation, hepatic disorders, and bone marrow toxicity [neutropenia, thrombocytopenia, anemia, and pancytopenia]). The relative risks (RR) (with associated 95% confidence limits) were calculated for all post-TEAEs of special interest.

Summary: The current report is a synopsis-style report of the 6-month exploratory follow-up (12 to 18 months and the cumulative safety of 0 to 18 months for the randomized and treated patients) and LTSS (18 to 36 months and the cumulative safety of 0 to 36 months for the LTSS safety population). As such, only the safety results and limited efficacy results are being presented. The results for the analyses of the primary and secondary efficacy endpoints and for the substudies have been presented in the TAMARIS CSR. Treatment blinding was maintained up to the end of the LTSS for patients and investigators.

Patient disposition: Overall, 880 patients were screened for the TAMARIS study. A total of 525 patients were randomized to treatment, and 523 randomized patients received at least 1 IMP administration (257 placebo, 266 riferminogene pecaplasmid). A subset of 309 patients (149 who had received placebo and 160 who had received riferminogene pecaplasmid) consented to the LTSS and had at least 1 visit/contact during the LTSS.

The main reason for non-participation in the LTSS were subject did not wish to participate or subject died.

At the end of the LTSS, 15 out of the 151 patients in the LTSS who had received placebo had died and 23 out of the 160 patients in the LTSS who had received riferminogene pecaplasmid had died. No patients in the entire LTSS were lost to follow-up. Two of the 151 patients in the placebo group who signed the LTSS consent died prior to Day 540 and were not included in the analyses of LTSS data.

Demographics and baseline characteristics: The 2 treatment groups of the LTSS population were well balanced for demographic characteristics.

Medical history:

Randomized population (0 to 18 months - 525 patients): Medical history and disease characteristics of patients in the riferminogene pecaplasmid and placebo groups were generally similar at baseline. About half of the patients had diabetes (52.3% in the riferminogene pecaplasmid group and 54.4% in the placebo group). In both groups, a high percentage of patients had hypertension (87.6% in the riferminogene pecaplasmid group and 82.2% in the placebo group) or hyperlipidemia (61.7% in the riferminogene pecaplasmid group and 59.1% in the placebo group). Medical history of congestive heart failure was reported in 19.9% of the riferminogene pecaplasmid group and 15.1% of the placebo group.

LTSS population (0 to 36 months - 309 patients): Medical history and disease characteristics of patients from the LTSS population in the riferminogene pecaplasmid and placebo groups were generally similar at baseline. Slightly over half of the patients had diabetes (56.3% in the riferminogene pecaplasmid group and 53.0% in the placebo group). In both groups, a high percentage of patients had hypertension (88.1% in the riferminogene pecaplasmid group and 81.9% in the placebo group) or hyperlipidemia (63.8% in the riferminogene pecaplasmid group and 58.4% in the placebo group). Medical history of congestive heart failure was reported in 16.9% of the riferminogene pecaplasmid group and 11.4% of the placebo group.

Efficacy:

Main efficacy results (0-12 months) are provided in the TAMARIS CSR.

Randomized population (0 to 18 months): There was no difference between the riferminogene pecaplasmid (41.0%) and placebo groups (40.9%) in the efficacy endpoint of first major amputation on the treated leg or death from any cause, whichever came first, at 18 months.

LTSS population (0 to 36 months): There was no difference between the riferminogene pecaplasmid (33.1%) and placebo (25.5%) groups in the efficacy endpoint of first major amputation on the treated leg or death from any cause, whichever came first, at 36 months.

Safety:

Adverse events

Randomized and treated population:

0 to 18 months: The overall incidence of patients who had TEAEs and post-TEAEs between 0 and 18 months was similar between the riferminogene pecaplasmid (84.6%) and placebo groups (84.4%). In both groups, the most frequently reported SOC was Infections and Infestations (49.2% in the riferminogene pecaplasmid group and 52.5% in the placebo group). Of note, more patients in the riferminogene pecaplasmid group than in the placebo group experienced events from the SOC Musculoskeletal and Connective Tissue Disorders (21.1% versus 12.5%), Metabolism and Nutrition Disorders (16.2% versus 9.3%), and Psychiatric Disorders (7.1% versus 4.3%).

The overall incidence of TEAEs and post-TEAEs leading to death was lower in the riferminogene pecaplasmid group (15.4%) compared to the placebo group (18.7%). Sudden death was reported with the same incidence (2.6% in the riferminogene pecaplasmid group compared to 2.3% in the placebo group) whereas death of unknown cause was reported with a higher incidence in the riferminogene pecaplasmid group (4.1%) compared to the placebo group (1.9%).

12 to 18 months: The overall incidence of patients who had post-TEAEs between 12 and 18 months was similar between the riferminogene pecaplasmid (33.1%) and placebo groups (30.4%). In both groups, the most frequently reported SOC was Infections and Infestations (10.2% in the riferminogene pecaplasmid group and 11.7% in the placebo group). Of note, more patients in the riferminogene pecaplasmid group than in the placebo group experienced events from the SOC Vascular Disorders (8.6% versus 3.9%). More patients in the placebo group than in the riferminogene pecaplasmid group experienced events from the SOC Cardiac Disorders (7.0% versus 4.9%); the most prominent AE was myocardial infarction with an incidence of 2.7% in the placebo group versus an incidence of 0.8% in the riferminogene pecaplasmid group.

The overall incidence of post-TEAEs leading to death was lower in the riferminogene pecaplasmid group (2.6%) compared to the placebo group (5.1%). The most frequently reported cause of death in the riferminogene pecaplasmid group was from the SOC Cardiac Disorders (1.1% compared to 1.9% in the placebo group) whereas in the placebo group the most frequently reported cause was from the SOC Infections and Infestations (2.3% compared to 0.4% in the riferminogene pecaplasmid group).

No new safety signal was identified during the 12 to 18 months follow-up period compared to the 0 to 12 months period (TAMARIS CSR).

Safety (cont'd):

LTSS safety population:

0 to 36 months: The overall incidence of patients who had TEAEs and post -TEAEs between 0 and 36 months was higher in the riferminogene pecaplasmid (85.6%) than in the placebo group (83.2%). In both groups, the most frequently reported SOC was Infections and infestations (56.3% in the riferminogene pecaplasmid group and 54.4% in the placebo group). Of note SOCs with an incidence greater than 10% in the riferminogene pecaplasmid group and an increase in frequency greater than 3% compared to placebo are the following: Vascular Disorders (41.3% versus 32.9%), Musculoskeletal and Connective Tissue Disorders (29.4% versus 17.4%), Cardiac Disorders (26.3% versus 20.8%), Metabolism and Nutrition Disorders (20.6% versus 10.7%), and Respiratory, Thoracic and Mediastinal Disorders (16.9% versus 8.7%).

The overall incidence of TEAEs and post-TEAEs leading to death was higher in the riferminogene pecaplasmid group (9.4%) compared to the placebo group (5.4%). Sudden death and death of unknown cause were reported with a higher incidence in the riferminogene pecaplasmid group (1.3% and 3.8%, respectively) compared to the placebo group (none and 2.7%, respectively).

18 to 36 months: The overall incidence of patients who had post -TEAEs between 18 and 36 months was higher in the riferminogene pecaplasmid (56.9%) than in the placebo group (45.6%). In both groups, the most frequently reported SOC was Infections and infestations (25.0% in the riferminogene pecaplasmid group and 19.5% in the placebo group). Of note, SOCs with an incidence greater than 10% in the riferminogene pecaplasmid group and an increase in frequency greater than 3% compared to placebo are the following: Vascular Disorders (15.6% versus 10.1%), Skin and Subcutaneous Tissue Disorders (15.6% versus 10.7%), Cardiac Disorders (14.4% versus 6.7%), Nervous System Disorders (11.9% versus 8.1%), and Respiratory, Thoracic and Mediastinal Disorders (10.0% versus 4.7%).

The overall incidence of post-TEAEs leading to death was higher in the riferminogene pecaplasmid group (9.4%) compared to the placebo group (5.4%). The most frequently reported cause of death in the riferminogene pecaplasmid group was from the SOC Nervous System Disorders (2.5% compared to 0.7% in the placebo group; all due to ischemic stroke) whereas in the placebo group the most frequently reported cause was from the SOC Infections and Infestations (2.0% compared to 1.9% in the riferminogene pecaplasmid).

Narratives are provided for all patients who died, had a serious AE, an AE leading to treatment discontinuation or an AE of special interest during the treatment period, 6-month exploratory follow-up period, and the LTSS period.

Adverse events of special interest (AESI):

Randomized and treated population (0 to 18 months): No relevant increased differences were observed with riferminogene pecaplasmid compared with placebo for any of the identified AESI, as shown in the table below.

LTSS safety population (0 to 36 months): No relevant increased differences were observed with riferminogene pecaplasmid compared with placebo for the identified AESI, except for cardiac failure (15.0% versus 6.0%, relative risk [95% confidence interval (CI)] 2.483 [1.193 to 5.168]), as shown in the table below.

LTSS safety population (18 to 36 months): No relevant increased differences were observed with riferminogene pecaplasmid compared with placebo for the identified AESI, except for cardiac failure (12 patients [7.5%] versus 5 patients [3.4%], RR [95% CI] 2.235 [0.807 to 6.193]), ischemic heart disease (12 patients [7.5%] versus 3 patients [2.0%], RR [95% CI] 3.725 [1.072 to 12.941]), and ischemic cerebrovascular conditions (10 patients [6.3%] versus 4 patients [2.7%], RR [95% CI] 2.328 [0.746 to 7.264]).

Number (%) of patients with adverse events of special interest cumulative up to 18 months – Randomized and treated population

Adverse Events of Special Interest	Placebo (N=257)	Riferminogene pecaplasmid (N=266)	Relative Risk (95% CI)
Malignant neoplasms[1]	6 (2.3%)	9 (3.4%)	1.449 (0.523 to 4.014)
Retinal disorders[2]	15 (5.8%)	15 (5.6%)	0.966 (0.482 to 1.936)
Ischemic cerebrovascular conditions[3]	13 (5.1%)	15 (5.6%)	1.115 (0.541 to 2.296)
Ischemic heart disease[4]	34 (13.2%)	31 (11.7%)	0.881 (0.559 to 1.389)
Ischemic colitis[5]	10 (3.9%)	2 (0.8%)	0.193 (0.043 to 0.873)
Immunological disorders[6]	7 (2.7%)	5 (1.9%)	0.690 (0.222 to 2.147)
Renal impairment[7]	23 (8.9%)	26 (9.8%)	1.092 (0.640 to 1.863)
Cardiac failures[8]	29 (11.3%)	35 (13.2%)	1.166 (0.735 to 1.850)
Injection site disorders[9]	4 (1.6%)	3 (1.1%)	0.725 (0.164 to 3.206)
Peripheral leg edema[10]	22 (8.6%)	24 (9.0%)	1.054 (0.607 to 1.831)
Hepatobiliary Disorders and Liver Investigations[11]	8 (3.1%)	15 (5.6%)	1.812 (0.781 to 4.199)
Hepatic Disorders[12]	8 (3.1%)	13 (4.9%)	1.570 (0.662 to 3.725)
Torsades de Pointes/QT Prolongation[13]	11 (4.3%)	11 (4.1%)	0.966 (0.426 to 2.189)
Neutropenia: agranulocytosis[14]	2 (0.8%)	0	Not estimable
Neutropenia: leukopenia[15]	1 (0.4%)	0	Not estimable
Thrombocytopenia[16]	2 (0.8%)	1 (0.4%)	0.483 (0.044 to 5.295)
Hemorrhages[17]	45 (17.5%)	35 (13.2%)	0.751 (0.500 to 1.129)
Anemia[18]	26 (10.1%)	25 (9.4%)	0.929 (0.551 to 1.565)
Pancytopenia[19]	1 (0.4%)	0	Not estimable

[1] MedDRA SMQ Malignant or unspecified tumours (Narrow selection); [2] MedDRA SMQ Retinal disorders (Broad and Narrow selection); [3] MedDRA SMQ Ischemic cerebrovascular conditions (Narrow selection); [4] MedDRA SMQ Ischemic heart disease (Broad and Narrow selection); [5] MedDRA SMQ Ischemic colitis (Broad and Narrow selection); [6] Primary and Secondary SOCs of Immune System Disorders; [7] MedDRA SMQ Acute Renal failure (Broad and Narrow selection); [8] MedDRA SMQ Cardiac failures (Narrow selection); [9] HLGT – Administration site reactions; [10] Sponsor defined SMQ; [11] MedDRA SMQ Liver investigations (Broad and Narrow selection) and SOC Hepatobiliary disorders; [12] MedDRA SMQ Hepatic disorders (Broad and Narrow selection); [13] MedDRA SMQ Torsades de Pointes – QT prolongation and HLT ECG Investigations; [14] MedDRA SMQ Agranulocytosis (Narrow selection); [15] MedDRA SMQ Haematopoietic Leukopenia (Narrow selection); [16] MedDRA SMQ Haematopoietic Thrombocytopenia (Narrow selection); [17] MedDRA SMQ Haemorrhages (Broad and Narrow selection); [18] HLGT Anaemias non-haemolytic and marrow depression; [19] PT=panocytopenia.
MedDRA 14.0
TEAE: Treatment emergent adverse event
n (%) = number and percentage of patients with at least one TEAE or post-TEAE of special interest

Number (%) of patients with adverse events of special interest cumulative up to 36 months – LTSS safety population

Adverse Events of Special Interest	Placebo (N=149)	Riferminogene pecaplasmid (N=160)	Relative Risk (95% CI)
Malignant neoplasms[1]	3 (2.0%)	6 (3.8%)	1.863 (0.474 to 7.314)
Retinal disorders[2]	14 (9.4%)	14 (8.8%)	0.931 (0.459 to 1.887)
Ischemic cerebrovascular conditions[3]	9 (6.0%)	14 (8.8%)	1.449 (0.646 to 3.247)
Ischemic heart disease[4]	18 (12.1%)	23 (14.4%)	1.190 (0.670 to 2.115)
Ischemic colitis[5]	4 (2.7%)	3 (1.9%)	0.698 (0.159 to 3.069)
Immunological disorders[6]	5 (3.4%)	6 (3.8%)	1.118 (0.348 to 3.585)
Renal impairment[7]	10 (6.7%)	12 (7.5%)	1.117 (0.498 to 2.510)
Cardiac failures[8]	9 (6.0%)	24 (15.0%)	2.483 (1.193 to 5.168)
Injection site disorders[9]	2 (1.3%)	1 (0.6%)	0.466 (0.043 to 5.082)
Peripheral leg edema[10]	17 (11.4%)	19 (11.9%)	1.041 (0.563 to 1.925)
Hepatobiliary Disorders and Liver Investigations[11]	7 (4.7%)	11 (6.9%)	1.463 (0.583 to 3.676)
Hepatic Disorders[12]	7 (4.7%)	8 (5.0%)	1.064 (0.396 to 2.863)
Torsades de Pointes/QT Prolongation[13]	7 (4.7%)	6 (3.8%)	0.798 (0.275 to 2.321)
Neutropenia: agranulocytosis[14]	1 (0.7%)	0	Not estimable
Neutropenia: leukopenia[15]	1 (0.7%)	0	Not estimable
Thrombocytopenia[16]	0	0	Not estimable
Hemorrhages[17]	30 (20.1%)	31 (19.4%)	0.962 (0.614 to 1.509)
Anemia[18]	14 (9.4%)	12 (7.5%)	0.798 (0.382 to 1.670)
Pancytopenia[19]	0	0	Not estimable

[1] MedDRA SMQ Malignant or unspecified tumours (Narrow selection); [2] MedDRA SMQ Retinal disorders (Broad and Narrow selection); [3] MedDRA SMQ Ischemic cerebrovascular conditions (Narrow selection); [4] MedDRA SMQ Ischemic heart disease (Broad and Narrow selection); [5] MedDRA SMQ Ischemic colitis (Broad and Narrow selection); [6] Primary and Secondary SOCs of Immune System Disorders; [7] MedDRA SMQ Acute Renal failure (Broad and Narrow selection); [8] MedDRA SMQ Cardiac failures (Narrow selection); [9] HLGT – Administration site reactions; [10] Sponsor defined SMQ; [11] MedDRA SMQ Liver investigations (Broad and Narrow selection) and SOC Hepatobiliary disorders; [12] MedDRA SMQ Hepatic disorders (Broad and Narrow selection); [13] MedDRA SMQ Torsades de Pointes – QT prolongation and HLT ECG Investigations; [14] MedDRA SMQ Agranulocytosis (Narrow selection); [15] MedDRA SMQ Haematopoietic Leukopenia (Narrow selection); [16] MedDRA SMQ Haematopoietic Thrombocytopenia (Narrow selection); [17] MedDRA SMQ Haemorrhages (Broad and Narrow selection); [18] HLGT Anaemias non-haemolytic and marrow depression; [19] PT=panocytopenia.
MedDRA 14.0
TEAE: Treatment emergent adverse event
n (%) = number and percentage of patients with at least one TEAE or post-TEAE of special interest

Safety (cont'd):

Cardiac failure events: Cardiac failure events were 13.2% and 11.3% in the riferminogene pecaplasmid group and in the placebo group, respectively, in the randomized and treated population during the 0-18 month period. Cardiac failure events were 15.0% and 6.0% in the riferminogene pecaplasmid group and in the placebo group, respectively, in the LTSS safety population during the 0-36 month period.

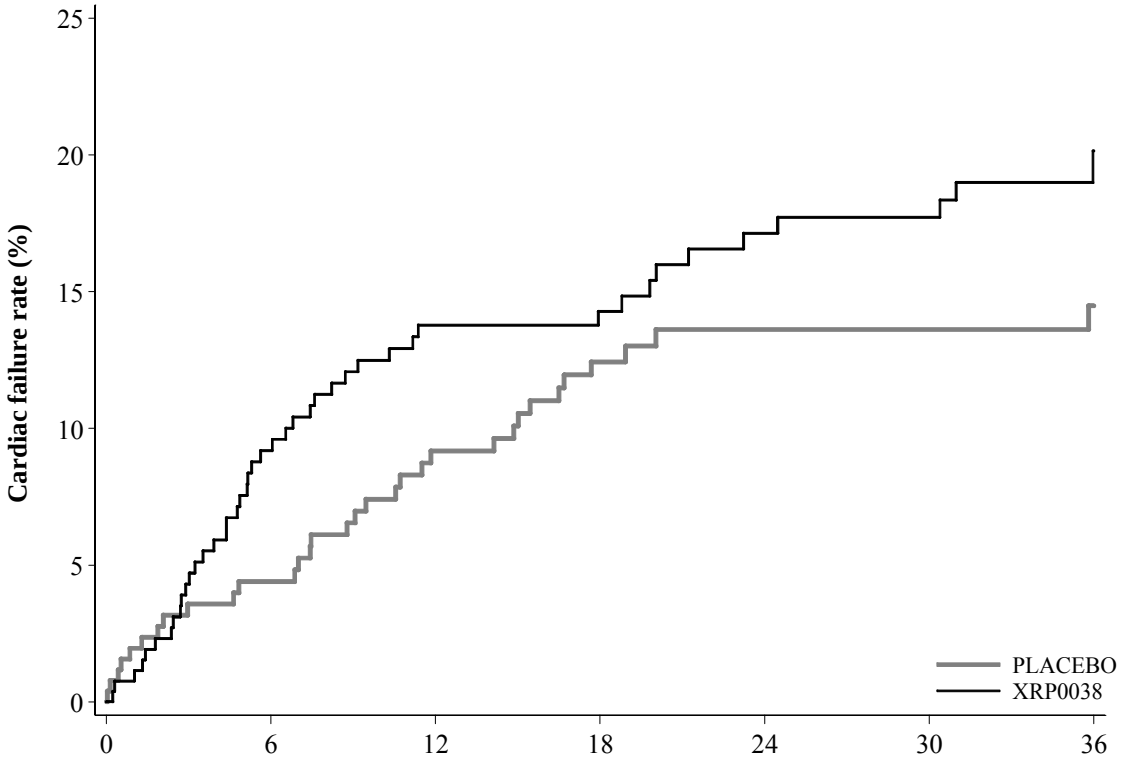
Overall, in the randomized and treated population, more patients have history of congestive heart failure at baseline in the riferminogene pecaplasmid group (53 out of 266 patients [19.9%]) compared to placebo (39 out of 257 patients [15.1%]).

Among all the randomized and treated patients who experienced congestive cardiac failure during the entire study (0 to 36 months), ie, 44 (16.5%) patients in the riferminogene pecaplasmid group and the 33 (12.8%) patients in the placebo group, 34.1% (15/44 patients) compared to 24.2% (8/33 patients), respectively, had a medical history of congestive cardiac failure at baseline.

Among the LTSS population, patients who experienced congestive cardiac failure during the study (0 to 36 months), ie, 24 (15.0%) patients in the riferminogene pecaplasmid group and the 9 (6.0%) patients in the placebo group, 25.0% (6/24 patients) compared to 44.4% (4/9 patients), respectively, had a medical history of congestive cardiac failure at baseline.

The figure below shows the time to onset for cardiac failure in the randomized and treated population.

Event rate for Cardiac Failures - All randomized and treated patients



Number at Risk

PLAC	257	226	205	174	138	137	84
XRP	266	221	197	170	142	132	68

Safety (cont'd):

Cardiac failure events leading to death

Randomized and treated:

0 to 18 month: There were 7 out of 257 patients (2.7%) in the placebo group and 7 out of 266 patients (2.6%) in the riferminogene pecaplasmid group who died due to cardiac failure events during the 0 to 18 months period.

12 to 18 months: There were 2 out of the 257 patients (0.8%) in the placebo group and 1 out of the 266 patients (0.4%) in the riferminogene pecaplasmid group who died due to cardiac failure events during the 12 to 18 months period.

LTSS population:

18 to 36 months: In the LTSS safety population, 1 out of 160 patients (0.6%) ( ) in the riferminogene pecaplasmid group had a cardiac failure (pulmonary oedema) that resulted in death versus none in the placebo group, during the 18 to 36 months period.

Conclusion: [redacted]

Date of report: 21-Jan-2013