A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia patients.

RACE study

Sponsor Protocol Number: 8409032

EudraCT TrialNumber: 2014-000363-40

Draft Version 3.1 02-Aug-2016

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This trial will be conducted in accordance with ICH-GCP and the appropriate regulatory requirements.

Protocol Revision History

Protocol Version	Date	Main changes
Version 3.1	02-Aug-2016	Stratification by centre Updating Protocol to include comments and changes from other ECs and CAs

		Clarification on processes
Version 2.0	17-December-2014	Safety data on ATGAM (NIMP) from Pfizer was added to section 8.

Confirmation of Trial Protocol / Signature page

A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia patients.

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The signatories declare that they agree to conduct their responsibilities within this trial in accordance with local law, the declaration of Helsinki, ICH-GCP and the trial protocol as presented.

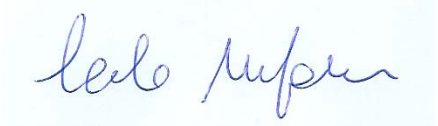
Approved by the following:

26-Jun-2016

Regis Peffault de Latour Coordinating Investigator	Signature	Date

26-Jun-2016

Antonio M Risitano Coordinating Investigator	Signature	Date



26-Jun-2016

Carlo Dufour EBMT Working Party Chair	Signature	Date

Protocol Agreement / Signature page for Investigator

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EudraCT Number: 2014-000363-40

I declare that I have read and understood the protocol and agree to conduct the trial accordingly. I will ensure that all persons working on the trial under my supervision are adequately informed about the protocol, the investigational medicinal product and their duties.

Name Hospital: _____

Name Investigator: _____

Signature Investigator: _____

Date: _____

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1. General Information

1.1 Trial Synopsis

Title of clinical trial	A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia patients.
Protocol Short Title/Acronym	RACE
Trial Phase	Phase III
Sponsor Details	European Society For Bone and Marrow Transplantation (EBMT)
Coordinating Investigator	Regis Peffault de Latour Antonio M Risitano
EudraCT number	2014-000363-40
Sponsor Protocol Code	8409032
Medical condition or disease under investigation	Severe aplastic anemia
Purpose of clinical trial	To improve the efficacy of the current treatment for aplastic anemia, by combining standard immunosuppression with a specific treatment that could rescue or improve the function of residual hematopoiesis.
Primary objective	The primary objective of this trial is to investigate whether Eltrombopag added to standard immunosuppressive treatment increases the rate of early (at three months) complete response in untreated AA patients.
Secondary objective (s)	The secondary objective of this trial is to investigate the impact of Eltrombopag added to standard treatment on all outcome measures in untreated AA patients.
Trial Design	Prospective open label randomised trial, 2 treatment arms
Endpoints	Primary: Rate of Complete response (defined as Hb >10 g/dL, ANC > 1,000/μL and Plt >100,000 μL) at 3 months since randomisation in untreated severe AA patients.

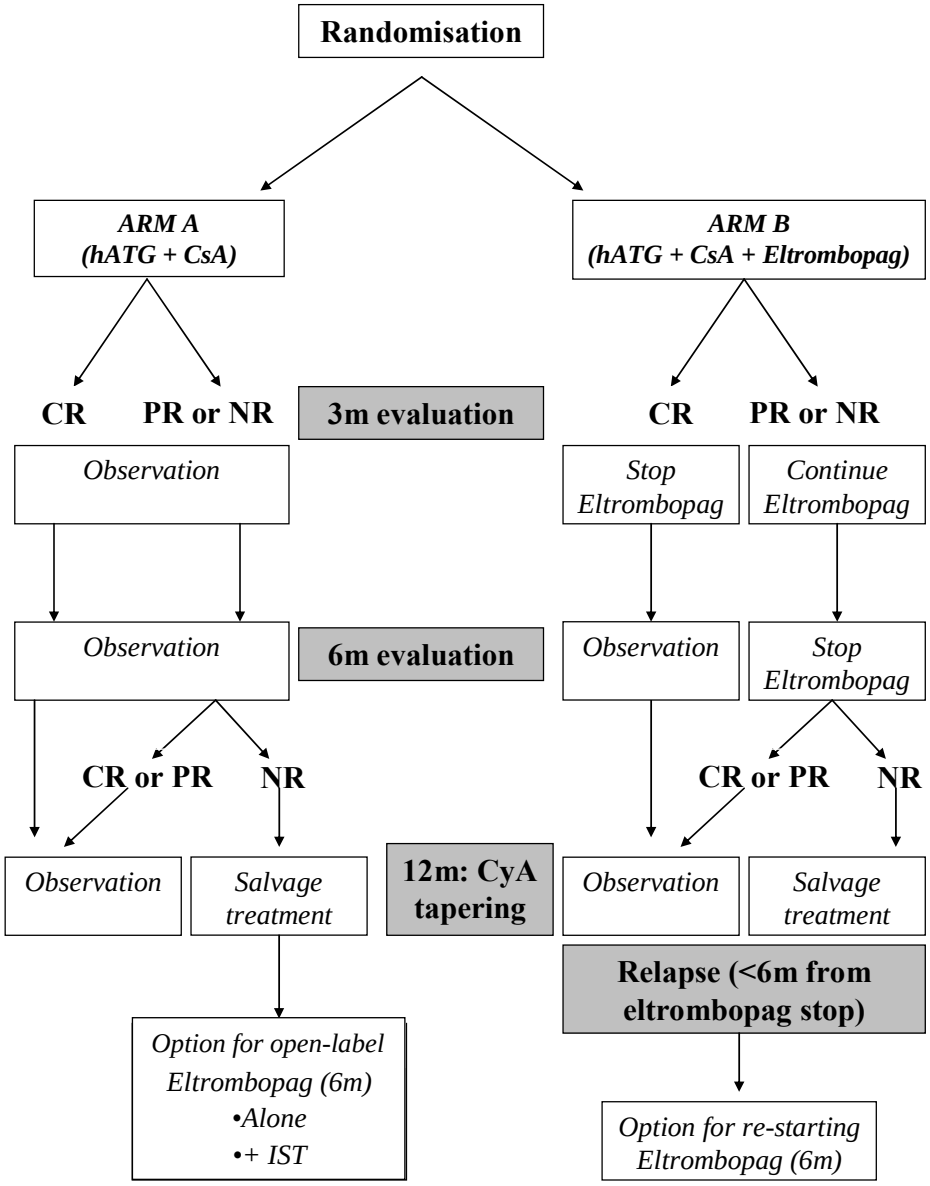
	Secondary: 1. Time to first hematological response (complete or partial) described by a cumulative incidence curve (see paragraph 9.6) 2. Time to best hematological response, described by a cumulative incidence curve (see paragraph 9.6) 3. Time to complete response (see paragraph 9.6) 4. Rates of hematological response (overall, complete, partial) at 6, 12, 18 and 24 months 5. Overall survival (OS) probability; OS is defined as time from randomisation to death, or last follow-up for patients alive 6. Event-free survival (EFS) probability; EFS is defined as time from randomisation to either relapse, death, treatment failure or clonal evolution (whichever occurs first), or last follow-up for patients alive in response 7. Cumulative incidence of relapse, from first hematological response (complete or partial) (see paragraph 9.6) 8. Cumulative incidence of clonal evolution (as defined below, see 9.5): AML, MDS or karyotypic abnormalities (see paragraph 9.6) 9. Cumulative incidence of PNH population occurrence and clinical hemolytic PNH occurrence (see paragraph 9.6) 10. Cumulative incidence of discontinuation of maintenance immunosuppressive therapy (CsA) 11. Rate of CsA-independent hematological response at 24 months 12. Need for transfusions (packed red cell units and platelet units) and number of transfusions required from treatment. 13. Need for any supportive care, including hospitalization 14. Quality of life (as assessed by the validated EORTC QLQ-C30 questionnaire)(changes over time and differences between treatment arms) 15. Safety and tolerability of the investigational treatment, eltrombopag, and ATGAM including SAE
Number of patients required	200 (100 patients in each arm)

Inclusion criteria	1. Diagnosis of severe or very severe aplastic anemia, defined by [29]: • At least two of the following: – Absolute neutrophil counts <0.5 x 10^9/L (severe) or <0.2 x 10^9/L (very severe) – Platelet counts <20 x 10^9/L – Reticulocyte counts <60 x 10^9/L • Hypocellular bone marrow (<30% cellularity), without evidences of fibrosis or malignant cells 2. Age ≥ 15 years; 3. Written informed consent 4. Willing and able to comply with all of the requirements and visits in the protocol 5. Understands that they can be randomised to either treatment arm 6. Negative pregnancy test for women of child bearing age 7. Written acceptance to use contraception (hormonal or barrier method of birth control; abstinence) for the entire duration of study participation.
Exclusion criteria	1. Prior immunosuppressive therapy with ATG (horse or rabbit) or any other lymphocyte depleting agent (i.e., alemtuzumab) 2. Eligibility to a sibling allogeneic stem cell transplantation 3. Evidence of a myelodysplastic syndrome, defined by the presence of myelodysplastic features, excess of blasts or karyotypic abnormalities typical of MDS (according to revised WHO 2008 criteria) [30], as well as other primitive marrow disease. Patients with diagnosis of AA with cytogenetic abnormalities which are recurrent in MDS (according to revised WHO 2008 criteria) [30] should be included in this category, and are not eligible for the study; ***patients with del(20q), +8 and –Y are not included in this category, and thus are eligible for this study.*** The list of karyotypic abnormalities which qualifies for the diagnosis of MDS are listed in the Appendix 1. 4. History or clinical suspect of constitutional aplastic anemia (i.e. Fanconi Anemia with positive DEB/MMC test or Dyskeratosis Congenita) 5. History of malignant tumors with active disease within 5 years from enrollment and/or previous chemo-radiotherapy 6. Previous history of stem cell transplantation 7. Treatment with cyclosporin A: • <4 weeks of cyclosporin A treatment before enrollment.

	• Wash out period of 2 weeks before enrollment. 8. CMV viremia, as defined by positive PCR or pp65 test 9. WHO performance status ≥3 10. Pregnant or breast feeding patients 11. Patients with hepatic, renal or cardiac failure, or any other life-threatening concurrent disease 12. Patients with HIV infection 13. Patients without social health care assistance 14. Participation in another clinical trial within 1 month before the start of this trial 15. Patients and/or female partners of male patients not using highly effective method of birth control i.e. intrauterine device (IUD), hormonal (oral pill, injection, implants), tubal ligation or partner's vasectomy 16. Subjects with known hypersensitivity to any of the component medications The presence of a Paroxysmal Nocturnal Hemoglobinuria clone **is not** an exclusion criterion. Hepatitis-AA (HAA) syndrome [34] is not an exclusion criterion; similarly, the evidence of HBV or HCV infection is not an exclusion critrion *per se*, provided that there is no evidence of hepatic failure (see exclusion criterion #11)
Therapy/Intervention	Detailed trial treatment plan included with protocol (appendix 2)
Maximum duration of treatment of a patient	12 months in total during the entire timeframe of the study
Definition of the end of the Trial	Last patient last visit (end of 2 year follow up)
Statistical Plan	This is a superiority trial aiming to increase the 3 month complete response rate. The sample size is calculated on the hypothesis that the experimental treatment will increase the 3 months response rate up to 21% (by 3 folds, based on the 7% expected in the control group as reported in Scheinberg et al [17]). Under these assumptions, the sample size to reject the null hypothesis is n=96 patients for each treatment arm (two-sided test; alpha-error 0.05; power 0.8). The actual sample size will be increased by 4% to account for possibly not evaluable patients (total number of 200 patients, 100 in each treatment arm). The primary analysis will evaluate complete response rate at 3 months after randomisation; this will be an intention-to-treat analysis. The null hypothesis of no difference in

	CR% at 3 months between the arms will be tested against the alternative of a difference in CR% by assessing the Mantel Haenszel pooled Odds Ratio for arm yielded by a model stratified for center size, age and disease severity (strata defined in Section 7.1; alpha level of .05). Other time-to-event outcomes will be analysed (again as intention-to-treat) by Kaplan-Meier or cumulative incidence curves as appropriate (see 12.3), and by Cox (cause-specific) hazard models including age, disease severity and other relevant predictive factors.

1.2 Trial Schema



1.3 Abbreviations

AA	Aplastic Anaemia
AE	Adverse Event
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AR	Adverse Reaction
ATG	Antithymocyte globuline
AUC	Area Under Curve
BCRP	Breast Cancer Resistance Protein
BMFS	Bone Marrow Failure Syndromes
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Coordinating Investigator
CLD	Chronic Liver Disease
CMV	Cytomegalovirus
CR	Complete Response
CRF(s)	Case Report Form(s)
CRO	Clinical Research Organisation
CSA	Cyclosporine A
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
CTMS	Clinical Trials Management System
CyA	Cyclosporine A
DFS	Disease Free Survival
DSUR	Development Safety Update Report
EBMT	European Society for Blood and Marrow Transplantation
EFS	Event-free Survival
GCP	Good Clinical Practice
GCSF	Granulocyte-Colony Stimulating Factor
GVHD	Graft-versus-Host-Disease
HAA	Hepatitis Aplastic Anaemia
hATG	horse Antithymocyte globuline
HB	Hemoglogin
HBV	Hepatitis B Virus
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

IMP	Investigational Medicinal Product
ISF	Investigator Site File
IST	Immune Suppressive Therapy
ITP	Immune Thrombocytopenia
IUD	Intrauterine Device
LDH	Lactate Dehydrogenase
MDS	Myelodysplastic Syndrome
NIH	National Institute of Health
NIMP	Non Investigational Medicinal Product
NR	No Response
OATP	Organic Anion Transporter Polypeptide
OS	Overall Survival
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PLT	Platelets
PNH	Paroxysmal Nocturnal Hemoglobinuria
PRBC	Packed Red Blood Cells
PI	Principal Investigator
PIL	Patient Information Leaflet (and consent form)
PR	Partial Response
QLQ	Quality of Life Questionnaire
RI	Relapse Incidence
SAAWP	Severe Aplastic Anaemia Working Party
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEE	Thromboembolic events
TPO-R	Thrombopoeitin Receptor
TMF	Trial Master File
TTP	Time To Progression
VSAA	Very Severe Aplastic Anaemia
WBC	White Blood Cells
WHO	World Health Organization

2. Background

Aplastic anemia (AA) is the most typical example of bone marrow failure syndromes (BMFS): the normal hematopoietic tissue is completely missing from the bone marrow, accounting for the subsequent pancytopenia [1]. AA can be either primary or secondary (to malignancies or iatrogenic), as well as inherited or acquired; here we focus on primary acquired forms of AA, also known as idiopathic AA. Idiopathic AA is considered an immune-mediated disease [2], as supported by a plethora of experimental data [3]. T cells play a pivotal role in the pathophysiology of the disease [4], accounting for the damage of hematopoietic stem cells via cell-cell interaction and inhibitory cytokines, such as IFN-γ, TNF-α and TGF-β. However, it has to be remarked that even apparently typical acquired AA may rarely harbor inherited abnormalities, actually being cryptic forms of constitutional AA [5]. Thus, the immune system, and especially T cells, are a conceivable target for therapeutic intervention in AA and related disorders; indeed, in the past three decades immunosuppressive therapy (IST) represented for AA patients a key treatment option, which is the only alternative to hematopoietic stem cell transplantation [6,7]. Since the eighties, anti-thymocyte globulin (ATG) has been the immunosuppressive agent proven effective for the treatment of AA [8]; in the following years the addition of cyclosporine A (CyA) resulted in improved outcomes [9,10], becoming the most utilized IS regimen for AA patients in developed countries. Further attempts to improve response rates or to reduce relapses by adding a third immunosuppressive agent to the backbone of ATG and CyA have been disapponting [17, 19].

ATG is a heterologous anti-serum obtained by injecting human lymphocytes in animals; thus, it is not a chemical drug, and the composition of the anti-serum may differ. This is especially true because various ATG formulations exist, which differ in stimulating antigens (peripheral lymphocytes, thymocytes or even T cell lines), and/or in the host animal (either horse or rabbit, recently even pig). However, the large randomized clinical trials which documented the efficacy of ATG consistently utilized a serum obtained from horse (h-ATG). This was ATGAM® (Upjohn; 40 mg/kg/day for 4 days) in the US [11,12],or Lymphoglobuline® (Genzyme; 15 mg/kg/day for 5 days) in Europe [13,14] or Japan [15]. Even if a formal comparison has not been done, both horse-ATG preparations showed similar efficacy for the treatment of AA, resulting in response rate of 60-70% in the most recent studies [16-18]; they are considered the standard IS regimen for AA patients. However, in the recent years the lack of availability in some Coutries (i.e., Europe) of h-ATG led to a more systematic use of rabbit ATG preparations (mostly Thymoglobuline®, Genzyme, that has shown a substantial activity as salvage treatment for AA patients refractory to or relapsed after a first IST course with h-ATG [19,20]). Unfortunately, in a large (120 untreated AA patients) randomized study (NCT00260689) conducted at the NIH comparing h-ATG (ATGAM) and r-ATG (Thymoglobuline, 3.5 mg/kg/day for 5 days), both in combination with CyA, r-ATG resulted significantly inferior as front-line treatment for AA [21]. In fact, the hematological response was 62% and 68% in the h-ATG arm (at 3 and 6 months, respectively), compared to 33% and 37% in the r-ATG arm ($p=0.002$ and $p<0.001$). Cumulative incidence of relapse (only in responders) and of clonal evolution did not differ in the two treatment arms. However, the striking difference in response rate led to statistically

different survival, which was 94% in the h-ATG arm, as compared with 70% in the r-ATG arm (p=0.008); overall survival remained significantly different even when the analysis was performed censoring transplanted patients at the time of transplant (96% vs 76%, p=0.04). The observation of disappointing hematological response after r-ATG treatment was also confirmed in a subsequent phase II, non-randomized, pilot study (NCT00471848) conducted by the Severe Aplastic Anaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT SAAWP), that investigated Thymoglobuline (3.75 mg/kg/day for 5 days) plus CyA in a cohort of 35 AA patients. The 6-month response rate was as low as 39% (with only 7% of complete responses), resulting in a 2-year overall survival of 68%, which in a retrospective matched-paired analysis was significantly reduced in comparison to that of h-ATG (86%) [22]. Even if some other groups have reported additional series, with contradictory data [23-26], at the moment h-ATG (ATGAM®, 40 mg/kg/day for 4 days) and CyA is considered the standard immunosuppressive regimen for the front line treatment of AA patients [27].

More recently, the thrombopoietin mimetic agent eltrombopag has been investigated in a small phase II study (NCT00922883) in AA patients refractory to immunosuppression [28, 35]. Eltrombopag was used as a single agent at the dose of 50 mg orally, which could be increased, as needed, to a maximum dose of 150 mg daily, for a total of 12-16 weeks. Quite impressively, at 12 weeks, 11 of 25 patients (44%) had a hematologic response in at least one lineage: 9 patients no longer needed platelet transfusions, 6 patients had improved hemoglobin levels (3 become transfusion-independent) and 9 had increased neutrophil counts. Side effects were minimal and clinically irrelevant. In some patients haematological improvements included more than a single lineage, providing the proof that even in IS-refractory severe AA patients, eltrombopag may lead to multilineage haematological responses. Indeed, serial bone marrow biopsies in responding patients showed normalization of trilineage hematopoiesis. These data strongly support the concept that eltrombopag may improve the bone marrow function in AA patients by increasing the number of hematopoietic stem cells and progenitor cells surviving to the immune-mediated damage. We thus hypothesized that eltrombopag may work synergistically with immunosuppressive therapy and may possibly improve its efficacy in AA patients. A phase II clinical trial combining h-ATG, CyA and eltrombopag is currently ongoing at the NIH for untreated severe AA patients (NCT01623167) [33]; here we aim to investigate in a large randomized study the possible benefit of eltrombopag once added to the backbone of frontline standard immunosuppression, i.e. ATGAM and CyA.

2.1 Trial Rationale

This trial has been designed to improve the efficacy of the current treatment for aplastic anemia, by combining standard immunosuppression with a specific treatment that could rescue or improve the function of residual hematopoiesis. Horse-ATG and CyA remains the standard immunosuppressive regimen for the front line treatment of AA [27]; however, not all patients respond, and hematological responses are often partial and relatively late. Based on the positive results of eltrombopag in AA patients refractory to IST [28], we assume that this thrombopoietin mimetic agent, if added to ATGAM and CyA, may improve the quality of the hematological response.

2.2 Pre-Clinical Data

Detailed information is described in the Investigator Brochure (annex 4)

2.3 Clinical Data

Detailed information is described in the Investigator Brochure (annex 4)

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

Eltrombopag is a thrombopoietin mimetic agent approved for the treatment of idiopathic thrombocytopenic purpura (ITP) in 2010. Its use for this indication has not resulted in any specific risk, with the exception of rare thrombotic complications seen in patients with exaggerated platelet response secondary to the pharmacological effect of eltrombopag. Recent studies in AA have proven that, beyond its effect on platelet progenitors, eltrombopag may stimulate early hematopoietic progenitors including hematopoietic stem cells. Thus, it may theoretically stimulate even stem cells carrying (or which may develop later on) malignant or pre-malignant mutations. Given that the risk of clonal evolution is intrinsic to AA, it has to be carefully investigated if eltrombopag will have any effect on this possible late complication of AA.

2.4.2 Potential Benefits

Current treatment options have dramatically changed the prognosis of AA, which was inevitably fatal 50 years ago. However, both transplant and IST are very intensive treatments which carry significant medical risk, and high costs. While the majority of transplanted patients achieve the cure of their disease, IST often results in partial or transient haematological response, which in the end keep the patients at risk of life-threatening complication for weeks or even months, requiring costly supportive care. Thanks to its effect on hematopoietic progenitors, eltrombopag may be combined to IST to improve the response rate and the quality of haematological response. By improving the quality of the initial haematological response eltrombopag may have a relevant impact on the care of AA patients, who may achieve a more robust and faster increase in their blood counts. This will eventually result in a decreased risk of complications and of medical care, which obviously will also reduce the cost of the treatment of AA patients (especially considering the spare of costly and medically risky second-line treatments).

3. Overview of Trial Design

Prospective, randomized, open label, study aiming to investigate the possible contribution of eltrombopag to improve the robustness of hematological response of SAA patients receiving immunosuppressive treatment. The control arm is standard immunosuppression with hATG + CsA, which will be compared with the investigational treatment which include eltrombopag in combination with the standard immunosuppression.

This is a type B trial; indeed, eltrombopag has been proven safe and effective in the treatment of idiopathic thrombocytopenic purpura, as well as in refractory AA. In this latter setting long-term effect, in terms of impact of clonal evolution, have not been fully elucidated yet. On the other end, the anticipated effect of eltrombopag on platelet count should largely reduce the bleeding risk, which remains one of the main contributor to morbidity and mortality of AA patients. All together, these considerations let us to conclude that the addition of eltrombopag to standard immunosuppression may theoretically result in a somewhat higher risk in comparison to standard medical care.

4. Trial Objectives

4.1 Primary Objective

To increase the rate of complete response (defined as Hb >10 g/dL, ANC > 1,000/μL and Plt >100,000 μL) at 3 months in untreated severe AA patients.

4.2 Secondary Objectives

To evaluate:

1. Time to first hematological response (complete or partial)
2. Time to best hematological response
3. Time to complete response
4. Hematological response (overall, complete, partial) at 6, 12, 18 and 24 months
5. Overall survival (OS)
6. Event-free survival (EFS), considering as failure (event) relapse, death, treatment failure or clonal evolution (whichever occurs first)
7. Relapse rate from first hematological response (complete or partial)
8. Rate of clonal evolution (defined in Section 9.5): AML, MDS or karyotypic abnormalities
9. Rate of PNH population occurrence and clinical hemolytic PNH occurrence
10. Rate of discontinuation of immunosuppressive therapy
11. Rate of CsA-independent hematological response at 24 months
12. Need for transfusions (packed red cell units and platelet units) and number of transfusions required from treatment.
13. Need for any supportive care, including hospitalization
14. Quality of life (as assessed by the validated EORTC QLQ-C30 questionnaire) before treatment and at 6, 12, and 24 months
15. Safety and tolerability of the investigational treatment, including SAE.

5. Trial Endpoints

5.1 Primary Endpoint

Rate of Complete response (defined as Hb >10 g/dL, ANC > 1,000/μL and Plt >100,000 μL) at 3 months since randomisation in untreated severe AA patients.

5.2 Secondary Endpoints

1. Time to first hematological response (complete or partial) described by a cumulative incidence curve (see paragraph 9.6)
2. Time to best hematological response, described by a cumulative incidence curve (see paragraph 9.6)
3. Time to complete response (see paragraph 9.6)
4. Rates of hematological response (overall, complete, partial) at 6, 12, 18 and 24 months
5. Overall survival (OS) probability; OS is defined as time from randomisation to death, or last follow-up for patients alive
6. Event-free survival (EFS) probability; EFS is defined as time from randomisation to either relapse, death, treatment failure or clonal evolution (whichever occurs first), or last follow-up for patients alive in response
7. Cumulative incidence of relapse, from first hematological response (complete or partial) (see paragraph 9.6)
8. Cumulative incidence of clonal evolution (as defined below, see 9.5): AML, MDS or karyotypic abnormalities (see paragraph 9.6)
9. Cumulative incidence of PNH population occurrence and clinical hemolytic PNH occurrence (see paragraph 9.6)
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13. Need for any supportive care, including hospitalization
14. Quality of life (as assessed by the validated EORTC QLQ-C30 questionnaire)(changes over time and differences between treatment arms)
15. Safety and tolerability of the investigational treatment, including SAE

6. Patient Selection and Withdrawal

All patients must meet all of the inclusion criteria and none of the exclusion criteria listed below. Protocol waivers are not acceptable in this trial.

6.1 Inclusion Criteria

In order to be enrolled in the study patients have to meet all the following criteria:

1. Diagnosis of severe or very severe aplastic anemia, defined by [29]:
   - At least two of the following:
     - Absolute neutrophil counts <0.5 x 10^9/L (severe) or <0.2 x 10^9/L (very severe)
     - Platelet counts <20 x 10^9/L
     - Reticulocyte counts <60 x 10^9/L
   - Hypocellular bone marrow (<30% cellularity), without evidences of fibrosis or malignant cells
2. Male or female age ≥ 15 years;[1]
3. Written informed consent
4. Willing and able to comply with all of the requirements and visits in the protocol
5. Understands that they can be randomised to either treatment arm
6. Negative pregnancy test for women of child bearing age
7. Written acceptance to use contraception (hormonal or barrier method of birth control; abstinence) for the entire duration of study participation.

6.2 Exclusion Criteria

Patients with one or more of the following criteria cannot be included in the study:

1. Prior immunosuppressive therapy with ATG (horse or rabbit) or any other lymphocyte depleting agent (i.e., alemtuzumab)
2. Eligibility to a sibling allogeneic stem cell transplantation
3. Evidence of a myelodysplastic syndrome, defined by the presence of myelodysplastic features, excess of blasts or karyotypic abnormalities typical of MDS (according to revised WHO 2008 criteria) [30], as well as other primitive marrow disease. Patients with diagnosis of AA with cytogenetic abnormalities which are recurrent in MDS (according to revised WHO 2008 criteria) [30] should be included in this category, and are not eligible for the study; ***patients with del(20q), +8 and –Y are not included in this category, and thus are eligible for this study.*** The list of karyotypic abnormalities which qualifies for the diagnosis of MDS are listed in the Appendix 1.
4. History or clinical suspicion of constitutional aplastic anemia (i.e. Fanconi Anemia with positive DEB/MMC test or Dyskeratosis Congenita)
5. History of malignant tumors with active disease within 5 years from enrollment, and/or previous chemo-radiotherapy
6. Previous history of stem cell transplantation

[1]Children in Care (CiC) are not excluded from this study, provided that the agency, organization, institution (or entity of the courts, the government or a government body) will work as legal guardian in signing the informed consent. CiC are defined as children who have been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of CiC can include children cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a CiC does not include a child who is adopted or has an appointed legal guardian.

7. Treatment with cyclosporin A:
    - <4 weeks of cyclosporin A treatment before enrollment.
    - Wash out period of 2 weeks before enrollment.
8. CMV viremia, as defined by positive PCR (≥ 3.5 logarithm) or pp65 test (≥5 cells)
9. WHO performance status ≥3
10. Pregnant or breast feeding patients[2, 3]
11. Patients with end-stage hepatic, renal or cardiac failure, or any other life-threatening concurrent disease
12. Patients with HIV infection
13. Patients without social health care assistance
14. Participation in another clinical trial within 1 month before the start of this trial
15. Patients and/or female partners of male patients not using highly effective method of birth control i.e. intrauterine device (IUD), hormonal (oral pill, injection, implants), tubal ligation or partner's vasectomy
16. Patients with known hypersensitivity to any of the component medications

The presence of a Paroxysmal Nocturnal Hemoglobinuria clone **is not** an exclusion criterion.

Hepatitis-AA (HAA) syndrome [34] is not an exclusion criterion; similarly, the evidence of HBV or HCV infection is not an exclusion critrion *per se*, provided that there is no evidence of hepatic failure (see exclusion criterion #11)

6.3 Early withdrawal of a patient / patient drop-out from the trial treatment

The site investigator should withdraw a patient from the trial treatment whenever continued participation is no longer in the patient's best interests. In particular, change of protocol treatment is expected in case of treatment failure (as defined in paragraph 9.4) for those patients who are eligible for second-line treatment (i.e., transplantation or second course of immunosuppression).

In addition reasons for discontinuing treatment may include:

1. the occurrence of a serious adverse event:
2. unrelated medical illness or clinical conditions representing a potential risk - at judge of the investigator, including pregnancy.
3. significant protocol violation or non-compliance (including unmotivated refusal by the subject for prescribe study procedures and post-treatment follow up).
4. a patient's own request to end treatment.

[2]Eltrombopag was not teratogenic when studied in pregnant rats and rabbits but caused a low incidence of cervicalribs (a fetal variation) and reduced fetal body weight at doses that were maternally toxic. There are no adequate and well-controlled studies of eltrombopag in pregnant women. The effect of eltrombopag on human pregnancy is unknown. Therefore women of childbearing potential must agree to use adequate contraception prior to (hormonal or barrier method of birth control; abstinence) and for the duration of study participation. If a woman becomes pregnant or suspects she is pregnant while on study, her treating physician should be informed immediately.

[3] ATGAM was not teratogenic when studied in rats or monkeys at a dose up to 20 mg/kg. However, 20 mg/kg/day ATGAM for 16 days during organogenesis in cynomolgus monkeys was fetotoxic. No fetal or maternal toxicity was seen with 10 mg/kg/day ATGAM administered for 16 days during organogenesis. There are no adequate and well-controlled studies in pregnant women. It is also not known whether ATGAM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

If a patient is withdrawn from treatment for any reason, he or she remains in the trial and is followed through the regular follow ups for the normal duration of the described participation as per protocol, unless the patient specifically withdraws consent from the trial.

6.4 Early withdrawal of a patient / patient drop-out from the trial

According with the current revision of the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his future medical care by the physician. A patient may decide at any time that they no longer wish to continue in the trial without their medical care being affected and without having to provide a reason for discontinuation. In this event, the investigator should try and establish the reason why the patient no longer wishes to participate in the trial and record the reasons in the CRF as well as in the patient's notes; the patient is not obliged to supply this.

Any patient who is withdrawn from the trial at any time for any reason before the last follow up visit is considered an early withdrawal. A complete set of data including the reason for withdrawal should be collected for every early withdrawal patient up to the time of withdrawal from the trial. **Regardless of the reasons for discontinuing in the trial, patients should be followed up for a minimum of 90 days after the last dose of IMPs in order to obtain safety data**.

6.5 Patients lost to follow-up

Every effort should be made to obtain information on patients who do not attend a scheduled appointment, to obtain at least minimal efficacy and safety data (including Serious Adverse Events). A patient will be considered lost to follow-up if they miss 3 consecutive visits and cannot be contacted by the site on 3 separate, consecutive attempts (these attempts must be documented on patient' notes).

6.6 Termination of an investigator's participation in the trial

The investigator may terminate his or her site's participation in the trial. If this occurs they must provide a written statement of the reasons for terminating participation and should provide the EBMT Clinical Trials Office (CTO) with all available and up-to-date trial data.

The trial steering committee may also decide to terminate participation of an investigator or trial site for the following reasons:

- Breach of agreement
- Serious non-compliance with International Conference on Harmonisation for Good Clinical Practice (ICH-GCP) standards (see section 14)
- Insufficient patient recruitment

For composition of the Trial Steering Committee the please refer to appendix 10.
If a participating site closes, or is closed, prior to termination of the whole trial, the EBMT requires that data from patients already entered into the trial will be reported as per protocol,

unless the patient(s) have withdrawn consent for data collection. In addition, the treatment of the patients already included in the trial will be discussed and agreed with the EBMT.

The end of the trial is defined in section 11.

7. Patient Treatment and Visit Schedule

7.1 Patient Registration/ Randomisation

To register a patient in the trial the site must complete the RACE registration form and fax this to the EBMT CTO. The registration form must be signed by the PI or Co-Investigator listed on the staff delegation log.
On receipt of the patient registration form the patient data will be entered in the Clinical Trials Management System (CTMS) and the patient will be assigned a unique patient number. The EBMT CTO will send a registration confirmation to the site.
A patient will be considered enrolled in the study when registration of the patient is confirmed by the EBMT Clinical Trials Office.

Randomisation will take place on the day or day before hATG is started. The time between registration and randomisation should be no longer than 7 days.
To randomise a patient the site must complete the RACE randomisation form and fax this to the EBMT CTO. The randomisation form must be signed by the PI or Co-Investigator listed on the staff delegation log.
The patient data will be entered in the CTMS and the patient will be randomised to either the standard or the investigational arm. The EBMT CTO will send the randomisation result to the site.

Randomisation ratio will be 1:1. Randomisation will follow a stratified variable length block design. Stratification will be done according to patient's age and disease severity to ensure homogeneity between treatment arms, according to the following subgroups:

Disease severity:

- Severe aplastic anemia (SAA)
- Very severe aplastic anemia (VSAA: SAA plus ANC <200/μL)

Age:

- ≥15 and <40 year old
- ≥40 year old

A stratification by centre will be considered as an additional balancing factor for randomisation, based on the center size (i.e. the number of patients expected to be entered into a center in this trial). A center is classified as "large" if the anticipated number of patients to be entered exceeds 20. Otherwise the center is classified as "small". All centers classified as small will be treated as one single stratum; all large centers have their own stratum. Hence randomisation will be balanced within each large center on disease severity and age; and likewise within the pool of all small centers.

Patient registration and randomisation forms will be processed Monday to Friday from 09.00 -17.00 CET.

- Forms received after 17.00 will be processed the next day.
- Forms received over the weekend will be processed the following Monday morning.

7.2 Trial Procedure and Treatment

7.2.1 Outline of Treatment Plan

Patients will receive standard or investigational treatment according to the table below.

Standard treatment:

Treatment	*Dose (units)*	*Route*	*Treatment Period*
ATGAM (Pfizer)	*40 mg/kg/day*	*i.v., 12-18 h infusion*	*Day 1, 2, 3 and 4*
Cyclosporine A	*5 mg/kg/day*	*Orally*	*Day 1-365 (adjusted on blood levels)*

Investigational treatment:

Treatment	*Dose (units)*	*Route*	*Treatment Period*
ATGAM (Pfizer)	*40 mg/kg/day*	*i.v., 12-18 h infusion*	*Day 1, 2, 3 and 4*
Cyclosporine A	*5 mg/kg/day*	*Orally*	*Day 1-365 (adjusted on blood levels)*
Eltrombopag	*150 mg every 24 h (50 mg tablets x3)*	*Orally*	*Day 14-90 (or 14-180)*

7.2.2 Treatment Assignment

Administration of randomisation is separated from the clinical investigators. Randomisation will be stratified according to center (each center of expected size>=20 being a single stratum and all smaller centers lumped together), age (≥15 and <40 year old vs. ≥40 year old) and disease severity (severe aplastic anemia vs. very severe anemia). The ratio of patients included in each arm for standard treatment versus investigational treatment is to be 1 : 1.

7.2.3 Duration of Patient Participation

Patients will be included in the trial following informed consent. Following registration patient will start hATG within 7 days. Patients have to be randomised at, or the day before, start of hATG treatment.

Patients will remain on the trial for 2 years (for treatment and subsequent follow up); the duration of the treatment with the IMP will be initially 3 or 6 months (depending on hematological response). However, given that re-introduction of the IMP is allowed for 6 additional months, the treatment duration may be extended up to 18 months from enrolment. Per protocol, eltrombopag (the investigational agents) will be administered for a maximum period of 12 months: maximum 6 months at enrolment, plus additional maximum 6 months in

case of early relapse. As long-term effects of investigational treatments are an objective of the study, the follow-up of patients will cover a minimum of 24 months from initial randomisation. The long term follow up of the patients will be conducted outside of the protocol and will be extended up to 10 years from treatment, through the EBMT official database (updated EBMT Registry Database).

7.2.4 Evaluation and Visit Schedule

Visit schedule (see also flowchart in the appendix 2)

7.2.4.1 Baseline (Visit 0)

Refer to the table/flow chart in the appendix 2 for the list of baseline tests.

All patients must provide fully informed written consent before any procedures are done. All baseline tests must be completed within30 days before registration.
All the tests except for the cataract check up are part of routine clinical care of AA patients, therefore results from tests that are performed no more than 30 days prior to registration can be used to assess the patients eligibility.
The following tests will be performed at the baseline visitin all patients.

- Medical history, including all concomitant diseases
- Review diagnosis of aplastic anemia, including subclassification
- Physical examination, including review of systems
- Review of signs and symptoms of AA (including infections)
- Hematology (WBC with complete differential, platelets, reticulocytes, hemoglobin) within 2 week prior enrollment
- Past history of packed red blood cells (PRBC) and platelet transfusions
- Bone marrow aspirate, including:
  - Cytology study
  - Flow cytometry study
  - Karyotype study (centralized)
  - Molecular studies (for research purpose only: sample to be centralized)
- Bone marrow trephine biopsy
- Peripheral blood immunophenotyping looking for:
  - Expression of glycosylphosphatidylinositol anchored proteins for screening of a PNH clone on erythrocytes, neutrophils, monocytes and lymphocytes
  - Analysis of lymphocyte subsets (CD3+, CD4+, CD8+, CD56+, CD19+)
  - Additional immunologic studies including study of activation and effector markers (Th1/Tc1, Th2/Tc2, Th17, Tregs, T naïve, T central memory, T effector memory, T effector) (for research purpose only: sample to be centralized)
- Chromosomal breakage test for all subjects <20 years of age and >20 years of age suspicious for constitutional aplastic anemia (i.e. Fanconi's Anemia or Dyskeratosis Congenita)
- Complete screening for hepatic, cardiac and renal function (including serum creatinine, BUN, bilirubin, LDH, AST, ALT, total proteins, albumin, Na, K)
- Telomere length (centralized)
- Quality of life questionnaire (EORTC QLQ-C30)[3]

[3] The QoL questionnaire will be administered to the patient before the visit, and, according to standard guidelines, it will be filled independently from the treating physician to avoid biased information.

- Review all records to be included in CRF
    - Blood transfusions
    - Clinical infections, including type, duration, treatment and outcome
    - Adverse effects
    - Signs and symptoms of serum-sickness
- Concomitant medications
- Pregnancy test (HCG) in women of child bearing potential
- Cataract check up

More information about the additional tests performed at the central lab are provided in the Lab manual (Appendix 8).

7.2.4.2 Follow Up visits

See flowchart (appendix 2)

7.2.4.3 Research Samples

In addition to the routine assessments and tests that are done during the baseline and follow up visits (appendix 2), additional procedures and samples will be taken purely for future research purposes (these are unrelated to the RACE study and will not be analysed within the RACE study):

Visit	Procedure	Tests
Baseline	Bone Marrow Aspirate *This is a standard procedure but extra sample will be taken for research purposes. In some cases it may be an additional procedure if a clinical sample was taken within 30 days of registration.*	Molecular studies
visit 12 & 22	Bone Marrow Aspirate *This is a standard procedure but extra sample will be taken for research purposes*	Molecular studies
Baseline, visit 12 & 22	Blood Sample *This is a standard procedure but extra sample will be taken for research purposes*	Immunophenotype & Telomere length

Research samples taken from adults (patients aged =>18 years of age) will be sent to the Central Tissue Bank in the UK. Research samples in minors (<18years of age) can be collected and stored at local institutions / tissue banks, providing they follow their local regulations for human tissue collection and storage.

Patients will be asked to sign a second specific consent form in addition to the RACE trial consent form for the collection of the additional samples. Although the samples are being taken from patients in the RACE trial, they are being stored at the King's tissue bank for future research which is separate and not part of the RACE clinical trial. Instead the samples will be part of a future research study that is going to be funded separately.

8. Trial Medication

Eltrombopag is the IMP in this clinical trial, and it will be provided by the company Novartis for the entire duration of this trial. EBMT or Novartis will not provide the drug if the trial has ended (whether prematurely or planned).
ATGAM® (hATG) is a NIMP in this clinical trial and it will be provided by the company Pfizer Inc. (Pfizer) for the entire duration of this trial. When the trial has ended, either planned or prematurely, Pfizer will no longer provide ATGAM to participating institutes.
The other agent, Cyclosporine A is considered standard treatment and the participating sites will provide all the medications according to local practice.

8.1 Trial Medication Description

Described in appendix 3

8.1.1 Eltrombopag

Patients will receive eltrombopag orally at the dose of 150 mg daily, as 50 mg tablets, starting from day 14 (after starting ATGAM).
A 50% dose reduction (50 mg + 100mg eltrombopag on alternating days) is recommended for patients of East Asian heritage (i.e., Japanese, Chinese, Taiwanese and Korean).[4] Allow at least a 4-hour interval between eltrombopag and other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium fortified juices), or supplements containing polyvalent cations such as iron, calcium, aluminium, magnesium, selenium, and zinc.
No dose adjustment is necessary in patients with renal impairment.[5] Eltrombopag will not be used in patients with hepatic impairment, which are excluded from this study (see exclusion criteria).[6]

Treatment will be continued at least up to 3 months (75 days of treatment), and then adjusted according to hematological response (see below).
Dose delay or dosing interruptions: eltrombopag dose may be interrupted when clinically indicated at the discretion of the investigator. Interruptions will not be reported as deviations; however when the interruption is consequence to a serious adverse event, the interruption will be included in the report.

[4] A 50% reduced dosing for subjects of fully (both parents) East Asian heritage (i.e., Japanese, Chinese, Taiwanese and Korean) is recommended because plasma eltrombopag AUC(0-τ) concentrations were approximately 80% higher in healthy Japanese subjects compared to non-Japanese healthy subjects who were predominantly Caucasian. Similarly, in patients with ITP, plasma eltrombopag exposure was approximately 70% higher in East Asian subjects as compared to non–East Asian subjects.
[5] Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis.
[6] Eltrombopag should not be used in patients with hepatic impairment (i.e. mild, moderate or severe hepatic impairment (Child-Pugh score ≥5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily.

8.1.1.1 Interaction of eltrombopag with other medicinal products and food

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors
In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103 % (90 % CI: 82 %, 126 %) and $AUC_{0-\infty}$ 55 % (90 % CI: 42 %, 69 %). Interactions are also expected with other HMG-CoA reductase inhibitors, including pravastatin, simvastatin and lovastatin, however, clinically significant interactions are not expected between eltrombopag and atorvastatin or fluvastatin. When co‑administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin side effects should be undertaken.

OATP1B1 and BCRP substrates
Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution.

Cytochrome P450 substrates
In studies utilizing human liver microsomes, eltrombopag (up to 100 µM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered.

Effects of other medicinal products on eltrombopag

Polyvalent cations (Chelation)
Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70 % (90 % CI: 64 %, 76 %) and C_{max} y 70 % (90 % CI: 62 %, 76 %). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours apart from eltrombopag dosing to avoid significant reduction in eltrombopag absorption due to chelation.

Food interaction
Administration of a single 50 mg-dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{0-\infty}$ by 59 % (90 % CI: 54 %, 64 %) and C_{max} by 65 % (90 % CI: 59 %, 70 %). Food low in calcium [< 50 mg calcium] including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma

eltrombopag exposure, regardless of calorie and fat content (see section on eltrombopag administration).

Lopinavir/ritonavir
Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag.[7] However, no patient in this study is expected to receive concomitant lopinavir/ritonavir.

8.1.1.2 Continuation of eltrombopag treatment based on 3 month hematological response

The extension of treatment with eltrombopag up to 6 months is based on hematological response at 3 months.

- Eltrombopag will be discontinued in all patients achieving complete response at 3 months
  - For these patients, re-introduction of eltrombopag is allowed in case of relapse, as described below;
- Eltrombopag will be continued up to 6 months, at the same dose, in:
  - Patients achieving partial response at 3 months;
  - Patients with no hematological response at 3 months.

8.1.1.3 Re-introduction of eltrombopag

For patients achieving hematological response (either complete or partial) who have discontinued eltrombopag, the agent can be re-introduced in case of relapse (see paragraph 9.3) or lack of robustness of hematological response occurring ***within 6 months from discontinuation of eltrombopag***.

The following patients are eligible for re-introduction of eltrombopag within this study:

- Patients in CR at 3 months, who have discontinued eltrombopag as per protocol, with subsequent relapse (defined as no longer meeting the criteria of CR);
- Patients who have discontinued eltrombopag at 6 months as per protocol, and:
  - Were in CR at 6 months, with subsequent relapse (defined as no longer meeting the criteria of CR);
  - Were in PR at 6 months, with subsequent relapse (defined as no longer meeting the criteria of PR);
  - Were in PR at 6 months, with subsequent lack of robustness of their PR, defined as follows (any of these):
    - Drop in Hb >2 gr/dL (with Hb <10 gr/dL);
    - Drop >50% in ANC (with ANC <1,000/µL);
    - Drop >50% in Plt count (with Plt <50,000/µL).

In all these circumstances the second course of eltrombopag treatment will be started at the same dose of 150 mg/day, and will be continued for 3 months in case of complete response at

[7] A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17 % (90 % CI: 6.6 %, 26.6 %). Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

3 months from re-introduction, or up to 6 months. After these additional 6 months of treatment, eltrombopag may be continued outside the protocol by the physician in charge of the patients but won't be furnished anymore by Novartis. Patients with transient falls in blood counts secondary to infectious complication or any other medical conditions do not qualify for re-introduction of eltrombopag. Similarly, patients with late relapses (>6 months from eltrombopag discontinuation), at time of CsA tapering or discontinuation, do not qualify for re-introduction of eltrombopag within this study.

8.1.2 Horse ATG (ATGAM)

Patients will receive horse-ATG (ATGAM) for 4 consecutive days (days 1-4), at the dose of 40 mg/kg/day, as a i.v. infusion lasting 12-18 hours. As prevention of ATGAM-related side effects, including serum sickness, corticosteroids will be administered at the dose of 1 mg/kg/day (either intravenously or orally) for at least 7 days (see below) and then tapered and stopped within 2-3 weeks post treatment. A pre-medication with paracetamol (e.g. 1000 mg) and/or anti-histaminic medications (e.g. clorpheniramine 10 mg) are allowed as well.

For obese patients ATGAM will be dosed according to average between 1.3 x IBW and actual weight.

Obesity is defined as any weight above 1.3 x IBW (BMI will not be used).

IBW calculation can be found on: http://www.manuelsweb.com/IBW.htm

IBW
Estimated ideal body weight in (kg)
Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet

In case the final weight used for dosing is > 100 kg, the infusion volume has to be increased > 1 l.

8.1.2.1 Interaction of ATGAM with other medicinal products and food

Effects of ATGAM on other medicinal products

Dextrose injection
Dilution of ATGAM in dextrose injection, USP, is not recommended, as low salt concentrations may result in precipitation.

Highly acidic infusion solutions
The use of highly acidic infusion solutions is not recommended because of possible physical instability over time.

Effects of other medicinal products on ATGAM

Corticosteroids and other Immunosuppressants
When the dose of corticosteroids and other immunosuppressants is being reduced, some previously masked reactions to ATGAM may appear. Under these circumstances, observe patients especially carefully during therapy with ATGAM.

8.1.3 Cyclosporine A

Patients will receive oral cyclosporin starting on day 1 of treatment at the dose of 5 mg/kg orally, and then adjusted on blood levels (150-250 ng/mL using the monoclonal assay, 200-400 ng/mL using the polyclonal assay). Treatment will be continued for at least 12 months, and then slowly tapered according to clinical conditions (see below).

8.1.3.1 Interaction of Cyclosporine A with other medicinal products and food

Effects of Cyclosporine A on other medicinal products

Cyclosporine A is an inhibitor of CYP3A4 and of multiple drug efflux transporters and may increase plasma concentrations of co-medications that are substrates of CYP3A4, P-glycoprotein, or organic anion transporter proteins.

Cyclosporine A may reduce the clearance of:

Digoxin

Severe digitalis toxicity has been seen within days of starting cyclosporine A in several patients taking digoxin. If digoxin is used concurrently with cyclosporine A, serum digoxin concentrations should be monitored.

Colchicine

There are reports on the potential of cyclosporine A to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. Concomitant administration of cyclosporine A and colchicine results in significant increases in colchicine plasma concentrations. If colchicine is used concurrently with cyclosporine A, a reduction in the dosage of colchicine is recommended.

HMG-CoA reductase inhibitors (statins)

Literature and postmarketing cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of cyclosporine A with lovastatin, simvastatin, atorvastatin, pravastatin, and rarely, fluvastatin. When concurrently administered with cyclosporine A, the dosage of these statins should be reduced according to label recommendations. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis.

Repaglinide

Cyclosporine A may increase the plasma concentrations of repaglinide and thereby increase the risk of hypoglycemia. In 12 healthy male subjects who received two doses of 100 mg cyclosporine A capsule orally 12 hours apart with a single dose of 0.25 mg repaglinide tablet (one half of a 0.5 mg tablet) orally 13 hours after the cyclosporine A initial dose, the repaglinide mean Cmax and AUC were increased 1.8 fold (range: 0.6 to 3.7 fold) and 2.4 fold (range 1.2 to 5.3 fold), respectively. Close monitoring of blood glucose level is advisable for a patient taking cyclosporine A and repaglinide concomitantly.

Ambrisentan

Co-administration of ambrisentan (5 mg daily) and cyclosporine A (100 to 150 mg twice daily initially, then dosing to achieve Cmin 150 to 200 ng/mL) for 8 days in healthy subjects resulted mean increases in ambrisentan AUC and Cmax of approximately 2-fold and 1.5-fold, respectively, compared to ambrisentan alone. When coadministering ambrisentan with

cyclosporine A, the ambrisentan dose should not be titrated to the recommended maximum daily dose.

Anthracycline antibiotics
High doses of cyclosporine A (e.g., at starting intravenous dose of 16 mg/kg/day) may increase the exposure to anthracycline antibiotics (e.g., doxorubicin, mitoxantrone, daunorubicin) in cancer patients.

Aliskiren
Cyclosporine A alters the pharmacokinetics of aliskiren, a substrate of P-glycoprotein and CYP3A4. In 14 healthy subjects who received concomitantly single doses of cyclosporine A (200 mg) and reduced dose aliskiren (75 mg), the mean Cmax of aliskiren was increased by approximately 2.5-fold (90% CI: 1.96 to 3.17) and the mean AUC by approximately 4.3 fold (90% CI: 3.52 to 5.21), compared to when these subjects received aliskiren alone. The concomitant administration of aliskiren with cyclosporine A prolonged the median aliskiren elimination half-life (26 hours versus 43 to 45 hours) and the Tmax (0.5 hours versus 1.5 to 2.0 hours). The mean AUC and Cmax of cyclosporine A were comparable toreported literature values. Coadministration of cyclosporine A and aliskiren in these subjects also resulted in an increase in the number and/or intensity of adverse events, mainly headache, hot flush, nausea, vomiting, and somnolence. The coadministration of cyclosporine A with aliskiren is not recommended.

Bosentan
In healthy subjects, co-administration of bosentan and cyclosporine A resulted in time-dependent mean increases in dose-normalized bosentan trough concentrations (i.e., approximately 21-fold on day 1 and 2-fold on day 8 (steady state)) compared to when bosentan was given alone as a single dose on day 1. (See also Effect of Drugs and Other Agents on Cyclosporine A Pharmacokinetics and/or Safety) Co-administration of cyclosporine A with bosentan should be avoided.

Dabigatran
The effect of cyclosporine A on dabigatran concentrations had not been formally studied. Concomitant administration of dabigatran and cyclosporine A may result in increased plasma dabigatran concentrations due to the P-gp inhibitory activity of cyclosporine A. Coadministration of cyclosporine A with dabigatran should be avoided.

Potassium sparing diuretics
Cyclosporine A should not be used with potassium-sparing diuretics because hyperkalemia can occur. Caution is also required when cyclosporine A is co-administered with potassium-sparing drugs (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists), potassium-containing drugs as well as in patients on a potassium-rich diet. Control of potassium levels in these situations is advisable.

Nonsteroidal Anti-inflammatory Drug (NSAID) Interactions
Clinical status and serum creatinine should be closely monitored when cyclosporine A is used with NSAIDs in rheumatoid arthritis patients. Pharmacodynamic interactions have been reported to occur between cyclosporine A and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by 99mTc-diethylenetriaminepentaacetic acid (DTPA) and (p-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood concentrations of cyclosporine A, it has been associated with approximate doubling of

diclofenac blood levels and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

Methotrexate Interaction
Preliminary data indicate that when methotrexate and cyclosporine A were coadministered to rheumatoid arthritis patients (N=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine A concentrations do not appear to have been altered (N=6).

Sirolimus
Elevations in serum creatinine were observed in studies using sirolimus in combination with full-dose cyclosporine A. This effect is often reversible with cyclosporine A dose reduction. Simultaneous coadministration of cyclosporine A significantly increases blood levels of sirolimus. To minimize increases in sirolimus blood concentrations, it is recommended that sirolimus be given 4 hours after cyclosporine A administration.

Nifedipine
Frequent gingival hyperplasia when nifedipine is given concurrently with cyclosporine A has been reported. The concomitant use of nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side effect of cyclosporine A.

Methylprednisolone
Convulsions when high dose methylprednisolone is given concomitantly with cyclosporine A have been reported.

Other Immunosuppressive Drugs and Agents
Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression.

Effects of other medicinal products on Cyclosporine A

Drugs That May Potentiate Renal Dysfunction
Concomitant use of nonsteroidal anti-inflammatory drugs with cyclosporine A, particularly in the setting of dehydration, may potentiate renal dysfunction. Caution should be exercised when using other drugs which are known to impair renal function.

Grapefruit juice
Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine A, thus should be avoided.

Bosentan
Co-administration of bosentan (250 to 1000 mg every 12 hours based on tolerability) and Cyclosporine A (300 mg every 12 hours for 2 days then dosing to achieve a Cmin of 200 to 250 ng/mL) for 7 days in healthy subjects resulted in decreases in the cyclosporine A mean dose-normalized AUC, Cmax, and trough concentration of approximately 50%, 30% and

60%, respectively, compared to when cyclosporine A was given alone. Co-administration of cyclosporine A with bosentan should be avoided.

Boceprevir
Co-administration of boceprevir (800 mg three times daily for 7 days) and cyclosporine A (100 mg single dose) in healthy subjects resulted in increases in the mean AUC and Cmax of cyclosporine A approximately 2.7-fold and 2-fold, respectively, compared to when cyclosporine A was given alone.

Telaprevir
Co-administration of telaprevir (750 mg every 8 hours for 11 days) with cyclosporine A (10 mg on day 8) in healthy subjects resulted in increases in the mean dose-normalized AUC and Cmax of cyclosporine A approximately 4.5-fold and 1.3-fold, respectively, compared to when cyclosporine A (100 mg single dose) was given alone.

St. John's Wort
There have been reports of a serious drug interaction between cyclosporine A and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine A, resulting in sub therapeutic levels, rejection of transplanted organs, and graft loss.

Rifabutin
Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine A has not been studied. Care should be exercised when these two drugs are administered concomitantly.

8.1.4 Corticosteroids
Corticosteroids will be used as premedication and prevention of heterologous serum side effects, as well as immunosuppressive agents. Corticosteroids will be administered as Methylprednisolone at the dose of 1 mg/kg (or Betamethasone at equivalent dose), intravenously or orally, from day 1 to 4. Corticosteroids may be increased up to 2 mg/kg, if clinically needed. After day 4, corticosteroids will be continued at least until day 7 and then tapered off within 2-3 weeks post treatment, by a half-dose reduction every 2-4 days.

8.2 Dose Rationale
Eltrombopag has proven beneficial for the treatment of refractory AA, at the dose of 150 mg per day, orally. [28]

8.3 Side Effects
Main side effects of eltrombopag, ATGAM and Cyclosporine A are described below. However, we strongly encourage physicians to refer to the investigator brochures (appendix 4).

8.3.1 Adverse events seen during eltrombopag use

Some adverse events have been previously reported during the use of eltrombopag; they are summarized below.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function. In clinical studies with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed.

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥ 3x the upper limit of normal [ULN]) and are:

• progressive, or

• persistent for ≥4 weeks, or

• accompanied by increased direct bilirubin, or

• accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Excerise caution when administering eltrombopag to patients with hepatic disease (see section on eltrombopag administration)

Thrombotic/Thromboembolic complications

Platelet counts above the normal range present a theoretical risk of thrombotic/thromboembolic complications. In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels. The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology; in these patients, prophylaxis of thromboembolic events is allowed at judge of the investigator, with the agents that he will find more appropriate.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 79 patients with chronic liver disease (37 mild hepatic impairment, 40 with moderate hepatic impairment, and 2 with severe hepatic impairment). Based on estimates from the population pharmacokinetic analysis, patients with hepatic impairment had higher plasma eltrombopag AUC(0-τ) values as compared to healthy volunteers, and AUC(0-τ) increased with increasing Child-Pugh score. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 87 % to 110 % higher plasma eltrombopag AUC(0-τ) values and patients with moderate hepatic impairment had approximately 141 % to 240 % higher plasma eltrombopag AUC(0-τ) values.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section on eltrombopag administration).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur upon discontinuation of treatment with eltrombopag, at least in ITP patients. Following discontinuation of eltrombopag, platelet counts may return to baseline levels within 2 weeks in the majority of ITP patients, which increase the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. In this study for AA, eltrombopag will be discontinued per protocol as described above; if treatment with eltrombopag is discontinued, treatment with eltrombopag may be restarted within the protocol as described above. Additional medical management for bleeding may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts should be monitored weekly for 4 weeks following discontinuation of eltrombopag.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibers within the bone marrow. The relevance of this finding, as with other TPO-R agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, complete blood count (CBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Malignancies and progression of malignancies
TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

Cataracts
Cataracts were observed in toxicology studies of eltrombopag in rodents. The clinical relevance of this finding is unknown. Routine monitoring of patients for cataracts is recommended.

Loss of response to eltrombopag
A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

8.3.2 Adverse events seen during ATGAM use
During > 5 years of post approval marketing experience, the frequency of adverse reactions in voluntarily reported cases is as follows: fever 51%; chills 16%; thrombocytopenia 30%; leukopenia 14%; rashes 27%; systemic infection 13%. Events reported in 5% to 10% of reported cases include abnormal renal function tests; serum sickness-like symptoms; dyspnea/apnea; arthralgia; chest, back, or flank pain; diarrhea and nausea and/or vomiting. Events reported with a frequency of less than 5% include: hypertension, Herpes Simplex infection, pain, swelling or redness at infusion site, eosinophilia, headache, myalgias, or leg pains, hypotension, anaphylaxis, tachycardia, edema, localized infection, malaise, seizures, GI bleeding or perforation, deep vein thrombosis, sore
mouth/throat, hyperglycemia, acute renal failure, abnormal liver function tests, confusion or disorientation, cough, neutropenia or granulocytopenia, anemia, thrombophlebitis, dizziness, epigastric or stomach pain, lymphadenopathy, pulmonary edema or congestive heart failure, abdominal pain, nosebleed, vasculitis, aplasia or pancytopenia, abnormal involuntary movement or tremor, rigidity, sweating, laryngospasm/edema, hemolysis or hemolytic anemia, viral hepatitis, faintness, enlarged or ruptured kidney, paresthesias, and renal artery thrombosis.

The recommended management for some of the adverse reactions that could occur with treatment with ATGAM follows:

Anaphylaxis and allergic reactions
Anaphylaxis is uncommon, but may occur at any time during therapy with ATGAM. More frequently, allergic reaction include skin rash, fever and chills. Prophylactic administration of corticosteroids and/or anti-histamine may decrease the frequency of this reaction.

Hemolysis
Can usually be detected only in the laboratory. Clinically significant hemolysis has been reported rarely. Appropriate treatment of hemolysis may include transfusion of erythrocytes; if necessary, administer intravenous mannitol, furosemide, sodium bicarbonate, and fluids. Severe and unremitting hemolysis may require discontinuation of therapy with ATGAM.

Respiratory distress
May indicate an anaphylactoid reaction. Discontinue infusion of ATGAM. If distress persists, administer an antihistamine, epinephrine, corticosteroids, or some combination of the three.

Pain in chest, flank, or back
May indicate anaphylaxis or hemolysis. Treatment is that indicated above for those conditions.

Hypotension
May indicate anaphylaxis. Stop infusion of ATGAM and stabilize blood pressure with pressors if necessary.

Chills and fever
Occur frequently in patients receiving ATGAM. ATGAM may release endogenous leukocyte pyrogens. Prophylactic and/or therapeutic administration of antihistamines, antipyretics, or corticosteroids generally controls this reaction.

Chemical phlebitis
Can be caused by infusion of ATGAM through peripheral veins. This can often be avoided by administering the infusion solution into a high-flow vein. A subcutaneous arterialized vein produced by a Brescia fistula is also a useful administration site.

Itching and erythema
Probably result from the effect of ATGAM on blood elements. Antihistamines generally control the symptoms.

Serum-sickness like symptoms
In aplastic anemia patients have been treated with oral or IV corticosteroids.
Resolution of symptoms has generally been prompt and long-term sequelae have not been observed. Prophylactic administration of corticosteroids may decrease the frequency of this reaction.

Hepatic and Renal Function tests
In patients with aplastic anemia and other hematologic abnormalities who have received ATGAM , abnormal tests of liver function (SGOT, SGPT, alkaline phosphatase) and renal function (serum creatinine) have been observed.

8.3.3 Adverse events seen during Cyclosporine A use

Hypertension
Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Glomerular Capillary Thrombosis
Glomerular capillary thrombosis has been found in patients treated with cyclosporine A and may progress to graft failure. The pathologic changes resemble those seen in the hemolytic-uremic syndrome and include thrombosis of the renal microvasculature, with platelet-fibrin thrombi occluding glomerular capillaries and afferent arterioles, microangiopathic hemolytic

anemia, thrombocytopenia, and decreased renal function. Similar findings have been observed when other immunosuppressives have been employed post transplantation.

Hypomagnesemia
Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine A therapy. Although magnesium-depletion studies in normal subjects suggest that hypomagnesemia is associated with neurologic disorders, multiple factors, including hypertension, high-dose methylprednisolone, hypocholesterolemia, and nephrotoxicity associated with high plasma concentrations of cyclosporine A appear to be related to the neurological manifestations of cyclosporine A toxicity.

The following reactions occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart, and liver transplants: *Renal dysfunction, hirsutism, acne, tremor, convulsions, headache, gum hyperplasia, diarrhea, nausea, hepatotoxicity abdominal discomfort, paresthesia, flushing, leukopenia, lymphoma, sinusitis, gynecomastia.*

The following reactions occurred in 2% or less of patients: *allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus*

The following reactions occurred rarely: *anxiety, chest pain, constipation, depression, hair breaking, hematuria, joint pain, lethargy, mouth sores, myocardial infarction, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, weight loss.*

8.4 Labelling, Packaging, Handling and Storage of IMP and NIMP
Sites will receive labeled Eltrombopag and labeled ATGAM. There is no special handling and storage requirement for the IMP. For the NIMP, storage and shipment at 2-8 °C is required.

8.5 IMP and NIMP Accountability
Accountability for the trial IMP and NIMP at the trial site is the responsibility of the PI. The PI may delegate the responsibility of receipt, dispensing and destruction, as applicable, to the local pharmacist, or other appropriate personnel, however, this must be written in the site's delegation of authority log.

The PI will ensure that the trial drug is used only in accordance with this protocol.

Drug accountability records (logs) that are provided as part of the trials manual or sites own logs, maintained by the trial site, should indicate:

- IMP stored at site (tracking number, lot number & batch number)
- NIMP stored at site (tracking number, lot number & batch number)
- use by each patient (including IMP/NIMP name, lot number, batch number & tracking number)
- disposal of unused IMP/NIMP or destruction of used IMP/NIMP (date, lot number, batch number & tracking numbers)

8.6 Dose Modifications and Delay

8.6.1 Eltrombopag stopping rules

- Eltrombopag will be immediately discontinued at any time during the treatment in case of thrombocytosis with Plt count >400,000/μL.
- In these patients, if still prescribed as per protocol, eltrombopag will be re-introduced when Plt count <150,000/μL. Eltrombopag will be re-introduced starting with a half-dose (50 mg and 100mg from a day to another), and possibly escalated to 150 mg daily in case of Plt count remains <150,000/μL.

8.6.2 ATGAM stopping rules

- ATGAM administration will be immediately discontinued when a patient has a severe systemic reaction (e.g. anaphylactic reaction). Sign or symptoms of serum sickness or other allergic reaction should be managed without stopping ATGAM (i.e., increasing steroid dose and extending the duration of ATGAM infusion).

8.6.3 Cyclosporin A dose adjustment

The drug-drug interaction potential between eltrombopag and CsA is unknown. Both CsA and eltrombopag are inhibitors of OATP and BCRP drug transporters, and eltrombopag is a substrate of BCRP in vitro. It is not known if the combination will result in any PK changes to either drug.

Patients will be monitored for signs of CsA toxicity during the study, and therapeutic drug monitoring can be instituted as required. Cyclosporin A levels should be adjusted to maintain concentration of 200-400ng/mL (using a polyclonal assay) or 150-250 ng/mL (using a monoclonal assay). Dose may be decreased at any time in case of CsA-related adverse effects, such as hypertension, increased serum creatinine, peripheral neuropathy; dose reduction should be targeted to the higher dose effective in controlling abnormalities. In case of persisting and clinically significant abnormalities, the investigator may decide to discontinue the drug.

Rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, or malignancies should not receive Cyclosporine A.

Psoriasis patients who are treated with Neoral should not receive concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar or radiation therapy. Psoriasis patients with abnormal renal function, uncontrolled hypertension, or malignancies should not receive Cyclosporine A.

Nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to rejection episodes, care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to cyclosporine A dosage reduction.
Due to the potential for additive or synergistic impairment of renal function, caution should be exercised when co-administering Cyclosporine A with other drugs that may impair renal function.

Renal and liver functions will be assessed repeatedly by measurement of serum creatinine,

serum bilirubin, and liver enzymes.

Eltrombopag dosing may be interrupted based on platelet count, reducing the potential impact of an underlying PK interaction (see paragraph 8.6.1: Eltrombopag stopping rules).

8.7 Assessment of Treatment Compliance

Will be checked by the physician in charge (see flowchart appendix 2)

8.8 Post-Trial Arrangement

Eltrombopag will only be provided to trial patients during the trial duration.
Novartis or EBMT will not provide the IMP after the protocol treatment has been completed.

Detailed work instructions will be provided on when eltrombopag and ATGAM will be delivered and how to order resupplies during the protocol duration.

8.9 Concomitant Treatment

Throughout the study the investigator may prescribe any other concomitant medications or treatments deemed necessary to manage concomitant extra-hematological diseases. Drugs potentially interfering with hematopoietic function should be avoided, if possible.

8.9.1 G-CSF

G-CSF will not be used routinely in the patients enrolled in this study; however, its use is allowed in particular clinical conditions which at judge of the investigator may take advantage of G-CSF, such as infectious complications in patients with severe neutropenia.

8.9.2 Antimicrobial and anti-fungal prophylaxis

All patients will receive antimicrobial and anti-fungal prophylaxis according to their institution's standard practice. In particular, anti-bacterial and anti-fungal agents have to be administered whenever throughout the study ANC $<0.5 \times 10^9$/L. An anti-fungal agent active on mould infections (i.e., invasive fungal infections) should be included (e.g., posaconazole or voriconazole). Prophylaxis against *Pneumocystis jirovecii)* should be performed by trimetoprim-sulphamethoxazole bidaily thrice weekly, until CD4+ lymphocytes exceed 250/µL.

8.9.3 Anti-viral and anti-CMV prophylaxis

All patients should receive anti-viral prophylaxis by daily valacyclovir, orally. Anti-CMV prophylaxis will not be administered routinely. However, monitoring of CMV viremia and subsequent pre-emptive treatment by valganciclovir or other agents is allowed.

8.9.4 Transfusion support

Red blood cell and platelet transfusions will be given according to standard policy at investigator's discretion. As general rule, red cell transfusion should be given to maintain hemoglobin level >8gr/dL, or in case of clinically significant symptoms; platelet transfusions should been given when platelets $<10 \times 10^9$/L or regardless platelet count in case of bleeding episodes. All red cell and platelet transfusions should be irradiated for life during (to prevent transfusion associated GVHD)

8.10 Excluded medications

There is no medicine for Eltrombopag and ATGAM which is prohibited per protocol in this study, provided that it is indicated according to the clinical judgement of the investigator.
Excluded medications for Cyclosporine A, due to serious drug interactions are: *St. John's Wort* (reduction in the blood concentrations of cyclosporine A), *Stiripentol* (inhibits CYP3A4 metabolism), *Bosentan* (decreases in the cyclosporine A mean dose-normalized AUC and C_{max}) and *Rosuvastatin* (Cyclosporine A causes a 7-fold increase in hepatic take up from Rosuvastatin).

8.11 Rescue medications for treatment failures

Patients who do not achieve complete or partial response at 6 months from randomisation are considered treatment failures, and will be eligible for additional treatments. Second-line treatment will be chosen at discretion of the investigator, and it will not be prescribed as per protocol. Indeed, in case of no response at 6 months a patient may exit from the study (see paragraph 6.3: early withdrawal of a patient) to receive the most appropriate second-line treatment (including bone marrow transplantation), at judge of the investigator. For these non-responder patients, bone marrow transplantation should be considered, according to established EBMT guidelines (age <= 65 years, 10/10 HLA identical unrelated donor).

However, some patients may be eligible to receive a rescue treatment within this study (see below).

8.11.1 Open-label eltrombopag treatment

The following patients will be eligible for open-label eltrombopag treatment:

- Patients randomized in the control arm (ATGAM + CsA without eltrombopag) who:
  - Show no hematological response at 6 months;
  - Do not demonstrate any clonal evolution at 6 months (as confirmed by bone marrow karyotyping);

(See section 12 for related methodological issues)

All these patients are eligible to receive a course of eltrombopag; at judge of the investigator, eltrombopag will be offered as either:

- Single agent treatment;
- Eltrombopag associated with second course of immunosuppression (without any restriction concerning the anti-lymphocyte agent).

Eltrombopag treatment will be started at the same dose of 150 mg/day, and will be continued for 3 months in case of complete response at 3 months from re-introduction, or up to 6 months. After these 6 months of treatment, eltrombopag will be discontinued in any case independently from hematological response; the patients will continue the follow up, as prescribed per protocol (see paragraph 7.2).

8.12 Tapering and discontinuation of treatment

All patients will be treated according to the assigned treatment and dose adjustments described above for at least 1 year; starting from this time point patients showing stable response (at least 30 days) will taper their treatment according to established guidelines [32]. Cyclosporin A may be discontinued after slow tapering in the next 6-12 months (about 10%

per month); thus, patients should remain on CsA treatment for at least 18 months before withdrawal. In case of decrease on blood counts, the investigator may re-institute or re-escalate CsA therapy at his/her discretion.

9. Assessment of Efficacy

9.1 Definition of hematological response

Hematological response will be assessed at 3, 6, 12, 18 and 24 months from treatment starting; hematological response has to be demonstrated by a minimum of 3 determinations over a period of at least 2 weeks, starting at least 2 week after last transfusion. The first time patients will obtain remission will be considered as timepoint. The investigator will classify hematological response into complete, partial and no response as follows, according to NIH criteria [17].

For the main endpoint (section 9.6.1) a valid response has to be measured between month 3 minus 10 days and month 3 plus 10 days; in case of more than one measurement available in this time period, the best response will be taken.

9.1.1 Complete response (CR)

Patients will be considered as complete responders (CR) if achieving all the following:

- Following peripheral blood counts:
  - Hemoglobin >10 gr/dL
  - Absolute neutrophils >1.0 x 10^9/L
  - Platelets >100 x 10^9/L
- No evidence of clonal evolution (by marrow cytogenetic and flow cytometry, see below 9.5)

9.1.2 Partial response (PR)

Patients will be considered as partial responders (PR) if achieving **all** the following:

- No longer meet criteria for diagnosis of SAA
- Transfusion independence (defined as no need of any PRBC or platelet transfusion)
- Peripheral blood counts:
  - Hemoglobin >8 gr/dL
  - Absolute neutrophils >0.5 x 10^9/L
  - Platelets >20 x 10^9/L

9.1.3 No response (NR)

Any patient not meeting any of the response criteria defined above will be classified as a non-responder.

9.2 Definition of CsA-dependent and CsA-independent hematological response

Starting from day 365 from the beginning of treatment, responses will be also classified according to the possibility to taper off cyclosporin A. The same classification described above will be utilized, with the addition of the prefix CsA independent (CI) or CsA dependent (CD). For instance, complete responders at day 365 will subsequently classified at the following visit as CD-CR or CI-CR if they still require or do not require drugs to sustain response, respectively. Based on the guidelines [32] which suggest a monthly 10% tapering of therapeutic CsA, a patient will qualify for CI-CR if he is able to achieve a CsA dose reduction of at least 25% at 15 months, 50% at 18 months, 75% at 21 months and 100% (CsA discontinuation) at 24 months, providing no hematological relapse has occurred.

9.3 Definition clinical relapse (Cl-Rel)

Clinical relapse is considered as the occurrence of any of the following event in a patient who had showed a hematological response (CR or PR):

- meeting again the criteria for SAA
- requirement of transfusion support (if not due to independent medical conditions)
- decrease in any of the peripheral blood counts as follows
  - Decrease to less than 50% of the medium sustained count during remission if:
    - absolute neutrophils < 1.0 x 10^9/L
    - platelets <50 x 10^9/L

  Or

  - In any case if:
    - absolute neutrophils < 0.5 x 10^9/L
    - platelets <20 x 10^9/L

To qualify a relapse peripheral blood count decrease has to be

- not due to any independent concomitant medical condition
- demonstrated for a minimum of 3 determination over a period of 2 weeks
- not responding to re-introduction of low dose cyclosporin A

9.4 Definition of treatment failure

Any of following events are considered as treatment failure:

- No response at 6 months from treatment starting
- Clinical relapse
- Requirement of further (in addition to ATGAM and CyA) immunosuppressive treatment to sustain response, anytime

9.5 Definition of clonal evolution

Standard karyotype and FISH for chromosomes 7, 8 and 5 will be performed at 3, 6, 12, 18 and 24 months.

Clonal evolution is defined as any of the following [30]:

- Diagnosis of acute leukemia
- Diagnosis of MDS, according to established criteria (by morphology, flow cytometry and karyotype) as defined by WHO 2008 criteria [30]. *The demonstration of a cytogenetic abnormality by itself does not qualify for the diagnosis of MDS, provided that it is not included in the list in Appendix 1*

- Occurrence of any cytogenetic abnormality (in absence of other criteria qualifying for the diagnosis of MDS) which can be demonstrated in at least 10% of bone marrow cells in at least two bone marrow specimens drawn with an interval of at least 3 months.

9.6 Statistical criteria and definition of endpoints

9.6.1 Response rate (main endpoint)

The primary analysis will evaluate complete response rate at 3 months from randomisation in an intent-to-treat (ITT) population containing all randomized patients. A valid response has to be measured at month 3 plus and minus 10 days; in case of more than one measurement in this period, the best response will be taken. Death before 3 months will be considered a failure (i.e. no response). We expect a very limited number of cases alive at 3 months and non-evaluable, or withdrawals before 3 months; these cases will be excluded from the primary analysis, and sensitivity analyses will be performed to check the validity of conclusions.

9.6.2 Time to first response

Time to first response is defined as time from randomisation until the first assessment of partial or complete response confirmed in at least 3 consecutive determinations; it will be described by a cumulative incidence curve, considering as competing event any of the following events occurring prior to response achievement: death for any cause, stem cell transplant (SCT), any new specific AA treatment and clonal evolution (as defined in 9.5) (observations will be censored for patients event-free at last follow-up).

9.6.3 Time to best response

Time to best response is defined as time from randomisation until the date of assessment of the best response (partial or complete) confirmed in at least 3 consecutive determinations; it will be described by a cumulative incidence curve, considering as competing event any of the following events occurring prior to response achievement: death for any cause, stem cell transplant (SCT), any new specific AA treatment and clonal evolution (as defined in 9.5) (observations will be censored for patients event-free at last follow-up).

9.6.4 Time to complete response

Time to complete response is defined as time from randomisation until the date of achievement of complete response confirmed in at least 3 consecutive determinations; it will be described by a cumulative incidence curve, considering as competing event any of the following events occurring prior to response achievement: death for any cause, stem cell transplant (SCT), any new specific AA treatment and clonal evolution (as defined in 9.5).

9.6.5 Overall survival (OS)

Overall survival is defined as time from randomisation until death; observations will be censored for patient alive at last follow-up.

9.6.6 Event-free survival (EFS)

Event-free survival is defined as time from randomisation to either relapse, death, treatment failure or clonal evolution (whichever occurs first), censoring observations at last follow-up for patients alive event-free.

9.6.7 Relapse incidence (RI)

Time to relapse is defined as time from first hematological response (complete or partial) until relapse, death without prior relapse, SCT and clonal evolution (as defined in 9.5) will be considered competing events.

9.6.8 Clonal evolution, PNH and immunosuppression discontinuation

Incidence and time to clonal evolution will be evaluated in a competing risks framework, considering death and SCT before clonal evolution as competing events.
Incidence and time to PNH will be evaluated in a competing risks framework, considering death and SCT before PNH as competing events.

Incidence and time to discontinuation of immunosuppressive therapy will be evaluated in a competing risks framework, considering death and SCT before discontinuation of IS as competing events.

9.6.9 Quality of life

Quality of life will be assessed by the EORTC QLQ-30 questionnaire, included in appendix 6. The 30 questions cover: global health status/QoL, 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, nausea/vomiting, pain) and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties due to treatment or illness). QoL data will be analyzed by mixed models, assessing changes over time and differences between treatment arms; according to standard statistical methods (details will be provided in a separate appendix). For the purpose of this study, QoL assessment will focus on the following nine scales: global health status/QoL, all five functional scales, two symptom scales (fatigue and pain) and one single items (financial difficulties).

9.6.10 Other secondary endpoints

Other secondary endpoints (CsA-independent hematological response at 24 months, Need for transfusions, Need for any supportive care including hospitalization, safety and tolerability) will be described by standard summary statistics (frequency tables for categorical variables, mean with standard deviations and quantiles for continuous variables).

10. Assessment of Safety

A trial specific Safety Monitoring Plan is included in appendix 5. In this trial, safety will be determined through the collection of Adverse Event (AE) data, laboratory tests, etc.
Timepoints are listed in the flowchart (appendix 3).
The reference safety information (RSI) for Eltrombopag is the SmPC. The RSI for ATGAM is the USPI.

10.1 Definitions of Adverse Events

The EU Clinical Trials Directive 2001/20/EC and the UK Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 give the following definitions:

Adverse Event (AE)
Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship with the trial treatment. An AE is therefore described as any unfavourable, noxious and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the trial treatment but also from medication error and use of a medicinal product outside of the terms of marketing authorisation (including misuse and abuse), whether or not related to the trial treatment.

Adverse Reaction (AR)
Any untoward, noxious and unintended response to a trial treatment but also from medication error and uses outside the terms of marketing authorisation (including misuse/abuse of medicinal product) related to any dose administered. A causal relationship between the trial treatment (or medication error, misuse/abuse of medicinal product) and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE)
Any untoward medical occurrence or effect in a patient treated on a trial protocol which does not necessarily have a causal relationship with the trial treatment (or medication error, misuse/abuse of medicinal product), that also, at any dose:

- Results in death
- Is life threatening
- Is a secondary cancer
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in congenital anomaly or birth defect
- Is otherwise medically significant (i.e. all accidental or intentional overdoses whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above)

Suspected Serious Adverse Reaction (SSAR)
This is defined as an adverse reaction, the nature or severity of which is consistent with the known trial treatment information (e.g. Summary of Medicinal Product Characteristics (SmPC), Investigator's Brochure (IB) or Investigator Medicinal Product Dossier (IMPD)).

Suspected Unexpected Serious Adverse Reaction (SUSAR)
This is defined as an adverse reaction, the nature or severity of which is not consistent with the known trial treatment information.
A serious event or reaction is not defined as a SUSAR when:

- it is serious but expected
- it does not fit the definition of an SAE, whether expected or not

10.2 Procedures for Adverse Event Reporting

10.2.1 All Adverse Events

All adverse events that occur between the first trial-related procedure (i.e. screening) until the last follow up visit (or after this date if the investigator feels the event is related to the trial treatment) must be recorded. Those meeting the definition of a serious adverse event (SAE) must be reported using the SAE Report form.
Investigators must record in the Case Report Form (CRF) and the patient notes their opinion concerning details of nature, onset, duration, severity of the SAE and assess any relationship to the investigational medicinal product. Medical terminology and medical diagnosis should always be used to describe any event. Investigators should avoid vague terms such as "sick".

10.2.1.1 Adverse Event Term

The PI (or delegate) must provide an adverse event term (preferred diagnosis as AE term, not symptoms) for each adverse event, preferably using the Short Name as listed in the Common Terminology Criteria for Adverse Events v4.03.0 (CTCAE), available online at: http://ctep.cancer.gov or http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf .

10.2.1.2 Severity

Severity for each adverse event, including any lab abnormality, will be determined by the PI using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) as a guideline, wherever possible. In those cases where the CTCAE criteria do not apply and where there is no accepted alternative grading system e.g. Bearman Scale, severity should be defined according to the following criteria:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities Life threatening: Immediate risk of death from the reaction as it occurred.

10.2.1.3 Causality

Relationship to trial treatment will be determined by the PI as follows:

Not Related	No relationship between the experience and the administration of the trial treatment; related to other etiologies such as concomitant medications or patient's clinical state. The current state of knowledge indicates that the relationship is unlikely
Related	A reaction that follows a plausible temporal sequence from administration of the trial treatment and follows a known response pattern to the suspected treatment. The reaction might also have been produced by the patient's clinical state or other modes of therapy administered to the patient. A reaction that follows a plausible temporal sequence from administration of the trial treatment and follows a known response pattern to the suspected treatment. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient. An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s).

10.2.1.4 Expectedness

An expectedness assessment needs to be conducted for all SAEs by the Sponsor (EBMT CTO) using the SmPC which is the Reference Safety Information (RSI) of eltrombopag and recorded appropriately on the SAE Report form. The RSI is to be used for the purposes of determining expectedness and thus SAE/SUSAR reporting. Expectedness of the event listed in section 4.8 of the RSI within the SmPC, to the investigational medicinal product will be determined as follows:

Expected	The event is listed in the RSI (SmPC) or the trial protocol as expected with the trial treatment or is commonly seen in clinical experience (patient population, dosage)
Unexpected	The event is not listed in the RSI (SmPC) or in the trial protocol, or the severity of the event is greater than that listed in the RSI (SmPC) or the trial protocol (e.g. mild nausea is listed as expected in the RSI (trial protocol but the event is moderate or severe nausea). In assigning expectedness, characteristics of the disease should be taken into account.

10.2.2 Reporting of Serious Adverse Events (SAE)

As Sponsor, the EBMT is responsible for pharmacovigilance. Events defined as serious must be reported by fax to the EBMT CTO using the SAE Report form, **within 24 hours** of

observing or learning of the event. If a copy of the SAE Report form is required, this can be obtained from the Clinical Trial Coordinator.

The following attributes must be assigned when reporting:

- Detailed description of the event
- Adverse event term (see Adverse Event Term section for details 10.2.1.1)
- Seriousness criterion
- Date of onset and outcome
- Severity of the event (see Severity section for details 10.2.1.2)
- Assessment of relatedness to the protocol treatment (see Causality section for definitions 10.2.1.3) and action taken
- Assessment of expectedness for the protocol treatment (see section 10.2.1.4)
- Other suspect concomitant drugs or devices

All SAEs regardless of relationship to investigational product will be collected from the time of informed consent until the end of the end of follow-up period. All SAEs regardless of causality will be collected until the end of the follow-up period.

All SAEs will be followed up until resolution. The investigator will be asked to provide interim and follow-up reports, as necessary, if the SAE has not resolved at the time of initial report.

All deaths occurring on trial must be reported as a SAE in the patient's notes, as an outcome on the SAE form and on the CRFs sent to the EBMT CTO. For all deaths, available autopsy reports (or death certificate if available) should be sent with the notification.

Please note death is the outcome of an SAE it cannot be the AE term.

ALL SAE's must be assessed and signed by the Principal or a Co-Investigator (this must be recorded on the staff delegation log).

Any SAE brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to IMP must be reported to the EBMT CTO during the trial duration.

It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require that the patients should be removed from the treatment. A patient may also voluntarily withdraw from treatment due to what they perceive as an intolerable adverse event. If either of these occurs, it must be made clear if the patient is being withdrawn from the trial or just the trial medication is being stopped.

If the patient is withdrawn or withdraws from the trial they must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition became stable. He or she remains in the trial and is followed through the regular

follow ups for the normal duration of the described participation as per protocol, unless the patient specifically withdraws consent from the trial.

See sections 6.3 and 6.4 for additional information on how to deal with patient withdrawal and patient end of treatment.

SAE will also be reported to Novartis and Pfizer, according to the details provided in the contracts between EBMT and Novartis and plus between EBMT and Pfizer (in brief, sites will send their SAE forms to the EBMT CTO by fax; within 24 hours and from the CTO it will be faxed or emailed to a Novartis or Pfizer as per agreement).

Out of hours emergency contact information:

Novartis: The list for the Novartis drug safety teams (per country) is held at the EBMT CTO and will be distributed to all investigators.

The Pfizer medical monitor for this study is:

Vai Katkade, MD, PhD
Medical Therapeutic Area Lead - Global
Diversified Products
Global Clinical and Medical Affairs, GEP
500 Arcola rd (F/03/F3232)
Collegeville, PA 19426
Tel: +1 484 865 3725
Cell: +1 267 933 7416
Fax: +1 212 973 7041
Email: vaibhav.katkade@pfizer.com

10.2.3 Expected adverse events

The following adverse events, for the purposes of the trial, will be considered as expected events that are disease/transplant related and do not require immediate reporting as an SAE:

- Infectious events which do not require intensive care unit support
- Bleeding which did not require red blood cell transfusion
- Clonal evolution (as defined 9.5)
- Some adverse events have been previously reported or anticipated during the use of eltrombopag; they are described in paragraph 8.3.1.

These events must still be recorded on the trial CRFs as AEs.

10.3 Expedited reporting of SUSAR

As of May 1st 2004, the sponsors of clinical trials conducted in the EU and EEA must ensure that all relevant information regarding suspected unexpected serious adverse reactions (SUSARs) are recorded and reported in an expedited fashion.

It is a legal requirement of the sponsor to report fatal or life-threatening SUSARs **within 7 calendar days** to the relevant Regulatory Authorities and the European Medicines Agency

after receiving first notification of the event. Non-fatal and non life-threatening SUSARs must be reported to the Regulatory Authorities and the European Medicines Agency **within 15 calendar days**. The EBMT CTO will have the responsibility for reporting such events to Ethics Committees, all applicable Regulatory Authorities and site principal investigators as well.

Therefore, all SAEs must be immediately reported to the CTO, to allow time for the expectedness assessment.

10.4 Safety Reports

The EBMT CTO will submit yearly DSUR to applicable Ethics Committees and Regulatory Authorities. This will commence one year from the date of first Regulatory Authority approval in the first country authorised.

10.5 Independent Data Monitoring Committee (see also paragraph 15.1.1)

The following independent physicians will serve as IDMC:

- Prof. Neal S Young M.D., chair, chief of the Hematology Branch of the National Institutes of Health (NIH), and Director of the Center for Human Immunology at the NIH in Bethesda, Maryland, US.
- Prof. Shinji Nakao M.D., Cellular Transplantation Biology (Hematology/Respirology), Kanawaza University, Kanawaza, Japan.
- Prof. Daniel Weisdorf M.D., Division Chief of Hematology, Oncology and Transplantation, and Director of the University of Minnesota Blood and Marrow Transplant Program, Minneapolis, US.
- Raphael Porcher, PhD, Bio-Statistician, St. Louis Hospital, Paris, France.

They will meet every 6 months in person or by tele-conference to review the safety data.

10.6 Pregnancy Reporting and Follow-up

Any pregnancy occurring during the trial must be reported to the EBMT CTO using the pregnancy report (and by the EBMT CTO to Novartis and Pfizer, as agreed in the contract); any pregnancy will be followed up until 6 weeks after patient or patient partner gives birth.

11. End of Trial

It is planned that the trial will be completed after the last patient last follow-up, i.e. after the last recruited patient has completed 2 years of follow-up from treatment start.

11.1 Early termination of the trial

The trial may be prematurely terminated, if in the opinion of the steering committee and/or the IDMC, there is sufficient reasonable cause. Written notification documenting the reason for trial termination will be provided to the investigator by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients.
- Failure to recruit patients at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Insufficient complete and/or evaluable data.
- Plans to modify, suspend or discontinue the development of the IMP.
- Emerging unacceptable safety profile as determined by the IDMC
- Other trial specific stopping rules: none

12. Statistics Methodology

12.1 Sample Size Justification

This is a superiority study aiming to increase the 3-months complete response (CR) rate. CR rate after standard immunosuppression with hATG+CsA is estimated to be below 10%, and equal to 7% in a recent study from the NIH[17]. The sample size is calculated on the hypothesis that the experimental arm will increase the 3-months response rate up to 21% (by 3 folds, based on the 7% reported in Scheinberg et al [17]). In these conditions, the sample size to reject the null hypothesis at 5% significance level and with 80% power (two-sided test) is n=96 patients for each treatment arm (in total 192 patients). Calculations are based on the Pass2000 algorithm for differences of percentages in two independent samples. The sample size will be increased by 4% to compensate for possibly not evaluable patients for a total number of 200 patients to be enrolled (100 each treatment arm).

12.2 Randomisation and Stratification

Randomisation will take place on the day or day before hATG is started. randomisation Randomisation ratio will be 1:1. Randomisation will follow a stratified variable-length block design. Stratification will be done according to center size, patient's age and disease severity to ensure homogeneity between treatment arms, according to the following subgroups:

Center size:

- Each center with expected accrual >=20 patients: one stratum
- All centers with expected accual <20 patiens: lumped together in one stratum

Disease severity:

- Severe aplastic anemia (SAA)
- Very severe aplastic anemia (VSAA: SAA plus ANC <200/μL)

Age:

- ≥15 and <40 year old
- ≥40 year old

12.3 Statistical Methods

The primary analysis will evaluate the complete response rate at 3 months from randomisation in an ITT population containing all randomized patients. Response is defined in section 9.6.1. We expect a very limited number of cases alive at 3 months and non-evaluable, or withdrawals before 3 months; these cases will be excluded from the primary analysis, and sensitivity analyses will be performed to check the validity of conclusions.

The null hypothesis of no difference in CR rate at 3 months between the arms will be tested against the alternative of a difference in CR rate by assessing the Mantel Haenszel pooled Odds Ratio for arm yielded by a model stratified for center, age and disease severity (strata defined in 7.1 and 12.2; alpha level of .05).

The analysis of survival-like endpoints (OS, EFS; defined in 9.6) will be done by Kaplan-Meier curves and stratified Log-Rank test and Cox regression (provided the absence of relevant deviations from the assumption of proportionality of hazards).

The analysis of time-to-event endpoints with competing risks (Time to first response, Time to best response, Time to CR, RI, Clonal evolution, PNH and immunosuppression discontinuation; defined in 9.6) will be done by crude cumulative incidence curves, Gray test, and Cox regression for cause-specific hazards (provided the absence of relevant deviations from the assumption of proportionality).

Other secondary endpoints (CsA-independent hematological response at 24 months, Need for transfusions, Need for any supportive care including hospitalization,Safety and tolerability) will be described by standard summary statistics (frequency tables for categorical variables, mean with standard deviations and quantiles for continuous variables).

QoL data will be analyzed by mixed models, assessing changes over time and differences between treatment arms.

Exploratory analyses of outcomes will also address the impact of other relevant predictive factors, which include:

- The presence of a PNH population
- The presence of HLA dr 15
- Pre-treatment absolute reticulocyte count
- Pre-treatment absolute lymphocyte count
- ANC at 1 month (time-dependent covariate)
- Platelets and absolute reticulocyte count at 3 months (time-dependent covariate

For all tests, the alpha level will be .05.All analyses will be performed in SPSS and / or R.

Further details will be specified in a separate Statistical Analysis Plan (SAP).

12.4 Interim Analysis

Not planned.

12.5 Procedures for reporting Deviations to Original Statistical Analysis Plan

If agreement has been reached between the coordinating investigator(s), the statistician and the trial steering committee to deviate or make amendments to the SAP, this will be reported (i.e. explained) in the clinical study report at the end of the trial.

12.6 The selection of patients to be included in the analysis

All efficacy analyses will be based on the intention-to-treat principle, including all patients randomized and comparing groups based on the arm assigned at randomisation. In the unlikely case of patients found to be not eligible after randomisation or going off-study before receiving the treatment, these cases would be excluded, and secondary analyses will be performed to check the sensitivity of conclusions when these cases are included.

As specified in 9.6.1 and 12.3, the analysis of the primary endpoint will include all cases evaluable at 3 months, considering death before 3 months as a failure to achieve CR. Patients alive at 3 months and non-evaluable or withdrawals before 3 months will be excluded from the primary analysis, and sensitivity analyses will be performed to check the validity of

conclusions. The scenarios will be : i) all cases failures ; ii) all cases CR ; iii) all experimental arm cases failures, all control arm cases CR.

The safety analyses will be performed on the subpopulation of cases who started the treatment.

13. Data Management

The EBMT software in use at time of the beginning of the trial will be adopted for this study.

13.1 Data Management Responsibility

It is the responsibility of the Principal Investigator (PI) at each site to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents must be completed in a timely, neat, legible manner to ensure accurate interpretation of data.

All source documents, CRFs, and laboratory reports must be reviewed by the PI's research team or Data Manager, who must ensure that they are accurate and complete before submitting CRFs to the CTO. Adverse events must be graded, assessed for severity and causality, and reviewed, dated and signed by the site PI or Co-Investigator (see section 11.2). All laboratory reports must be reviewed, dated and signed by the site PI or Co-Investigator.

13.2 Data Capture

Data for this trial will be captured in paper CRFs. CRFs must be completed in dark ink i.e. blue or black as this will ensure reproduced copies are clear.
All data requested on the CRFs must be recorded, and any missing data must be explained.
In an event where an entry error has occurred, correction must be made by crossing out the original entry with a single line, and writing the initials of the person making the change and the date of the change. The new data should be entered above or next to the strike-through. The original data must not be erased, overwritten and correction fluid/tape must not be used.

13.3 Definition of Source Data for the trial

The data that is reported on the CRFs is the source for EBMT. Sites need to retain a copy of the CRF and should retain all of the patient notes, lab results, etc. as that is their source.

14. Ethics and Regulatory Approvals

14.1 Good Clinical Practice (GCP)

The trial will be conducted in accordance with ICH-GCP, the Declaration of Helsinki, and the appropriate local regulatory requirements. Essential clinical documents will be collected and maintained by the EBMT CTO to demonstrate the validity of the trial and the integrity of the data collected.

The sponsor's Trial Master File (TMF) will be maintained at the EBMT CTO. Each participating site will maintain an investigator site file (ISF) as per the EBMT Clinical Trials Manual provided by the CTO. This sponsor's TMF and the ISF should be established at the beginning of the trial, maintained for the duration of the trial and retained according to the appropriate regulations.

The EBMT Clinical Trials Manual provides further guidance on the conduct of the trial.

14.2 Ethical and Regulatory Considerations

The ethics committee(s) and the appropriate regulatory authority(ies) will review all appropriate trial documentation in order to safeguard the rights, safety and well being of the patients. The trial will only be conducted at sites where ethics and regulatory approval has been obtained. The PI, EBMT CTO or CRO will provide the relevant ethics committee(s) and the regulatory authority(ies) with the final version of the protocol, patient information and informed consent form (ICF), any other written information given to patients, safety updates, annual progress reports, and any revisions to the trial protocol or any other required trial documentation.

This study is registered at on clinicaltrial.gov with the number NCT02099747.

14.3 Patient Information & Consent (appendix 7)

A generic patient information leaflet (PIL)/ Informed Consent Form (ICF) is provided in English in the Appendix of the protocol. This is a sample and should be amended as required to meet local requirements and will be translated into local language as necessary. Local versions should be appropriately version controlled, clearly stating whether it is country or site specific in the footer and dated to reflect the protocol with which it is associated. A copy of the local version must be provided to the CTO.

The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s) and must be approved by the Ethics Committee prior to use:

For patients who are 18+:

- A properly signed and personally dated informed consent form is required for each patient before any trial specific procedure. After the trial has been fully explained the patient should be given ample time to read the patient information sheet and consent form and ask questions. Written informed consent will always be obtained from the patient and/or his/her guardian or legal representative prior to trial participation.
- The informed consent process should be recorded in source documents (date of information and consent, parties present).
- The investigator is responsible for checking entries, and initials made by the patient on the consent form, and to request correction immediately in case of missing, illegible or incorrect dates. The person taking the patient consent should sign and date both consent forms to confirm he/she provided information to the patient.
- All entries on the consent forms must be permanent (no pencil).
- The Informed Consent form will be updated by the Investigator-Sponsor whenever important new information becomes available that may be relevant to patient's consent. This may be a result of amendments to the protocol, new information regarding the trial medication or alternative treatments. Revised versions must be approved by the relevant ethics committee(s) and regulatory authority(ies) before use.
- The revised consent form must be signed by patients who are entered in the trial and who have not yet completed trial treatment. In particular, if the consent form is updated with new safety information, a new version of the informed consent form must be provided to all patients in the trial in a timely manner as soon as written ethics and regulatory authority(ies) approval is obtained.
- Patient withdrawal of consent from the trial should be explicitly documented in the source documents and notified to the CTO via the early termination CRF.

For patients who are 15-18 years of age:

- A properly signed and personally dated informed consent form is required for each patient before any trial specific procedure. The informed consent of the parents or legal representative is required; consent must represent the minor's presumed will and maybe revoked at any time, without detriment to the minor;
- The minor is given information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits
- Minors who are capable of forming an opinion, assessing and understanding the purpose of the study and can assess its consequences need to be informed directly by their physicians and will receive an age appropriate information form. Their agreement with the study needs to be indicated with a signature on the consent form.
- After the study has been fully explained to the minor and to their parents/legal guardians, ample time must be given to read the consent forms and ask questions.
- The informed consent process should be recorded in source documents (date of information and consent, parties present).
- The investigator is responsible for checking entries made by the minor and parents/legal guardians on the consent form, and to request correction immediately in case of missing, illegible or incorrect dates. The person taking the patient consent

should sign and date both consent forms to confirm he/she provided information to the patient and to parents/legal guardian.

- All entries on the consent forms must be permanent (no pencil).
- The Informed Consent form will be updated by the Investigator-Sponsor whenever important new information becomes available that may be relevant to subject's consent. This may be a result of amendments to the protocol, new information regarding the trial medication alternative treatments. Revised versions must be approved by the relevant ethics committee(s) and regulatory authority(ies).
- Patient withdrawal of consent from the study should be explicitly documented in the source documents and notified to the CTO via the early termination CRF.

14.4 Patient Confidentiality and Access to Data

In order to maintain patient privacy, all CRFs, SAEs, trial drug accountability records, trial reports and communications will identify the patient by DOB and/or initials and the assigned patient trial number depending on each country's data protection rules. The full patient name should never be used in any correspondence with the Sponsor or on the CRFs.

The investigator will grant monitor(s) and auditor(s) from the EBMT and/or regulatory authority(ies) direct access to the patient's original medical records for verification of data gathered on the CRFs/SAE forms and to audit the data collection process. Direct access includes examining, analysing, verifying, and reproducing any recorded reports that are important to the evaluation of the monitoring of the trial. The investigator is obliged to inform the patient that his/her trial-related records will be viewed without violating their confidentiality and that the collected information will only be made publicly available to the extent permitted by the applicable laws and regulations, and according to the Data Protection Directive. This information must all be included in the Patient Information Leaflet.

14.5 Protocol Compliance and Serious Breaches

The investigator will conduct the trial in compliance with the protocol, after it has been given approval/favourable opinion by the ethics committee(s), the appropriate regulatory authority(ies) and, if required, institutional department(s) such as Research & Development Department.

The investigator will submit all protocol non-compliances to the CTO, and it is up to the CTO to decide if the protocol non-compliance should be submitted to the ethics committee and the regulatory authority(ies) in accordance with the governing regulations.

Any deviations from the protocol must be fully documented in the source documents. An explanatory note to file, signed by the Principal Investigator must be placed in the site file and a copy should be provided to the CTO with the CRFs.

The sponsor of a clinical trial must notify the UK regulatory authority in writing of any serious breach of the conditions and principles of GCP in connection with the trial, within 7 days of becoming aware of that breach. Therefore, the Investigator must notify the Sponsor immediately if there is a breach which is likely to effect to a significant degree (a) the safety

or physical or mental integrity of the patients of the trial; or (b) the scientific value of the trial.

14.6 Protocol Amendments

Changes to the protocol will require approval from the Sponsor, the Coordinating Investigators, the trial Steering Committee and written ethics committee opinion and the regulatory authority(ies) approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients (urgent safety measure). If an urgent safety measure must be made, the CTO must be immediately informed, and a protocol amendment must be submitted to the regulatory authorities and ethics committees within 3 days of the action.

Examples of substantial protocol amendments requiring prior approval include (but are not limited to):

- An increase in drug dosage or duration of exposure of patients
- A significant change in the trial design (e.g. addition or deletion of a control group)
- An increase in the number of invasive procedures to which patients are exposed
- Addition or deletion of a test procedure for safety monitoring

15. Quality Assurance & Monitoring

15.1 Monitoring

Monitoring of data to ensure adherence to the protocol and compliance with ICH-GCP and relevant EU Directive(s) will be done by remote monitoring of completed data and on-site monitoring visits as appropriate. More details are provided in the Safety Monitoring Plan (Appendix 5), the Risk Management Plan (Appendix 9) and the Trial Monitoring Plan.

15.1.1 Independent Data Monitoring Committee

An IDMC will be established, which will consist of 1 statistician and 3 physicians.

The IDMC will receive 6-monthly reports on the status of the trial and a listing of all AEs and SAEs and any other data relevant to the ongoing assessment of safety. The IDMC then recommends whether the trial should stop or how it should proceed.

When the first 50 patients have 6 month's follow-up, IDMC will:

- evaluate ethical & safety issues
- report their findings to the steering committee

15.1.2 Monitoring frequency

The frequency of monitoring will be defined in the agreed monitoring plan. Each trial site will be initiated (by telephone or initiation visit) as well as monitored during the trial. A close out visit or teleconference for participating trial sites will be conducted at the end of the trial.

15.1.3 Remote monitoring

Remote monitoring will be done to ensure adherence to the protocol and ICH-GCP and relevant EU Directive(s). Monitoring of clinical and safety data will be carried out by statistical analysis of data submitted on the CRFs.

As the most frequent cause of SAE reports is the hospitalisation of a patient from whatever cause, monitoring of SAE reporting will be carried out by checking the Adverse Event (AE) Data in the CRFs and cross referencing the number of AEs rated as serious with the number of SAEs submitted. Should such analysis identify discrepancies then this will trigger a query and/or on site visit to the relevant site.

15.1.4 On-site monitoring of participating trial sites

If on-site monitoring is required, it will focus primarily on safety data as well as all end point data. This data will be verified through source data verification.

The scope of work for on-site monitoring will include the following activities:

- Verify for each patient that Informed Consent was obtained prior to the patient's participation in the trial and that the correct version of the PIL/ICF consent was used
- Ensure all approval documents are in the site file
- Source Document Verification will be carried out as specified in the monitoring plan
- Ensure that all adverse events are appropriately recorded and that the process of reporting SAEs is followed as outlined in the adverse events section
- Document all activities and discussions with investigational staff in a written monitoring visit report and send to the EBMT CTO for approval.

- Arrange for appropriate follow-up of all action items as detailed in a post-monitoring visit follow up letter and in the monitoring visit report.

The monitor will need to request access to trial patient source data, CRF and trial related documents prior to his/her visit. During the visit, Investigators should have ample time to discuss problems and make corrections identified by the monitor.

15.1.5 Quality Assurance of Trial Endpoints

Each participating Investigator is responsible for reviewing all data in the CRF and in particular, the end point data of each patient at their site to:

- cross reference the source documentation against the submitted CRFs
- check that the evaluation of efficacy data points are correct

This should be carried out as each patient completes the trial treatment or as clinically indicated.

The data review will be documented and any changes required to CRFs made and any amended CRFs submitted to the CTO. The Coordinating Investigator will review all reviewed data from each site prior to the planned analysis of the trial.

All data relating to the trial objectives/endpoints will be checked prior to publication.

15.2 Audit & Inspection

In accordance with applicable laws participating sites will allow direct access for monitoring and audit by appropriate EBMT personnel and direct access for inspection by government and regulatory authorities. Access will be granted to all trial related documentation and sites (including source documentation, CRFs of patients, Investigator site file, patients files, clinics, laboratories and pharmacy).

The EBMT maintains the right to perform audits during the active phase of the clinical trial.

If the investigator site receives notice of an audit or inspection by a Competent Authority or Ethics Committee, the Investigator must immediately notify the EBMT CTO.

16. Storage and archiving of trial material

It is the responsibility of the principal investigator at the trial site to keep all essential documents relating to the trial for at least 15 years or for as long as it is required by the institution after the completion or premature termination of the clinical trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the institution complied with the principles and guidelines of good clinical practice.
The medical files of patients enrolled into the trial must be kept in accordance with national legislation and for the maximum period of time permitted by the institution. The archived data can be kept in electronic form, provided that a back-up copy is kept and that a paper copy can be provided if necessary.

The protocol, ethical and government approvals, together with all other documents concerning the trial, including any audit and inspection certificates are all to be kept as part of the Investigator Site File and the trial master file. All data about serious adverse events also need to be kept in this trial master file.

All trial related documents and files must be kept for a minimum of 5 years or for the duration specified by the institution and should be available for inspection by the appropriate authorities on demand.

17. Insurance and liabilities

As the trial sponsor the EBMT offers insurance coverage to cover the liability of participating investigators. Insurance for the trial will be provided for the treatment period.
All EBMT insurance is coordinated through the EBMT CTO in London.

The participating patients are insured by the following insurance company:
HDI Global SE
Überseering 10a
22297 Hamburg

For queries or to request a copy of the insurance certificate please contact the Clinical Trial Coordinator.

18. Financial Aspects

The funding for the trial is being provided by Novartis and Pfizer, according to the separate contracts signed by the EBMT and Novartis and Pfizer.

18.1 Interaction with the company funding the study

Novartis and Pfizer, as the companies funding the study will receive regular updates to how the study is progressing, according to the contract signed by the EBMT and Novartis and Pfizer. An annual progress report, any amendments to the protocol, and any change in the status of the protocol should be forwarded to Novartis study accountable person (see below). In addition, Novartis will receive quarterly accrual and toxicity information as detailed in the contract. In order to maintain subject confidentiality, all communications relating to the study will identify participants by assigned subject study numbers. No personally identifiable information will be sent to Novartis.
The Medical accountable person for Novartis for this study is:

Miona Stankovic, MD
Platelet Regional Medical Director
Medical Affairs
Novartis Oncology Region Europe HQ
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Any change in accountable person will be timely notified by the Novartis to the EBMT office.

In accordance with local and regional regulations, as specified in the contract between Novartis and the EBMT, the Investigator may allow Novartis personnel or their designee, access to all pertinent medical records in order to verify the data gathered and to audit the data collection process e.g. in the event a regulatory authority requests such an action.

19. Publication Policy

All publications must follow the EBMT publication policy and should be agreed in a trial specific publication plan. Authorship will reflect international conventions.

20. References

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21. Appendices

APPENDIX 1 List of cytogenetic abnormalities

List of cytogenetic abnormalities qualifying for the diagnosis of MDS according to WHO 2008 (from ref. 30)

Table 6. Recurring chromosomal abnormalities considered as presumptive evidence of MDS in the setting of persistent cytopenia of undetermined origin, but in the absence of definitive morphologic features of MDS

Unbalanced abnormalities	Balanced abnormalities
−7 or del(7q)	t(11;16)(q23;p13.3)
−5 or del(5q)	t(3;21)(q26.2;q22.1)
i(17q) or t(17p)	t(1;3)(p36.3;q21.1)
−13 or del(13q)	t(2;11)(p21;q23)
del(11q)	inv(3)(q21q26.2)
del(12p) or t(12p)	t(6;9)(p23;q34)
del(9q)	
idic(X)(q13)	

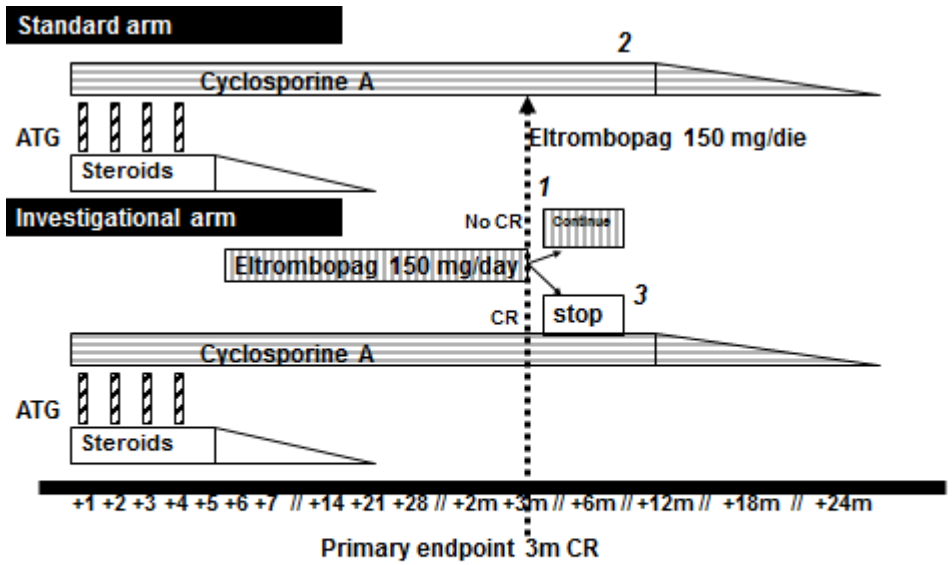
Complex karyotype (3 or more chromosomal abnormalities) involving one or more of the above abnormalities.

APPENDIX 2 Summary of Evaluation and Visit Schedule

Procedure	Visit 0	Visit 1	Visit 2,3,4,5	Visit 6,7,8	Visit 9	Visit 10,11	Visit 12	Visit 13,14	Visit 15	Visit 16,17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22
Time	Pre	d0-1	w1,2,3,4	m1.5,2,2.5	m3	m4,5	m6	m7,8	m9	m10,11	m12	m15	m18	M21	m24
Medical history	X														
Diagnosis	X														
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Signs and symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transfusion record	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bone Marrow[#]	X*				X[$]		X*				X				X*
Trephine biopsy	X						X				X				X
Immunophenotype	X*						X*				X				X*
DEB test	X^														
Biochemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telomeres	X*						X*								X*
QoL	X						X				X				X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
All record review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HCG	X^^														
CsA level			X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmologic function (cataracts)	X				X		X				X	X	X		X
Safety Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*: centralized samples
^: only in patients <=20y, or with familiar history of AA; ^^: female patients only
[$]in the case of CR, at 3 months bone marrow (BM) evaluation is to be performed.
[#]additional BM may be performed according to clinical needs and standard practice: clonal evolution implies BM evaluation, by definition.

APPENDIX 3 Flowchart of the study& IMP description



1. Patients in the investigational arm not achieving CR at 3 months will receive eltrombopag until 6 months
2. Patients in the standard arm who do not achieve CR or PR at 6 months are eligible for 3-6 months of eltrombopag (outside the protocol)
3. Patients in the investigational arm who relapse within 6 months from eltrombopag discontinuation are eligible for re-introduction of eltrombopag

APPENDIX 4 Reference Safety Information

Eltrombopag SmPC. Should be supplied by Novartis or found online by EBMT. EBMT CTO who will distribute it to participating sites.

ATGAM USPI (and if applicable annual updates to it) is supplied by Pfizer to EBMT CTO who will distribute it to the participating sites.

APPENDIX 5 Safety Monitoring Plan

Safety Monitoring Plan (SMP)

I. Assessment of Safety

In this trial, safety will be determined through the collection of (S) AE data, laboratory tests, etc. There will be a 6-monthly review by the IDMC of all SAE and AE data who will advise whether or not the trial can continue (for details of the IDMC see paragraphs 10.3 and 15.1 of this protocol).

All SAEs will be forwarded to the PV departments of Pfizer and Novartis. A request for more information regarding an SAE will be checked (confirmed or request for new information) if needed at the site.

II. Routine Monitoring

A. Monitors

Monitors will visit the hospital on behalf of the sponsor and perform activities such as (but not limited to) regulatory documentation checking and Source Data Verification (e.g. Informed Consent check, In-/Exclusion checking, SAE and AE data).

B. Report

A written report will be produced and provided to both the participating site and the sponsor, the sponsor is to follow up issues raised by the report till resolution / satisfactory explaination.

C. Frequency

Attempts will be made to perform a monitoring visit within 3 months of a site recruiting their first patient in the trial. After this initial visit regular follow up visits (at least on an annual basis) will be performed.

III. Specific Safety Issues

Special attention will be given to the occurrence of clonal evolution as defined in paragraph 9.5 of the protocol (diagnosis of acute leukemia/MDS or occurrence of any other significant cytogentic abnormality).

APPENDIX 6 Quality of life questionnaire: EORTC QLQ-C30 (English version)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 7 Patient Information Leaflet and Informed consent Template (English version)

Patient Information Leaflet RACE Study

***RACE Study*: A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia patients**

Dear Madam/Sir

We would like to invite you to take part in a scientific research study investigating the effect of adding eltrombopag to the standard treatment for aplastic anemia.
Before you decide, you need to understand why the research is being done and what it will involve.

Please, read this information leaflet carefully and discuss it with your partner, family or friends. Take as much time as you need to think about your participation in this study.

This study is being conducted by the European Society for Blood and Marrow Transplantation (EBMT), a not for-profit research organisation in the field of all aspects of transplantation of bone marrow/blood stem cells.

You are free to decide whether or not to take part in this trial. If you choose not to take part, this will not affect the care you get from your own doctors.

If you agree to take part, you will be asked to sign and date the consent form. You will be given this information leaflet and a copy of the consent form to keep.

Ask us if there is anything that is not clear or if you would like some more information.
You can also consult a doctor independent to the study who knows a lot about the study and can help you to better understand all the information in this leaflet. Their contact details are displayed in section 21. [IF AVAILABLE, ADD ANY COUNTRY SPECIFIC ADDITIONAL INFORMATION ABOUT RESEARCH].
If any new information becomes available that may influence your decision, this information will be given to you. If you decide not to participate, or to withdraw at a later date, this will not affect the type or quality of treatment you get in the future, and your doctor will discuss other suitable options for your disease.

1. Why have I been invited?

You have been invited to take part in this study because you have aplastic anaemia (AA), a disease of the bone marrow causing a lack of blood cells to be produced. This shortage of blood cells may lead to various symptoms and complications. The lack of red blood cells (known as anaemia) may result in fatigue, shortness of breath on exertion or headaches, for example. The lack of white blood cells (known as neutropenia) increases the risk for developing serious infections, and the lack of platelets (known as thrombocytopenia) increases the risk of bleeding.
Since these complications can be life-threatening, it is important that you receive a treatment which aims to make the bone marrow work again, and to reduce the risk of these potentially life-threatening complications.

For severe AA (SAA) there are two kinds of treatment that can make the bone marrow work again;

1. to undergo a bone marrow (stem cell) transplant or
2. to undergo a treatment called immunosuppressive therapy (IST) that prevents the body's own defence system from attacking the bone marrow.

For a bone marrow transplant, a sibling (sister or brother) matched (HLA-identical) donor of similar age to the patient is required.
Patients who are unable to have a bone marrow transplant receive the standard immunosuppression treatment (IST).

You are not eligible for a transplant and therefore you are invited to participate in this clinical study aiming to improve the current standard of IST for patients suffering from SAA.

2. Why is this study being done?

This study has been designed to improve the current treatment for SAA, by combining standard immunosuppression with eltrombopag, a drug that could improve blood cell production.

A combination of Horse-ATG (antithymocyte globulin (hATG)) and ciclosporin (CsA) is the current standard immunosuppressive treatment for SAA; however, not all patients respond, and improvement of blood cell production is often only partial and occurs relatively late.

In a recent clinical study it appeared that treatment with eltrombopag improved blood counts in SAA patients who had not responded to the standard IST. Based on this information, eltrombopag will be studied as an additional medicine combined with standard IST treatment (hATG + CsA). The purpose of this study is to determine the effect of this treatment combination.

3. How does Eltrombopag work?

Eltrombopag is not an immunosuppressive agent, but a drug that stimulates the functioning of the bone marrow to produce more platelets.

4. Which treatment is being studied?

In this study the treatment of eltrombopag combined with standard IST treatment (hATG + CsA) is being studied.

5. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do agree, we will ask you to sign a consent form before you receive any study treatment or have any study procedures. You are still free to withdraw at any time and without giving a reason. If you decide against taking part in this study or you join the study now but later decide that you want to change your mind, you are completely free to do so. This will not affect your relationship with the doctors and nurses looking after you or any further medical care.

6. What will happen to me if I do take part?

About 200 patients from 7 different European countries will take part in this study. This is a randomised study meaning sometimes we don't know which way of treating people is best. To find out, we need to compare different treatments and so we put people into groups and give each group a different treatment. The results are then compared to see if one is better. To try and make sure that the groups are equal, each participant is put into a group randomly (50/50 chance) by a computer.

Half of the patients will receive the standard hATG + CsA treatment while the other half will receive eltrombopag plus standard hATG + CsA treatment. Patients in both treatment arms of this study will need to be admitted to hospital for the treatment.

If you agree to take part in this study you will need to have an assessment and some tests to make sure that you are suitable. This assessment must be completed within 30 days before entering the trial (pre-Visit) and includes: reviewing your past medical history and current medical conditions, reviewing your diagnosis (including signs and symptoms), having a physical examination, blood tests, bone marrow samples, reviewing your medication, having a pregnancy test (for women of child bearing age) and completing a quality of life questionnaire.

All of these (except the quality of life questionnaire) are done as part of your standard treatment.

If you are suitable for this research study you will receive the following medications:

Name of medication	Administration procedure
hATG	Intravenously (via a vein)
Ciclosporin (CsA)	Orally (by mouth) as tablet or liquid formulation (possibly intravenous in case of intolerance)
50% of the patients (those in the investigational arm) will receive eltrombopag in addition to ATG and CsA	
Eltrombopag	Orally as tablets (3 tablets per day, taken at the same time)

hATG treatment is given over a 12-18 hours a day for 4 days. You will also receive drugs to help prevent allergic reactions that may occur during the administration of ATG (see section 9) and prophylactic ('preventative') antibiotics. Your doctor/nurse will also provide you with Patient Information Sheets on hATG and CsA that have more detailed information about these two drugs.

CsA treatment is usually given for at least 1 year. Blood levels are monitored during treatment and the dose adjusted accordingly.

Eltrombopag treatment will last for 3 months. Eltrombopag treatment might be extended for an additional 3 months if you have not had a complete response to the drug. If your symptoms return (relapse) after discontinuation of eltrombopag treatment, eltrombopag treatment may be reintroduced. If you are randomised to the standard arm (hATG and CSA), you may receive eltrombopag treatment at a later stage if your doctor decides you need it.

The trial will last for 2 years including treatment and follow up. You will need to be seen in clinic for the follow up visits. At each visit you will have a number of tests done, which are listed in the table on the next page.

Additional Research Samples

We would also like to collect additional blood and bone marrow samples at 3 different time points, which will be stored at our tissue bank and will be used in future research looking into the causes, diagnosis and treatment of Haematological Disorders such as AA. These samples will be collected at the same time as your routine samples are being taken and so will not cause you

any further pain or discomfort. The only exception to this is the first bone marrow sample which may be taken after your initial bone marrow assessment has been done. You will be asked to indicate on the consent form if you are happy for these samples to be taken. All samples held at the tissue bank will be anonymised.

Visits	**Tests**	**Visits and Tests; additional to standard follow up visits**
Screening	• Medical history • Checking diagnosis • Pregnancy test (females only) • Bone Marrow Aspirate • Trephine Biopsy • Quality of Life Questionnaire • Cataract check (eye check up) • Physical examination • Signs and symptoms • Blood tests: Hematology & Biochemistry • Checking of Transfusion Records • Checks for additional medications being taken • Checking all records	Additional blood sample Additional Bone Marrow Aspirate procedure Cataract check (eye check up)
Visit 1 Day 0	• Physical examination • Signs and symptoms • Blood tests: Hematology & Biochemistry • Checking of Transfusion Records • Checks for additional medications being taken • Checking all records	
All visits: Visit 2 week +1 (±2 days)	• Physical examination • Signs and symptoms • Blood tests: Hematology &	

Visit 3 week +2 (±2 days) Visit 4 week +3 (±2 days) Visit 5 month +1 (±2 days) Visit 6 month +1.5 (±1 week) Visit 7 month +2 (±1 week) Visit 8 month +2.5 (±1 week) Visit 9 month +3 (±1 week) Visit 10 month +4 (±10 days) Visit 11 month +5 (±10 days Visit 12 month +6 (±2 weeks) Visit 13 month +7 (±2 weeks) Visit 14 month +8 (±2 weeks) Visit 15 month +9 (±2 weeks) Visit 16 month +10 (±2 weeks) Visit 17 month +11 (±2 weeks) Visit 18 month +12 (±2 weeks) Visit 19 month +15 (±2 weeks) Visit 20 month +18 (±2 weeks) Visit 21 month +21 (±2 weeks) Visit 22 month +24 (±2 weeks)	Biochemistry • Checking of Transfusion Records • Checks for additional medications being taken • Checking all records • Checking CsA level • Checking if patient taking treatment and safety	
Visit 9 month +3 (±1 week)	• Bone Marrow Aspirate if patient is in complete response	
Visit 12 month	• Bone Marrow Aspirate	Additional blood sample

+6 (±2 weeks) Visit 22 month +24 (±2 weeks)	• Quality of Life Questionnaire • Cataract check (eye check up)	and Bone Marrow Aspirate Cataract check (eye check up)
Visit 18 month +12 (±2 weeks)	• Bone Marrow Aspirate	

7. What are the possible benefits and risks of participating in this study?

A possible benefit of participating in this study (for half of the patients) is that eltrombopag is added to your standard treatment, which may be effective in treating SAA patients and increasing the chance of responding to hATG and CsA.

8. What are the possible risks of taking part?

Some of the tests and procedures performed during the study may also have possible side effects. For example when you are having a blood sample taken there is a chance of pain, bruising and rarely, infection at the point where the needle goes into the skin.

You will also have had a bone marrow aspirate done in the past and may have experienced the mild soreness lasting 12-24 hours afterwards. Serious complications are extremely rare for this procedure. Your study doctor should be able to take the study samples at the same time as your routine samples and so will minimize any inconvenience and discomfort caused to you.

Another risk of taking part in this study are the possible side effects from taking eltrombopag which are talked about below

9. Which side effects could you expect?

The side effects to your health may be related to the disease, as well as to the specific treatment that you will receive. Because of your SAA, you have a high risk of infections and bleeding complications and for these reasons you will be given other medicines to help prevent these possible complications. Another risk of having SAA is that it may transform into a cancerous bone marrow disorder (myelodysplastic syndrome/'MDS' and/or acute leukemia). This risk is low and usually seen in the very long-term period, especially in patients who have not responded to IST. It is unknown if eltrombopag will have any impact on this risk, but will be investigated during this study.

Your participation in this study will not affect other medicines that your doctor may feel you need such as drugs to help prevent and/or treat infections. Nor will it affect any additional treatment you may need such as blood or platelet transfusions.
Your participation in this study will be stopped immediately if your doctor decides it to be in your best interest. Possible reasons for stopping are your reaction to the treatment or the availability of a more appropriate treatment for you (e.g. bone marrow transplantation).

- Eltrombopag

Eltrombopag is generally well tolerated and the side effects are generally acceptable. The most common side effect is abnormal liver function. For this reason your liver values will be monitored during the study by regular blood tests. Nausea, vomiting and headaches are other common side affects of eltrombopag.

Treatment with eltrombopag can increase the chance of blood clots. Your platelet count will be checked during your hospital visits to check for this and eltrombopag treatment will be stopped if the platelets increase above a set limit.

In some patients who suffer from myelodysplastic syndrome (MDS) and/ or new acute myelogenous leukemia (AML, a type of blood cancer), and from SAA and who are treated with eltrombopag, changes in bone marrow cells may occur and in some cases this may show a progression to cancer . The role of eltrombopag in these changes is not known. These changes have also been seen with other drugs in the same class of compound as eltrombopag. During this study, your blood and bone marrow will be periodically examined for signs of these changes.

Cataracts were seen in toxicology studies of eltrombopag in animals. The clinical importance of this finding is unknown so you will have regular eye checks to monitor this.

- hATG

Typical side effects of hATG include allergic reactions (skin rash, asthma attack/wheeze, chills, fever, and very rarely severe allergic reaction), water/fluid retention, and temporary further drop in blood counts. A later possible reaction is called serum sickness, which can cause tenderness and swelling of the joints or muscles, inflammation of the lung fleece, inflammation of the heart, fever and rash. This can occur between 1-2 weeks after the first dose of hATG.

hATG increases your susceptibility to infections so special precautions will be taken while you are in hospital and when you go home. Your doctor/nurse will provide you with aPatient Information Sheets on hATG (and ciclosporin (CsA)) which have more detailed information about these drugs. Please ask for them if you are not given them.

- CsA

Typical side effects of CsA include a rise in the blood pressure, reduction in kidney and liver function (as shown on blood tests), tremors, increase in body hair growth, swelling of the gums and headaches. Usually, the side effects are related to high doses of CsA so therefore

the CsA blood level will be monitored regularly to prevent this, and the dose of CsA will be adjusted according to changes in the level of CsA in your blood.

10. Pregnancy

A pregnancy test in women of childbearing age will be done at screening by a blood or urine sample.

If you are pregnant or think you may be, **tell your doctor immediately**. Eltrombopag and hATG **are not recommended to be used during pregnancy** unless clearly necessary. CsA is safe in pregnancy but your doctor will discuss this in more detail.

Pregnancies occurring during the study will be followed up until 6 weeks after the birth of the child.

Patients and/or female partners of male patients must use highly effective birth control method or a combination of 2 additionally effective birth control methods.

Examples of highly effective contraception are condoms or a diaphragm, combined with the spermicidal gel, an oral contraceptive pill, injection or subcutaneously, or abstinence.

11. What food interactions shall I be aware of?

Eltrombopag should be taken at least four hours before or after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc).

12. Are there any alternative treatments?

Your doctor will discuss any alternative treatments with you which are available outside of this research study.

13. What insurance cover is there for this study?

Every care will be taken in the course of this study. In the event of non-negligent harm arising as a consequence of this study then compensation may be available through the Sponsor, the EBMT. The EBMT will not be responsible for any injury or care that is related to the treatment or procedure, which is not in accordance with the study protocol. If you are harmed due to someone's negligence then you may have grounds for legal action for compensation against the EBMT but you may have to pay your legal costs. For this study the EBMT has taken out insurance coverage according to the legal requirements with *HDI-Gerling* Insurance Company.

It is important that you follow the instructions of the medical team overseeing your treatment. If you believe that you have suffered side effects, injuries, or illness related to the study, you should report this as soon as possible to your treating doctor and request information on how to proceed. Your doctor will ensure you continue to receive the best medical care and will give you advice during and after the study.
By signing the consent form, you are not giving up any of your legal rights.

14. What happens with your personal data and the results of the study?

A. Results

The results of this study will be published in a scientific journal and may be presented at scientific meetings (national or international). All records that hold your identification will be kept strictly confidential and will not be made publicly available. Your identity will remain confidential in all publications and after the results of the study are published. The study data will be stored in a secure database in the Netherlands.

B. Records

You will be given a unique study number when you enter the study and any data we collect on you will be stored using this unique number. Only the researchers involved in this study will be able to link the unique number to your name.

C. Samples

The additional bone marrow and blood samples (listed in section 6) will be shipped to a laboratory in the UK for future research.
You will not be identified in the research that is done on those samples.

15. Who will have access to my data?

Your general practitioner will be notified about the treatment.

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at your treating hospital and with the EBMT under the provisions of the 1998 Data Protection Act. Your name will not be passed to anyone else outside the research team or the Sponsor (EBMT), who is not involved in the trial. You will be allocated a trial number, which will be used as a code to identify you on all trial forms. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised (if it is applicable to your research).

Your records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Sponsor, which is the organisation responsible for ensuring that the study is carried out correctly. By signing the consent form you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study.

The information collected about you may also be shown to authorised people from the UK Regulatory Authority (the Medicines and Healthcare Products Regulatory Authority); this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.

If you withdraw consent from further study treatment, unless you object, your data and samples will remain on file and will be included in the final study analysis.

In line with the regulations, at the end of the study your data will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made.

16. Are there any extra costs involved when you decide to participate in this study?

There are no funds to cover travel expenses and you will not receive any payment for your participation in this study.

Your stay in hospital, medicines, as well as outpatient examinations and visits are part of the treatment of your disease and these costs are covered by the NHS.

17. What happens when the study ends?

When the study ends your doctor will decide on the best care for you.
Normally patients with SAA who respond to immunosuppression/IST (hATG + CsA), will have their treatment dose lowered and then later stopped.
Patients who do not respond may go on to have a bone marrow transplant or further IST.

18. Who has reviewed the study?

This study has been reviewed and approved by a medical expert committee of the Sponsor, the EBMT. It was also given a favourable ethical opinion by the [Enter Ethics Committee name]. The study has also been approved by the MHRA who are the national regulatory agency in the UK.

19. What if something changes during the study?

It is possible that unforeseeable circumstances will require a change in the treatment plan if there are new developments in your disease or general condition. This will be discussed with you in order to allow you to reconsider your participation in the study. Your treating doctor may decide, if necessary, to stop the treatment according to the study.

20. Assurances

You are **completely free** to decide whether you wish, or not, to participate in this study. If you decide to participate in the study, you may always withdraw **at any time** without explanation.

Whatever you decide, it won't change anything about the care and support of you and your family. If you decide not to participate, or withdraw during the study, alternative treatment options will be discussed with you.

If you agree to participate in the study, you will be asked to sign the consent form for this study. By signing this form you confirm that you are sufficiently informed about the procedures required from you and that you agree to participate in the study, and allow the use of your data and biological samples.

21. What if I have a complaint?

If you have a complaint in relation to your participation in this study please contact:

Principal Investigator within [INSERT HOSPITAL] [NAME, FUNCTION]	[TELEPHONENUMBER]
Independent physician [NAME, FUNCTION]	[TELEPHONENUMBER]
Complaint Committee [INSERT HOSPITAL]	[TELEPHONENUMBER]

INFORMED CONSENT FORM

***RACE Study*: A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia patients**

Sponsor: **EBMT**

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1. I have read the Patient Information Leaflet, version x, dd-Mmm-yyyy. I had the opportunity to ask questions and adequate answers were provided. I had an appropriate amount of time to decide if I want to participate. ☐
2. I agree to participate in this study. ☐
3. I understand that participation is completely voluntarily and I am free to withdraw at any time, without giving a reason, without my medical care or legal rights being affected. ☐
4. I give permission for my GP to be informed about my participation in this study. ☐
5. I understand that there is an equal chance (50:50) that I will receive either the experimental drug plus the standard treatment or the standard treatment alone. ☐
6. I give permission to responsible individuals from the study research team, Ethics Committee and regulatory authorities and other authorized personnel to review my medical records and all relevant biological information. ☐
7. I understand that my medical data will be collected for this study and may be used to help develop new research, and that data protection regulations will be observed, and strict confidentiality maintained. ☐
8. I agree that my data will be kept for the maximum duration of 15 years after the end of this study. ☐
9. I agree that there will be one additional bone marrow puncture, two additional bone marrow samples and three additional blood samples done which is outside of normal clinical practice. ☐
10. I agree to these samples being stored at the Tissue Bank and for being used in future research. I will not be identified in this future research ☐
11. I agree to notify my treating doctor if I or my partner become(s) pregnant during the study. I also agree for my treating doctor to follow up the pregnancy until 6 weeks after the birth of the child. ☐

* Cross if not applicable

I hereby declare that I have been fully informed this participant about the above mentioned study.

Name of the participant: _____

Signature: _____ Date: ___ / ___ / ___

In case information becomes available during the study which may influence the consent of the participant, I will inform him/her in time.

Name of physician (Investigator):_____

Signature: _____ Date: ___ / ___ / ___

Additional information is provided by (when applicable):

Name:
Function
Signature: _____ Date: ___ / ___ / ___

APPENDIX 8 Lab Manual

Visit schedule

Procedure	Visit 0	Visit 12	Visit 22
Time	Pre	m6	m24
Bone Marrow	X*	X*	X*
Immunophenotype	X*	X*	X*
Telomeres	X*	X*	X*

Bone Marrow (aspirate) Sampling

Time Points: Visit 0 (pre), visit 12 (6 months) and Visit 22 (24 months)

One 4ml lavender top tube (EDTA) and one 6ml green top tube (preservative free heparin)

Fill completely

Mix immediately by gently inverting the tube 8-10 times

Keep samples at room temperature and courier immediately

Blood Sampling

Time Points: Visit 0 (pre), visit 12 (6 months) and Visit 22 (24 months)

30-40mls of peripheral blood collected in lavender top tubes (EDTA)

Fill completely

Mix immediately by gently inverting the tube 8-10 times

Keep samples at room temperature and courier immediately

Packaging and Courier details

For the UK:

City Sprint (centre emails CitySprint for sample collection and packaging)

For all other countries:

Fedex (center calls Fedex)- to check on timings, packaging

Shipment address

Haemato-Oncology Tissue Bank

Leukaemia Science Laboratories, Rayne Institute,

123 Coldharbour Lane, London, SE5 9NU

Phone 020 7848 5815

Urgent Enquiries

Dr. Rajani Chelliah

Haematological Medicine

King's College Hospital

Fourth Floor, Hambledon Wing West

Denmark Hill, London SE5 9RS

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APPENDIX 9 Risk Management Plan

Risk Management Plan Version 1.0

09-Apr-2014

Version #	Implemented By	Revision Date	Approved By	Approval Date	Reason
1.0	*Alain Barrois*	*31/Oct/2014*		*<mm/dd/yy>*	Initial Risk Management Plan

The RACE trial is a Type B trial (somewhat higher risk than that of standard medical care)

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Risk Management Plan Approval

Risk Management Log 'live' version will be stored locally.

1. INTRODUCTION

1.1. Purpose of The Risk Management Plan

A risk is an event or condition that, if it occurs, could have a positive or negative effect on a project's objectives. Risk Management is the process of identifying, assessing, responding to, monitoring, and reporting risks. This Risk Management Plan defines how risks associated with the RACE trial will be identified, analyzed, and managed. It outlines how risk management activities will be performed, recorded, and monitored throughout the lifecycle of the trial and provides templates and practices for recording and prioritizing risks.

The Risk Management Plan is created by the clinical trials operations manager or other designee in the writing phase of the protocol and is monitored and updated throughout the project.

The intended audience of this document is the trial team, grant providers and EBMT management.

2. RISK MANAGEMENT PROCEDURE

2.1. Process

The clinical trials operations manager or other designee working with the PIs, participating sites and grant provider will ensure that risks are actively identified, analyzed, and managed throughout the life of the project. Risks will be identified as early as possible in the project so as to minimize their impact. The steps for accomplishing this are outlined in the following sections. The clinical trials operations manager or other designee will serve as the Risk Manager for this trial.

2.2. Risk Identification

Risk identification will involve the trial team, appropriate stakeholders, and will include an evaluation of environmental factors, organizational culture and the trial design including the project scope. Careful attention will be given to the project deliverables, assumptions, constraints, cost/effort estimates, resource plan, and other key project documents.

A Risk Management Log will be generated and updated as needed and will be stored electronically in the trial website at the CTO portal.

2.3. Risk Analysis

All risks identified will be assessed to identify the range of possible trial outcomes. Qualification will be used to determine which risks are the top risks to pursue and respond to and which risks can be just monitored.

2.3.1. Qualitative Risk Analysis

The probability and impact of occurrence for each identified risk will be assessed by the clinical trials operations manager or other designee, with input from other stake holders using the following approach:

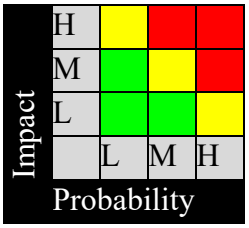
Probability

High – Greater than <70%> probability of occurrence

Medium – Between <30%> and <70%> probability of occurrence

Low – Below <30%> probability of occurrence

Impact
High – Risk that has the potential to greatly impact trial cost, trial schedule or performance
Medium – Risk that has the potential to slightly impact trial cost, trial schedule or performance
Low – Risk that has relatively little impact on cost, schedule or performance



Risks that fall within the RED and YELLOW zones will have risk response planning which may include both a risk mitigation and a risk contingency plan.

2.3.2. Quantitative Risk Analysis
Analysis of risk events that have been prioritized using the qualitative risk analysis process and their effect on trial activities will be estimated, a numerical rating applied to each risk based on this analysis, and then documented in this section of the risk management plan.

2.4. Risk Response Planning
Each major risk (those falling in the Red & Yellow zones) will monitored by the clinical trials operations manager or other designee to ensure it is noticed and dealt with if necessary.
For each major risk, one of the following approaches will be selected to address it:
Avoid – eliminate the threat by eliminating the cause
Mitigate – Identify ways to reduce the probability or the impact of the risk
Accept – Nothing will be done
Transfer – Make another party responsible for the risk (buy insurance, outsourcing, etc.)

For each risk that will be mitigated, the trial team will identify ways to prevent the risk from occurring or reduce its impact or probability of occurring. This may include prototyping, adding tasks to the trial schedule, adding resources, etc.
For each major risk that is to be mitigated or that is accepted, a course of action will be outlined for the event that the risk does materialize in order to minimize its impact.

2.5. Risk Monitoring, Controlling, And Reporting
The level of risk on a project will be tracked, monitored and reported throughout the trial lifecycle.
All trial change requests will be analyzed for their possible impact to the risks. Management will be notified of important changes to risk status.

3. TOOLS AND PRACTICES

A Risk Log will be maintained by the clinical trials operations manager or other designee and will be reviewed as a standing agenda item for trial team meetings.

Risk Management Plan Approval

The undersigned acknowledge they have reviewed the Risk Management Plan for the RACE trial. Changes to this Risk Management Plan will be coordinated with and approved by the undersigned or their designated representatives.

Signature:		Date:	
Print Name:	Alain Barrois		
Role:	Acting Clinical Trials Operations Manager		

		Date:	
Signature:			
Print Name:			
Role:			

APPENDIX 10 Members of the Trial Steering Committee

Regis Peffault de Latour, Paris, France (PI)

Antonio M Risitano, Naples, Italy (PI)

Andrea Bacigalupo, Genoa, Italy

Rodrigo Calado, Sao Paulo, Brazil

Carlo Dufour, Genoa, Italy

Austin Kulasekararaj, London, UK

Judith Marsh, London, UK

Jakob Passweg, Basel, Switzerland

Philip Scheinberg, Sao Paulo, Brazil

Hubert Schrezenmeier, Ulm, Germany

Britta Höchsmann, Ulm, Germany

Alicia Rovo, Basel, Switzerland

Gerard Socié, Paris, France

André Tichelli, Basel, Switzerland

Carlos Vallejo, San Sebastian, Spain