Protocol Synopsis

Protocol Title	A phase I/II dose escalation study evaluating safety and activity of autologous CD34$^+$-enriched hematopoietic progenitor cells genetically modified with a lentiviral vector encoding for the human interferon-α2 gene in multiple myeloma patients with early relapse after intensive front line therapy
Protocol Number	TEM-MM-101
EudraCT Number	2018-001741-14
Study Sponsor	Ospedale San Raffaele (OSR) via Olgettina 60 20132 Milano, Italy
Financial Sponsor	Genenta Science via Olgettina 58, 20132 Milano, Italy
Study Phase	I/II
Study Site	Ospedale San Raffaele (OSR), Milan, Italy
Indication	Multiple Myeloma (MM)
Objectives	• To evaluate safety and tolerability of escalating doses of Temferon[1] in multiple myeloma patients with early relapse after intensive front line therapy. • To evaluate biological activity and efficacy of escalating doses of Temferon as maintenance/consolidation treatment in multiple myeloma patients with early relapse after intensive front line therapy.

[1] Temferon = Investigational Advanced Therapy Medicinal Product (ATMP) consisting of autologous CD34$^+$-enriched Hematopoietic Stem and Progenitor Cells (HSPCs) exposed to transduction with a Lentiviral Vector (LV) encoding the human interferon-α2 (IFN-α2) gene (TIA126-LV).

Study Design

Non-randomized, open label, single center, phase I/II, therapeutic-exploratory, dose-escalation, prospective study, involving a single intravenous infusion of autologous $CD34^+$-enriched hematopoietic stem and progenitor cells (HSPCs) exposed to transduction with a third-generation, vesicular stomatitis virus-G (VSV-G) pseudo-typed lentiviral vector driving myeloid-specific interferon-α2 (IFN-α2) expression in 9 patients affected by multiple myeloma in early relapse after intensive front line treatment.

The study will enrol multiple myeloma patients that have experienced an ***early relapse after intensive front line treatment,*** have been treated with an approved second line combination treatment regimen and obtained at least a very good partial remission according to International Myeloma Working Group (IMWG) criteria.

Intensive front line treatment is defined as:

- Triplet induction (at least 3 cycles including a proteasome inhibitor and/or immunomodulatory drug [IMID]) followed by single or double autologous stem cell transplantation.

OR

- Triplet or quadruplet induction including at least a proteasome inhibitor and an IMID, followed by consolidation/maintenance treatment.

Early relapse is defined as disease progression, according to the IMWG response criteria, occurring within 24 months from the end of induction/consolidation treatment.

Any currently approved second line treatments is considered appropriate for the study and may including the following:

- Carfilzomib (Kyprolis) + lenalidomide (Revlimid) + dexamethasone (KRd);
- Daratumumab (Darzalex) + lenalidomide (Revlimid) + dexamethasone (DaraRd);
- Elotuzumab (Empliciti) + lenalidomide (Revlimid) + dexamethasone (EloRd);
- Daratumumab (Darzalex) + bortezomib (Velcade) + dexamethasone (DaraVd).

- Other approved combinations are also permitted as second line treatment.

HSPC Mobilization. Patients who experience a very good partial response (VGPR) or better will undergo up to 2 stem cell mobilization attempts with lenograstim and plerixafor to reach the mobilization target of $\geq$ 4.5 x10^6 $CD34^+$ cells/kg for Temferon production. Each mobilization attempt may require 1-3 days of apheresis in order to harvest sufficient cells for Temferon production, unmanipulated $CD34^+$ cells and backup. In the event of insufficient HSPCs for backup, allogeneic backup will be permitted (providing a donor has already been identified) according to the Investigator's judgement. For the first attempt, a minimum harvest of 2.5 x10^6 $CD34^+$ cells/kg (in 1 or 2 collections on consecutive days) is required to proceed with $CD34^+$ cell selection. If the number of recovered $CD34^+$ cells is above the minimum amount defined for each dose level, Temferon production will proceed from freshly isolated $CD34^+$ cells.

For patients failing this target, $CD34^+$ cells will be frozen, and a second mobilization attempt will be conducted. Cyclophosphamide may be used in addition to lenograstim and plerixafor for the second mobilization attempt. For the second attempt, a minimum harvest of 2.0 x10^6 CD34+ cells/kg (in 1 or 2 collections on consecutive days) is required to proceed with $CD34^+$ cell selection. Fresh $CD34^+$ cells isolated from second harvest will be pooled with frozen $CD34^+$ cells from first harvest for Temferon production. In case of further mobilization failure preventing the production of the Drug Product, patients will be withdrawn from the study and proceed with treatment according to alternative options of care.

Patients meeting the mobilization target will be offered maintenance treatment while Temferon is being produced and until conditioning/ASCT. Patients may receive any approved 2nd line treatment/maintenance regimen.

Once the Investigator receives confirmation that Temferon has been released for clinical use, patients will undergo ***reduced intensity conditioning (RIC)*** with melphalan (100 mg/m^2), followed by

autologous stem cell transplant (ASCT) with non-manipulated and/or $CD34^+$-enriched HSPCs.

After ASCT, patients will receive a single intravenous infusion of the **experimental gene transfer treatment, Temferon** (within 3h to 16h post ASCT).

After Day +100 from Temferon infusion, patients will resume anti-myeloma consolidation/maintenance treatment according to best clinical practice, unless the following criteria are fulfilled:

- Documented Temferon engraftment (vector copy number [VCN] ≥ 0.07 in myeloid cells at the Day +100 visit);

AND

- Absence of disease on Day +100 evaluations, documented by stringent complete response (sCR) according to the IMWG response criteria, imaging negativity, *AND* bone marrow minimal residual disease (MRD) < 10^{-4} by multi-parameter flow cytometry (MFC), to be confirmed by next generation sequencing (NGS).

In case the above-mentioned criteria are fulfilled on Day +100, patients may stay off maintenance treatment, as long as the following criteria are fulfilled:

- MRD ≤ 10^{-5} documented on bone marrow aspirates performed every 3 months, starting from the Day +180 visit.

Patients will restart preemptive maintenance if either MFC or NGS suggests the presence of monoclonal plasma cells above the 10^{-5} threshold.

Description of the Study Phases

Six phases are foreseen in the study:

1) Enrolment, with signing of the informed consent form.

2) Screening phase *(approximately 3 weeks, up to 12 weeks prior to Temferon infusion)*, during which inclusion/exclusion criteria will be assessed. Patients may complete another cycle of salvage therapy during this phase.

3) ***Temferon production, release and baseline evaluation phase*** *(approximately 7 weeks in case of a single mobilization attempt. This may be extended up to 7 months in case of multiple mobilization attempts, or need for 3rd line salvage treatment at the discretion of the Principal Investigator):* from the beginning of HSPC mobilization and harvest, including Temferon production and release for clinical use by qualified person (QP), and baseline evaluations. Patients will be offered maintenance treatment from successful HSPC collection until conditioning/ASCT.

4) ***ASCT (Day -2 to Day 0)*****:** from the end of the Temferon production, release and baseline evaluation phase until completion of the ASCT. Once the Investigator receives confirmation that Temferon has been released for clinical use, the reduced intensity conditioning regimen will be administered to the patient at Day -2, followed by ASCT at Day 0.

5) ***Experimental Gene Transfer phase (Day 0)*****:** Temferon infusion (3h to 16h post ASCT) at Day 0.

6) ***Follow-up phase*****:** from Day +1 until Day +730 post Temferon infusion. Patients will resume anti-myeloma consolidation/maintenance treatment after Day +100, according to best clinical practice, unless patients show documented Temferon engraftment (VCN ≥ 0.07 in myeloid cells) and a deep molecular, biochemical and imaging response.

Upon completion of the follow-up phase, patients will be invited to participate in a separate long-term follow-up study (according to applicable regulations) to further assess the long-term safety and efficacy of Temferon treatment.

A Data Monitoring Committee (DMC) will review safety outcomes for all patients who have been administered Temferon. Dose-escalation will not occur until the DMC has reviewed safety and vector copy number (VCN) data at Day +30 of the last patient enrolled in the cohort, along with dose-limiting toxicities (DLTs) together with cumulative safety data from preceding cohorts when available.

A DLT is defined as any CTCAE Grade 3-5 non-hematological adverse event (AE), as rated by the National Cancer Institute's Common

	Terminology Criteria for Adverse Events (CTCAE) version 5.0, deemed by the Investigator and confirmed by the DMC to be attributed to Temferon during the DLT observation period of 30 days post Temferon infusion. Any CTCAE ≥ Grade 4 hematological AE meets the DLT definition if it persists at Day +30 post-Temferon infusion, despite supportive therapy, and is deemed by the Investigator and confirmed by the DMC to be attributed to Temferon.
Inclusion / Exclusion criteria	*Inclusion Criteria* 1. Multiple myeloma patients with early relapse after intensive front-line treatment and disease measurable by serum biomarkers, who have obtained at least a VGPR after second-line salvage treatment. • Early relapse is defined as progressive disease within 24 months from the end of induction/consolidation treatment. • Progressive disease is defined according to the IMWG consensus criteria[2]: increase of 25% from lowest confirmed response value in one or more of the following criteria: ▪ Serum M-protein (absolute increase must be ≥ 0.5 g/dL); ▪ Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL; ▪ Urine M-protein (absolute increase must be ≥ 200 mg/24 h); ▪ Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD[3] of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis; ▪ ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL), if this is the only measure of disease. • VGPR is defined as a serum and urine M-protein detectable by immunofixation but not on electrophoresis, or a ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24h, according to the IMWG consensus criteria. 2. Able and willing to provide written informed consent. 3. Able to comply with study protocol and procedures.

[2] Kumar et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncology 2016.
[3] Sum of the products of the greatest diameters (SPD)

4. Male or Female.
5. Age 18-70 years.
6. Fit patients:
   - Performance status scores: ECOG[4] < 2 and Karnofsky > 70%;
   - Life expectancy of ≥ 6 months.
7. Adequate cardiac, renal, hepatic and pulmonary functions as evidenced by (<u>at screening and prior to conditioning</u>):
   - Left ventricular ejection fraction (LVEF) ≥ 45% by echocardiography and normal electrocardiogram (ECG) or presence of abnormalities not significant for cardiac disease. Absence of severe pulmonary hypertension;
   - Diffusing capacity of the lung for carbon monoxide (DLCO) >50% and forced expiratory volume in 1 sec (FEV1) and forced expiratory vital capacity (FVC) > 60% predicted (if non cooperative: pulse oximetry > 95 % in room air);
   - Serum creatinine < 2x upper limit normal (ULN) and estimated glomerular filtration rate (eGFR) > 30 ml/min/1.73m^2;
   - Alkaline phosphatase (ALP), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 x ULN, and total bilirubin ≤ 2.0 mg/dl.
8. Women of child-bearing potential enrolled in the study must have a negative pregnancy test at screening and agree to use two distinct acceptable methods of contraception during the trial.
9. Men enrolled in the study with partners who are women of child bearing potential, must be willing to use an acceptable barrier contraceptive method during the trial or have undergone successful vasectomy at least 6 months prior to entry into the study. Successful vasectomy needs to have been confirmed by semen analysis.

<u>Exclusion Criteria</u>

1. Use of other investigational agents within 4 weeks prior to experimental treatment (within 6 weeks if use of long-acting agents).

[4] Eastern Cooperative Oncology Group (ECOG)

2. Severe active viral, bacterial, or fungal infection at eligibility evaluation.
3. Active autoimmune disease or a history of clinically relevant autoimmune manifestations requiring immunosuppressive treatment, i.e. psoriasis, systemic lupus erythematosus, rheumatoid arthritis, vasculitis, immune-mediated peripheral neuropathies.
4. Active sarcoidosis requiring steroid or immunosuppressive treatment.
5. Primary amyloidosis.
6. History of neuropsychiatric illness including severe depression, schizophrenia, bipolar disorders, impaired cognitive function, dementia or suicidal tendency.
7. Neuropathy > grade 2.
8. History of severe cardiovascular disease such as prior stroke, coronary artery disease requiring intervention, unresolved arrhythmias.
9. Malignant neoplasia (except local skin cancer or cervical intraepithelial neoplasia) or family history of familial cancer syndromes.
10. Myelodysplasia, cytogenetic or molecular alterations specifically associated with clonal hematopoiesis of the myeloid lineage, or other serious hematological disorder other than the plasma cell dyscrasia.
11. Other clinical conditions judged by the Investigator non-compatible with the study procedures.
12. Positivity for human immunodeficiency virus type 1 or 2 (HIV-1, HIV-2) (serology or RNA), and/or Hepatitis B Virus Surface Antigen (HbsAg) and/or Hepatitis B Virus (HBV) DNA and/or Hepatitis C Virus (HCV) RNA (or negative HCV RNA but on antiviral treatment) and/or Treponema Pallidum or Mycoplasma active infection.
13. Active alcohol or substance abuse within 6 months of the study.
14. Pregnancy or lactation.

	15. Previous allogeneic bone marrow transplantation, kidney or liver transplant, or gene therapy. 16. <u>Prior to conditioning:</u> inability to meet the target mobilization cell number needed to manufacture the Drug Product after at least 2 attempts of HSPC collection.
Endpoints	<u>*Primary Endpoints*</u> • **Engraftment of Temferon** after reduced intensity conditioning (vector copy number [VCN] ≥ 0.07 in myeloid cells between Day +30 and Day +100 in at least 2 patients). • **The proportion of patients achieving hematologic recovery by Day +30** from ASCT with non-manipulated and/or $CD34^+$-enriched autologous HSPC[5] and infusion of Temferon. Hematologic recovery is defined as the first of at least 3 consecutive days with a neutrophil count > 0.5 x 10^9/L and platelet count > 20 x 10^9/L. • **Safety of Temferon.** This will be measured through the 24 months post Temferon infusion as: 1) **Short-term tolerability** of Temferon (through 24 hours post Temferon infusion); 2) **Stable blood counts** and **absence of cytopenias > grade 2**, unless related to myeloma progression or concomitant medications; 3) **Absence of systemic interferon-alpha (IFN-α) toxicity** including: a. Constitutional or neurologic symptoms requiring medical treatment; b. Emergence of autoimmune manifestations requiring treatment;

[5] Non-manipulated and/or $CD34^+$-enriched autologous HSPCs = autologous non-selected or $CD34^+$-enriched HSPCs that did not undergo any genetic manipulation.

c. Any organ toxicity (> grade 2 according to CTCAE v5.0) that can be ascribed to IFN-α exposure;

4) **Absence of Replication Competent Lentivirus** (RCL);

5) **Absence of hematologic malignancy** that is distinct from progression of the primary neoplasm.

Secondary endpoints

- **Presence of an IFN-α gene signature** in the bone marrow (BM) of Temferon-treated patients.
- **Presence of transduced myeloid cells** in BM aspirate and peripheral blood (PB) at Day +30 and Day +100 post Temferon infusion as determined by VCN.
- **Persistence of transduced myeloid cells** in PB and BM as assessed by VCN. Persistence is defined as a VCN above the level of detection evident for at least 12 weeks.
- **Overall response rate (ORR):** proportion of patients that obtain partial response (PR), very good partial response (VGPR), complete response (CR) and stringent complete response (sCR) according to IMWG response criteria.
- **Fraction of patients achieving complete response (CR) with minimal residual disease (MRD) levels ≤ 10^{-5} and 10^{-6}** on BM aspirate.
- **Duration of maintenance of response** during the 24 months post Temferon infusion, according to the IMWG extended criteria[6].
- **Progression-free survival (PFS) and overall survival (OS)** at 24 months post Temferon infusion.
- **Change in health-related quality of life (HRQOL)** at 6, 12 and 24 months post Temferon infusion compared to screening.
- **Change over time in performance status scores (ECOG and Karnofsky)** through 24 months post Temferon infusion.

Exploratory endpoints

[6] Kumar et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncology 2016.

	BM and PB samples will be collected and stored frozen for subsequent optional exploratory analyses, according to feasibility: • Characterization of myeloid BM subpopulations. • Characterization of marrow-infiltrating lymphocytes in the BM and PB T cells at diagnosis, pre- and post Temferon infusion. • IFN-α response signature in monoclonal plasma cells. • Assessment of plasma cell neoantigen load and single cell transcriptomic analysis of the Tie-2 expressing monocytes (TEM) pre- and post Temferon infusion. • IFN-α2 concentration in blood and BM plasma/serum. • Histopathologic analysis of BM biopsy for vessel density and immune infiltrates. • Clonal tracking of hematopoiesis derived from Temferon infusion. • Assessment of MRD levels in the CD34 negative cell fraction and in Temferon by NGS.
ATMP, Dosage, and Treatment Plan	Temferon is an investigational Advanced Therapy Medicinal Product (ATMP) consisting of autologous $CD34^+$-enriched HSPCs exposed to transduction with a Lentiviral Vector (LV) encoding the human IFN-α2 gene (TIA126-LV). ***HSPC mobilization and harvest, as per institutional practice*** The first HSPC mobilization attempt will be done with lenograstim and plerixafor as follows: - Lenograstim (Myelostim) 10 µg/kg/day divided in 2 administrations (5 µg/kg each) by subcutaneous injection (s.c.) until a sufficient number of $CD34^+$ cells is mobilized and the leukapheresis/-es has/have been concluded. Monitoring of $CD34^+$ cells in the PB will be performed daily every morning from day 4. - Plerixafor (Mozobil) 0.40 mg/kg s.c. 5h before commencement of leukapheresis, starting from day 4. If required, additional leukaphereses will be performed the following day(s), preceded by additional plerixafor dose(s) 5 hrs before. Mobilization target is ≥ 4.5 x10^6 $CD34^+$ cells/kg (pool of 2 collections on consecutive days):

- The following are the minimum cell numbers ($CD34^+$/kg after $CD34^+$ cell enrichment) required for Temferon production:
  - Dose cohort 1: 1.5 x10^6 $CD34^+$ cells/kg
  - Dose cohort 2: 2.5 x10^6 $CD34^+$ cells/kg
  - Dose cohort 3: 3.5 x10^6 $CD34^+$ cells/kg
- $CD34^+$ cells exceeding the dose cohort-specific target will be frozen as non-transduced cells.

In case the dose cohort-specific minimum cell number will not be reached, $CD34^+$-enriched cells will be frozen and a second mobilization will be attempted. Cyclophosphamide may be used in addition to lenograstim and plerixafor for the second mobilization attempt, as follows:

- Cyclophosphamide (Endoxan) 4 g/m^2 by intravenous infusion (i.v.) on day 1;
- Lenograstim (Myelostim) 5 µg/kg/day s.c. from day +5; 5 µg/kg/bid from hematologic recovery (leukocytes > 1000 cells/µL) to apheresis;
- Plerixafor (Mozobil) 0.40 mg/kg s.c., 5h before commencement of leukapheresis.

If required, $CD34^+$-enriched cells from second remobilization will be pooled with thawed $CD34^+$-enriched cells from first remobilization to produce a single batch of Temferon.

An aliquot of the CD34-negative fraction from the harvest(s) and Temferon may be tested for MRD by Clonoseq, to prospectively acquire data on potential contamination by monoclonal plasma cells, as exploratory analyses (for information only).

Patients meeting the mobilization target will be offered maintenance treatment until conditioning/ASCT. Patients may receive any approved 2nd line treatment/maintenance regimen.

ASCT following non-myeloablative chemotherapy

Once the Investigator has received confirmation that Temferon has received QP release for clinical use and the patient is ready for treatment, the following RIC regimen will be implemented:

- Melphalan 100 mg/m^2 i.v. on Day -2;

Followed by:

- ASCT on Day 0, as an i.v. infusion of autologous HSPCs into a central vein. Target dose is 3.0 x10^6 $CD34^+$ cells/kg, with a minimum dose of 2.0 x10^6 $CD34^+$ cells/kg. HSPCs for ASCT can be obtained from an exceeding number of non-manipulated and/or $CD34^+$-enriched cells collected during the HSPC mobilization and harvest phase of the study, from a prior non-manipulated front-line harvest (unfractionated apheresis), or from a combination of both.

Experimental Gene Transfer Treatment

Infusion of Temferon on Day 0, as an i.v. infusion into a large peripheral vein or, if not feasible, into a central vein, within 3 hours to 16 hours post ASCT.

Granulocyte colony stimulating factor (G-CSF) will not be given on a routine basis, but will be reserved to patients showing prolonged neutropenia (grade 3/4 neutropenia beyond day 21 post chemotherapy).

The following dosing scheme for Temferon infusion will be applied:

	Temferon ($CD34^+$ cells/kg body weight)
Dose level 1	0.5* x10^6
Dose level 2	1.0* x10^6
Dose level 3	2.0* x10^6

***** The actual Temferon dose to be administered will be rounded to the nearest available aliquot size (maximum tolerance: +10%).

Temferon dose adjustments will be performed by the Sponsor of the manufacturing of Temferon (Genenta Science), in agreement with the Principal Investigator, according to the VCN indicated in the release documents. Should the VCN indicated in the release documents fall onto the dose-adjustment cutoffs, a VCN value expressed with 2 decimals will be considered for decision-making. The adjusted dose will be released to the Investigator for administration:

VCN	**Level 1**	**Level 2**	**Level 3**
< 0.4	0.8 x10^6	1.5 x10^6	3.0 x10^6

0.4-1.0	0.5 x10^6	1.0 x10^6	2.0 x10^6
1.1-1.5	0.4 x10^6	0.8 x10^6	1.5 x10^6
>1.5	0.3 x10^6	0.5 x10^6	1.0 x10^6

Follow up treatment:

After the evaluation on Day +100 post Temferon infusion, patients will resume anti-myeloma consolidation/maintenance treatment according to best clinical practice, unless patients show documented Temferon engraftment (VCN ≥ 0.07 in myeloid cells) and a deep molecular, biochemical and imaging response.

At any time upon suspected disease progression, patients will undergo a complete disease re-evaluation (including biochemical response, BM analysis, MRD assessment, positron emission tomography [PET], computerized tomography [CT]), and nuclear magnetic resonance [NMR] imaging at Investigator's discretion) and, in the case of documented progressive disease (PD), will be treated according to best clinical practice, at the discretion of the treating physician.

Management of potential side effects from Temferon:

The cell-based gene therapy approach that is being utilized in this study is designed to allow local, low dose IFN-α2 release at the tumor site, reducing the potential for systemic side effects.
As a benchmark for a "worst case scenario", potential adverse drug reactions related to systemic delivery of IFN-α (well described in the Summary of Product Characteristics of approved medicines such as IntronA [7]), for which warnings exist, are listed below and will be managed as appropriate:

- Central nervous system and psychiatric effects;
- Hypersensitivity reactions ;
- Abnormal liver function and prolongation of coagulation markers ;
- Myelosuppression ;
- Hypotension & need for adequate hydration ;
- Pyrexia ;

[7] IntronA SPC: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000281/WC500034679.pdf

	• Pulmonary conditions ; • Ocular adverse events ; • Obtundation, coma and encephalopathy ; • Patients with pre-existing cardiac abnormalities ; • Hypertriglyceridemia ; • Auto-antibodies and autoimmune disorders ; • Thyroid disorders. All patients are required to dispose of a non-manipulated and/or $CD34^+$-enriched autologous back-up of at least 2.0 $x10^6$ $CD34^+$ cells/kg, harvested during front line treatment and/or during the HSPC mobilization and harvest phase of the study. In the event of insufficient autologous $CD34^+$ cells for backup, allogeneic backup will be permitted (providing a donor has already been identified) according to the Investigator's judgement. In the event that hematological recovery does not occur, or in case of severe/persisting side effects not satisfactorily managed by the indicated treatments, patients may undergo transplant from back-up cells, ablating the genetically engineered graft with myeloablative conditioning regimen, as a rescue strategy.
Sample Size	Up to 9 patients in 3 cohorts. There can be less or more than 3 patients per cohort, for the following reasons: • In case the first 2 patients treated with dose level 1 show minimal *in vivo* engraftment of Temferon (VCN < 0.07 at Day +30 in BM myeloid cells), the third patient planned for dose level 1 will become the first patient in dose level 2. • In case the first 2 patients treated with dose level 2 show minimal *in vivo* engraftment of Temferon (VCN < 0.07 at Day +30 in BM myeloid cells), the third patient planned for dose level 2 will become the first patient in dose level 3. • If the minimum cell number for a cohort-specific dose is not reached, but is reached for a lower Temferon dose production, the patient may be assigned to a lower-dose cohort, even if 3 patients have already been dosed in the cohort, providing that adequate Temferon engraftment (≥ 0.07 VCN/genome on BM

	myeloid cells) has been demonstrated at Day +30 for at least one patient in that cohort.
Duration of Patient Participation	Each patient's study participation duration is expected to be approximately 28 months from time of consent (including 24 months of follow-up post Temferon infusion). Patients will then be invited to consent for a long-term follow-up study of another 6 years.
Estimated Study Duration	From enrollment of the first patient to post Temferon infusion follow-up of the last patient enrolled, the study duration is expected to be up to 49 months (including a 22-month enrollment period).
Data Monitoring Committee (DMC)	A DMC with a minimum of 3 members with relevant medical and scientific expertise will be constituted before the study start. A charter describing the composition and conduct of the DMC will be issued by Ospedale San Raffaele and Genenta Science and agreed to by all DMC members prior to the DMC's initial meeting. The DMC will review safety and efficacy data within a dosing cohort and make a recommendation about proceeding to the next dosing cohort.
Enrollment Suspension Criteria	In the event that a patient death that is attributed to Temferon occurs within 90 days of Temferon administration, further enrollment will be suspended. All other SAEs that result in death and are attributed to Temferon, will be reviewed by the DMC who will advise on whether recruitment into the study should be suspended.
Statistical Methods	This is a Phase I/II gene therapy study for which no formal statistical analysis is required.