Name of sponsor/company: Universitätsklinikum Hamburg-Eppendorf	Individual study table referring to part of the dossier *not applicable* 17-04-2019	
Name of finished product: • e.g. Prednison • Certican (Everolimus)		
Name of active ingredient: • Prednisone • Everolimus		

Title of study:
Treatment of newly diagnosed moderate or severe chronic graft-versus-host disease with prednisone and everolimus (PredEver first) - A prospective multicenter phase IIA study -

Investigators:

- Center no. 001 | Prof. Dr. med. Nicolaus Kröger | Hamburg | Germany
- Center no. 002 | PD Dr. med Herbert Sayer, Anne Klink | Jena| Germany
- Center no. 003 | Dr. med. Eva Maria Wagner | Mainz| Germany
- Center no. 004 | Prof. Dr. med. Daniel Wolff | Regensburg| Germany
- Center no. 005 | Dr. med. Stephanie von Harsdorf | Ulm| Germany
- Center no. 006 | Wiesbaden| Germany *
- Center no. 007 | Dresden| Germany *
- Center no. 008 | PD Dr. med. Christian Könecke | Hannover| Germany
- Center no. 009 | Prof. Dr. med. Dr. h.c. Dietger Niederwieser | Leipzig| Germany *

**These sites did not enroll patients. Missing investigator information due to lack of consent to be mentioned by name.*

Study center(s): 9

- Center no. 001 | Universitätsklinikum Hamburg-Eppendorf; Interdisziplinäre Klinik für Stammzelltransplantation; Hamburg, Germany
- Center no. 002 | Universitätsklinikum Jena; Klinik für Innere Medizin II; Abteilung Hämatologie und Internistische Onkologie; Jena, Germany
- Center no. 003 | Universitätsmedizin der Johannes Gutenberg-Universität Mainz; III. Medizinische Klinik und Poliklinik; Mainz, Germany
- Center no. 004 | Klinikum der Universität Regensburg; Klinik und Poliklinik für Innere Medizin III; Allogene Transplantation / chronische GvHD; Regensburg, Germany
- Center no. 005 | Medizinische Universitätsklinik Ulm; Klinik für Innere Medizin III; Ulm, Germany
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- Center no. 007 | Universitätsklinikums Carl Gustav Carus Dresden; Medizinische Klinik und Poliklinik I, Dresden, Germany
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Studied period (years):	5 years	**Phase of development:**	IIa
Date of first enrolment	06-Mar-2013		

Date of last completed 07-Feb-2018 Recruitment has not been interrupted and the study was completed regularly.	

Objectives:

Primary objective

- The primary endpoint is the rate of treatment success at 6 months after initiation of treatment for cGvHD.

Secondary objectives

Secondary objectives are:

- To evaluate the overall survival rate of patients treated with prednisone and everolimus for cGvHD.
- To evaluate the speed of response (time to achievement of CR or PR) of patients treated with prednisone and everolimus for cGvHD.
- To evaluate the time to treatment failure, treatment failure being defined as progression of cGvHD after ≥ 2 weeks in any organ, lack of response (CR/PR) after 12 weeks and/or addition of secondary systemic treatment for cGvHD.
- To evaluate the relapse rate of underlying malignancies of patients treated with prednisone and everolimus for cGvHD.
- To assess the side effects of prednisone and everolimus in patients with cGvHD.

Methodology:

Open-label, uncontrolled, single-arm, prospective multicenter phase IIa-study

Number of patients (planned and analyzed):

Planned: 60 Analyzed: 36

Diagnosis and main criteria for inclusion:

Trial indication:

Chronic graft-versus-host disease (cGvHD)

Inclusion criteria:

1) Patient's written informed consent
2) Women and men capable of reproduction must agree to use adequate contraceptive measures (condom, intrauterine devices, oral contraceptives) until three months after termination of treatment
3) Age ≥ 18 years
4) Diagnosis of classic cGvHD according to NIH criteria and fulfilment of criteria for moderate or severe cGvHD
   or
   Diagnosis of overlap syndrome according to NIH criteria and fulfilment of criteria for moderate or severe cGvHD and ≤ clinical grade 2 of acute GvHD of the gut and no grade 4 acute GvHD of the skin.

NB: A maximum of 30 patients with overlap syndrome were included in the trial.

Exclusion criteria:

1) Late persistent or recurrent acute GvHD without evidence of cGvHD
2) Relapsed or progressive malignant disease (other than minimal residual disease diagnosed by molecular methods)
3) Severe uncontrolled infections
4) Pregnant or lactating women
5) Inability to tolerate 1 mg/kg prednisone
6) Inability to take oral medication
7) Known hypersensitivity to everolimus
8) History of mTOR inhibitor associated non-infectious pneumonitis
9) Participation in another interventional clinical trial with intervention within < 30 days
10) Prior use of mTOR inhibitor (everolimus or sirolimus) for treatment of acute GvHD
11) Prior systemic treatment of cGvHD > 72 h. Patients treated for > 72h for cGVHD may be included in the trial if cGVHD was mild and no systemic steroids and/or mTOR-Inhibitors were used.
12) Psychiatric illness that would prevent granting of informed consent
13) Active viral infection with HIV, hepatitis B or hepatitis C
14) Severe cardiovascular disease (uncontrolled arrhythmias, congestive heart failure NYHA III or IV, or symptomatic ischemic heart disease)
15) History of mTOR inhibitor or CNI-associated TMA that led to discontinuation of mTOR inhibitor or CNI
16) Patients with neutrophils < 1,000/µl and/or platelets < 20,000/µl at time of screening
17) Donor lymphocyte infusion within the last 30 days
18) Pre-existing hyperlipidemia prior to treatment with calcineurin inhibitor or mTOR inhibitor
19) Wound healing complications
20) Active lymphoma as well as other malignancies
21) Edema (angioneurotic or peripheral)
22) Peptic ulcer
23) Severe colitis ulcerosa
24) Diverticulitis
25) Severe osteoporosis
26) Poorly controlled hypertension
27) Glaucoma (angle closure or open angle)
28) Cornea ulcer or cornea-injuries
29) Severe diabetes mellitus

Test product, dose and mode of administration, batch number:

Test product and mode of administration:

Prednisone:

- orally or intravenous (if patients are unable to take oral formulations)
- Initial dose: 1mg/kg bodyweight o.i.d. (morning) for ≥2 weeks
- Stepwise tapering upon CR:
  Duration of each step 2 weeks (1.0 mg to 0.3 mg) or 4 weeks (0.2 mg – 0 mg)
  Steps: 1.0 mg, 0.8 mg, 0.6 mg, 0.4 mg, 0.3 mg, 0.2 mg, 0.1 mg, 0.05 mg, 0.05 mg (every other day), 0.025 mg (every other day), 0 mg.
  In case of flare, tapering may be halted or prednisone increased two to three steps back.
- Stepwise tapering upon PR:

Duration of each step 2 weeks (1.0 mg to 0.6 mg), 3 weeks (0.5 mg to 0.4 mg) or 4 weeks (0.3 mg – 0.05 mg [every other day])
Steps: 1.0 mg, 0.8 mg, 0.6 mg, 0.4 mg, 0.3 mg, 0.2 mg, 0.1 mg, 0.05 mg, 0.05 mg (every other day).
In case of flare, tapering may be halted or prednisone increased two to three steps back.

Everolimus (RAD001; Certican®):

- p.o. (whole tablets or dispersible tablets)
- Initial dose: 0.75 mg b.i.d.
  Dose adjustment to targeted serum trough level of 3-8 µg/l measured by HPLC or immunosassay 4 to 5 days after each preceding dose adjustment step.
  Dose adjustments according to clinical judgement.
- Initial dose for patients with abnormal liver function: 0.25 mg b.i.d.
  Increment of daily dose: maximum 0.5 mg per week.

Batch numbers:

- Everolimus
  0.25 mg: S0006 VMLK/2008-1560 (PCN 10275); S0006A; S0008B; S0014B
  0.50 mg: S0142 VMLK/2011-0158 (PCN 10276); S0001A; S0013; S0031; S0024; S0146; S0147
  0.75 mg: S0049 VMLK/2010-1349 (PCN 10271); S0038A; S0045B, S0051A
  1.00 mg: S0001

- Prednisone
  Merchandise: not recorded

Duration of treatment:

Treatment on protocol for maximum 12 months. Patients still responding can continue with treatment off protocol at the discretion of the local physician.

Reference therapy, dose and mode of administration, batch number:

Not applicable. Single arm, open label study.

Criteria for evaluation

Efficacy:

- Response to treatment had to be assessed
  - two weeks and one, three, six, nine and twelve months after initiation of treatment
  - before introduction of secondary treatment
  - in case of premature study withdrawal.

  Response assessment had to be performed prospectively as described in the publication by Martin et al., 2009 and retrospectively according to NIH consensus recommendations [Pavletic et al., 2006].

- Rate of treatment success at 6 months after initiation of treatment.

  Treatment success defined as: Patient being alive and having achieved a complete response (CR) or partial response (PR) of cGvHD without addition of secondary systemic treatment

for cGvHD (see below) and without development of relapse of underlying disease. Addition of any immunesuppressive or immunomodulatory systemic therapy aimed at treating or controlling symptoms of cGvHD is considered treatment failure. Examples of secondary systemic therapies include (but are not limited to) ciclosporin A (CSA), tacrolimus, methotrexate, mycophenolate, rituximab, azathioprine, pentostatine, cyclophosphamid, chloroquine, imatinib, dasatinib, thalidomide, alemtuzumab, etanercept, antithymocyte globulin, infliximab, basiliximab, daclizumab, extracorporeal photopheresis, psoralen with UVA-irradiation (PUVA), pulsed steroid exceeding a dose of 2 mg/kg/day.

- Overall survival rate of patients treated with prednisone and everolimus, i.e. proportion of deaths
- Speed of response (time to achievement of CR or PR) of patients treated with prednisone and everolimus for cGvHD; Kaplan-Meier Analysis
- Time to treatment failure; Kaplan-Meier Analysis
  Treatment failure being defined as progression of cGvHD after ≥ 2 weeks in any organ, lack of response (CR/PR) after 12 weeks and/or addition of secondary systemic treatment for cGvHD.
- Relapse rate of underlying malignancies of patients treated with prednisone and everolimus for cGvHD, i.e. proportion of relapses.

Safety:

- Evaluation of all adverse events
- Particular emphasis on:
  - Thrombotic microangiopathy (TMA)
  - Non-infectious pneumonitis (NIP)
  - Avascular osteonecrosis

Statistical methods:

- Analysis sets:
  Safety set (SAF): All enrolled patients who received at least one dose of study medication are included in the SAF.
  Analyses of primary/secondary efficacy variables and safety variables were performed with the SAF.
  Enrolled set: The Enrolled set includes all screened patients with all inclusion/exclusion criteria met.

  Note: In the primary analysis two patients out of 36 patients which were deemed screening failure retrospectively were not regarded as screening failures in the primary analysis set (Safety Set; SAF) by the statistic vendor. In addition, classification of treatment failure and treatment success by the statistic vendor was not conclusive. Furthermore, the statistic vendor provided no patient listings showing reasons for classification. Due to these reasons, the primary and secondary endpoints were reanalyzed with a revised Analysis Set. In the revised Analysis Set, the two additional screening failures were regarded as screening failure and excluded from analysis. Furthermore, a reassessment of the classification of patients in respect to treatment success and treatment failure was performed for the revised Analysis Set.

- General:
  Descriptive statistics are provided for all variables according to the type of variable summarized.
  Quantitative variables are summarised by using n, arithmetic mean, SD, median and range (minimum and maximum).

Categorical variables are summarised by using frequency distributions and percentages.

Hypothesis testing was carried out at the alpha = 0.05 level (two-sided). For all inferential analyses, p-value were rounded to three decimal places. Statistical significance was declared if the rounded p-value was less than or equal to 0.05.

No multiplicity adjustment was implemented. No formal interim analysis was planned or conducted for this study. No subgroup analyses were planned or conducted for this study.

Definitions of endpoints:

- Analysis of the primary endpoint:
  - Rate of treatment success at 6 months after initiation of treatment for cGvHD.

    Treatment success was defined as:
    - patient being alive at 6 months from study medication first intake: reached if patient did not have death event reported or the death event is after 6 months from treatment first intake and
    - with no development of relapse of underlying disease until 6 months from study medication first intake: reached if patient did not have relapse event reported or the relapse event is after 6 months from study medication first intake
    - having achieved a CR or PR of cGvHD at 6 month evaluation (Visit 9 - Week 24) without addition of secondary systemic treatment for cGvHD* (concomitant at any timepoint) until 6 months from study medication first intake: reached if patient did not take a secondary systemic treatment for cGvHD or if the patient takes a secondary systemic treatment after 6 months from treatment first intake

    Hence, treatment success was reached if all of the above conditions were true.

    The number and percentage of patients classified as treatment success/treatment failure at Visit 9 (Week 24) were presented and a 95% binomial proportion CI was computed using the Wilson score method.

    **Addition of any immunosuppressive or immunomodulatory systemic therapy aimed at treating or controlling symptoms of chronic GvHD is considered treatment failure, examples of therapeutic classes are antimycobacterials, antineoplastic agents, antiprotozoals, antipsoriatics, corticosteroids for systemic use, immunostimulants or immunosuppressants. Per protocol previous immune-suppressants which were given concomitant but were tapered out after baseline as well as systemic steroid (H02AB) which did not exceed a dose of 2 mg/kg/day were not considered secondary systemic treatment for cGvHD.*

- Analysis of the secondary endpoints:
  - Evaluation of the overall survival rate of patients treated with prednisone and everolimus for cGvHD, i.e. proportion of deaths.

    Patients completing the 1-year treatment phase and joining the FU phase were observed until end of FU or were censored upon discontinuing FU Phase for reasons other than death.
    Patients discontinuing treatment prematurely or discontinuing treatment phase for reasons other than death were censored at the date of study discontinuation.

  - Evaluation of the speed of response (time to achievement of CR or PR) of patients treated with prednisone and everolimus for cGvHD; Kaplan-Meier analysis

For patients with at least one response (either CR or PR), speed of first response was calculated as the weeks between the date of first study medication intake and the date of visit at which the first response occurs.

Patients without the first event or who are discontinued before having it were considered as "censored" at the date of end of study.

In order to determinate the speed of first response, the following rules were applied in case of partial dates:
- if only the day was missing, the 15th of the month was assumed;
- if the day and the month are missing, 30th June was assumed;
- if at least one of the dates for the calculation was missing or unknown, the speed of response wasn´t calculated.

- Evaluation of the time to treatment failure; Kaplan-Meier analysis

  Treatment failure was defined as:
  - progression of cGvHD after or at two weeks (from first intake of study medication) in any organ: reached if a patient worsened in any of the organ responses (higher score) starting from Week 2 visit; and/or
  - lack of response (CR/PR) after twelve weeks: reached if a patient didn´t report a CR or PR result after Week 12 visit; and/or
  - addition of secondary systemic treatment for cGvHD, reached if a patient had been treated with a secondary systemic treatment for cGvHD during the study.

  Hence, treatment failure was reached if one or more of the above conditions was true.

  Time to first treatment failure was calculated as time to whichever of the described events above comes first (using either dates of visits, in case of progression and lack of response, or medication start date if in presence of secondary systemic treatment).

  Particularly, in case of reached lack of response after twelve weeks, date of event was specifically calculated as date of the last visit with lack of response (i.e. neither CR nor PR).

  For patients with event, time to first treatment failure was calculated as the weeks between the date of first study medication intake and the date at which the treatment failure occurs (whichever event occurs first).

  Patients without the event or who discontinued before having it were considered as "censored" at the date of end of study.

- Evaluation of the relapse rate of underlying malignancies of patients treated with prednisone and everolimus for cGvHD, i.e. proportion of patients with relapses.

  A relapse was defined as:
  - a recurrence of malignancies.

Patients completing the 1-year treatment phase and joining the FU phase were observed until end of FU or were censored upon discontinuing FU Phase for reasons other than a recurrence of malignancies.
Patients discontinuing treatment prematurely or discontinuing treatment phase for reasons other than a recurrence of malignancies were censored at the date of study discontinuation.

- Assessment of the side effects of prednisone and everolimus in patients with cGvHD.

Statistics:

- The number and percentage of patients who experience death and who experience at the least one relapse were presented and a 95% binomial proportion CI was computed using the Wilson score method.

- Time to first treatment failure and speed of first response was analyzed using the Kaplan-Meier estimator. The number of event-free patients at the beginning of the period, the cumulative number of patients with event at the end of the period and the probability of being event-free at the end of the period with the associate 95% CIs were presented by treatment for the following study periods:
[0-2] weeks, [2-4] weeks, [4-6] weeks, [6-8] weeks, [8-12] weeks, [12-16] weeks, [16-20] weeks, [20-28] weeks, [28-36] weeks, [36-44] weeks and [44-EoT].
The point estimates and the relative 95% CIs were presented by treatment for the 75^{th}, 50^{th} and 25^{th} percentiles.
- Adverse events were categorized into pre-treatment adverse events, treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse drug reactions (ADRs), adverse events leading to treatment discontinuation.
Two AEs with the same Preferred Term (PT) and classified in the same category (pre-treatment AE or TEAE) were considered as two different events when calculating the "number of events".
Pre-treatment AEs and TEAEs were presented separately. Pre-treatment AEs were presented in the listings only. The number of treatment-emergent AEs, SAEs, ADRs, serious ADRs, AEs leading to treatment discontinuation, and the number and the percentage of patients experiencing treatment-emergent AEs, SAEs, ADRs, serious ADRs, AEs leading to treatment discontinuation were summarised.
AEs were coded using the MedDRA dictionary (version 15.1). The number of AEs, and the number and the percentage of patients with at least one AE were presented by SOC and PT for treatment-emergent AEs and SAEs.

Summary – Conclusions

Study information and demographics

This study was a prospective multicenter phase IIA study to evaluate the treatment of patients with newly diagnosed moderate or severe chronic graft-versus-host disease with prednisone and everolimus. The study was conducted at nine sites in Germany of which six sites recruited patients. In total, 38 patients had been recruited of which 36 were included in the basic analysis sets (Safety Set/Enrolled set).

Mean (±SD) duration in the treatment phase was 250.0 ± 130.8 days, mean time of follow-up was 304.0 ± 135.2 days and mean total study duration 554.0 ± 213.9 days.

The study population (N=36) comprised 13 female and 23 male patients and was significantly shifted towards male patients. Mean age of the study population was 52.4±14.3 years, mean height 174.2±11.3 cm and mean weight 75.2± 20.6 kg. Evaluation of vital signs at baseline revealed a mean heart rate of 82.5±20.8 bpm and mean systolic/diastolic blood pressure of 122.5±19.0/76.4±10.1 mmHg, respectively. Mean body temperature at baseline was 36.3±0.4 °C. In respect to disease severity, the majority of patients (61.1%) presented with moderate disease. The mean time since diagnosis for all patients was 11.3±28.7 days.

The most common past diseases were PT Gamma-glutamyltransferase increased | SOC Investigations affecting 25.0% of the patients, followed by PT Blood alkaline phosphatase increased | SOC Investigations and PT Hypertriglyceridaemia | SOC Metabolism and nutrition disorders affecting 16.7% of the patients each. 13.9% of the patients each were affected by PT Acute myeloid leukaemia | SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps), PT Alanine aminotransferase increased | SOC Investigations and PT Aspartate aminotransferase increased | SOC Investigations. In respect to medical history, any of the other reported medical concepts was attributed to less than 12.5% of the patients.

The most common concurrent diseases were PT Hypertension | SOC Vascular disorders affecting 33.3% of the patients, followed by PT Diabetes mellitus | SOC Metabolism and nutrition disorders and PT Oedema | SOC General disorders and administration site conditions affecting 13.9% of the patients each. 11.1% of the patients each were affected concurrently by PT Hypercholesterolaemia | SOC Metabolism and nutrition disorders and PT Benign prostatic hyperplasia | SOC Reproductive system and breast disorders. In respect to concurrent diseases, any of the other reported medical concepts was attributed to less than 10.0% of the patients.

The most common prior medications were calcineurin inhibitors from Anatomic Main Group Antineoplastic and immunomodulating agents used by 16.7% of the patients. In respect to prior medications, substances from other chemical subgroups were used by less than 7.5% of the patients.

The most common concomitant medications were Nucleosides and nucleotides excl. Reverse Transcriptase Inhibitos and Triazole derivates (both allocated to Anatomic Main Group Antiinfectives for systemic use) used by 91.7% of the patients each**,** Proton pump inhibitors (Anatomic Main Group Alimentary tract and metabolism) were used by 88.9% of the patients. 72.4% of the patients used combinations of sulfonamides and trimethoprim (Anatomic Main Group Antiinfectives for systemic use), 66.7% of the patients Magnesium (Anatomic Main Group Alimentary tract and metabolism) and 61.1% of the patients used Macrolides (Anatomic Main Group Antiinfectives for systemic use) concomitantly to the study medication. About half of the patients (52.8%) each used Fluoroquinolones (Anatomic Main Group Antiinfectives for systemic use), Vitamin D and analogues (Anatomic Main Group Alimentary tract and metabolism) or Sulfonamides (Anatomic Main Group Cardiovascular System). In respect to concomitant medications, substances from other chemical subgroups were used by less than 50% of the patients.

Patients were on everolimus treatment on average for 35.4±18.0 weeks and on prednisone treatment for 34.7±17.2 weeks. Estimated mean everolimus dose was 0.8±0.5 mg and estimated mean serum level was 7.2±3.2 µg.

Efficacy results:

Note: In the primary analysis two patients out of 36 patients which were deemed screening failure retrospectively were not regarded as screening failures in the primary analysis set by the statistic vendor. In addition, classification of treatment failure and treatment success by the statistic vendor was not conclusive. Furthermore, the statistic vendor provided no patient listings showing reasons

for classification. Due to these reasons, the primary and secondary endpoints were reanalyzed with a revised Analysis Set. In general, results did not differ significantly between the two analysis sets. However, time to treatment failure was significantly shorter for the revised Analysis Set.

The primary efficacy endpoint was the proportion of patients with treatment success in week 24. Upon analyzing the Safety Set, more than half of the patients (55.6%; 95%CI: 40 to 70%) showed treatment success in week 24. Upon analyzing a revised Analysis Set which was corrected for erroneously included patients, the proportion of patients with treatment showed even higher success rates (55.9%; 95%CI: 39 to 71%).

The number of patients experiencing death during the study course was 22% (95%CI: 12 to 38%) for the Safety Set and 20.5% (95%CI: 10 to 37%) for the revised Analysis Set, respectively.

The estimated median time to first response was 2.3 weeks (95%CI: 2.0 to 2.6 weeks) for the Safety Set and 2.3 weeks (95%CI: 2.1 to 2.6 weeks) for the revised Analysis Set, respectively.

The median time to treatment failure was estimated to 38.1 weeks (95% CI: 19.9 to 54.0 weeks) for the Safety Set and 24.7 weeks (95% CI: 20.0; - weeks) for revised Analysis Set, respectively.

The number of patients experiencing a relapse was 8.3% (95%CI: 3 to 22%) for the Safety set and 5.9% (95%CI: 2 to 19%) for the revised Analysis Set, respectively.

Evaluation of the proportion of patients showing predefined side effects, i.e. thrombotic microangiopathy, pneumonitis and osteonecrosis revealed only one patient showing pneumonitis in the Safety Set. In the revised Analysis Set none of the patients showed either of the pre-defined side-effects.

Safety results:

Analysis of adverse events was performed with the safety population, which includes 36 patients and analysis of SAEs was done for a modified Safety Set which includes all patients that received study treatment but were later on deemed screening failure (N=38). Until completion of the study, 603 treatment emergent adverse events (AEs) for 36 patients (100.0%) and 45 treatment emergent serious adverse events (SAEs) for 19 patients (50.0%) were reported. For 316 of the AEs (affecting 31 patients [86.1%]) and 16 of the SAEs (affecting ten patients [26.3%]) a causal relationship to the study drug was anticipated. In total, eight patients had to discontinue treatment due to AEs.

More than 50% of the patients suffered from at least one treatment emergent AE originating from SOC Infections and infestations (27 patients [75.0%]), SOC Investigations (27 patients [75.0%]), SOC Metabolism and nutrition disorders (26 patients [72.2%]), SOC Gastrointestinal disorders (22 patients [61.1%])and SOC General disorders and administration site conditions (19 patients [52.8%]). Less than 50% of the patients each suffered from AEs of other SOCs.

The most common treatment emergent AEs were hypertriglyceridaemia (PT Hypertriglyceridaemia | SOC Metabolism and nutrition disorders) affecting 17 patients (47.2%), followed by diarrhoea (PT Diarrhoea | SOC Gastrointestinal disorders) affecting 14 patients (38.9%) and increased alanine aminotransferase levels (PT Alanine aminotransferase increased | SOC Investigations) affecting 12 patients (33.3%). Eleven patients (30.6%) each were affected by nasopharyngitis (PT Nasopharyngitis | SOC Infections and infestations), increased γ-GT levels (PT Gamma-glutamyltransferase increased | SOC Investigations) and peripheral oedema (PT Oedema peripheral

| SOC General disorders and administration site conditions). Less than 30% of the patients each were affected by AEs of other medical concepts.

During the course of the study, 45 AEs for 19 patients (50.0%; modified Safety Set) were assessed as serious by the investigators. Of note, twelve of these SAEs for eight patients (from nine SAE reports) were not captured as AE on the CRF and not entered in the study database. These SAEs were added after database lock to the analysis.
Seven SAEs concerning four patients (10.5%) led to death.

Most patients suffered from at least one treatment emergent SAE originating from SOC Respiratory, thoracic and mediastinal disorders (6 patients [15.8%]) and SOC Infections and infestations (5 patients [13.2%]). Three patients (7.9%) each had at least one SAE originating from SOC Cardiac disorders or SOC Gastrointestinal disorders, respectively.

One to three patients suffered from a distinct SAE within a particular SOC.

The most common treatment emergent SAEs affecting more than 5% of the patients in total were diarrhea (PT Diarrhoea | SOC Gastrointestinal disorders) affecting three patients (7.9%), followed by pneumonia (PT Pneumonia | SOC Infections and infestations), Depression (PT Depression | SOC Psychiatric disorders), renal failure (PT Renal failure | SOC Renal and urinary disorders) and back pain (PT Back pain | SOC Musculoskeletal and connective tissue disorders) affecting two patients (5.3%) each. Any of the other SAEs was observed only for one particular patient.

In respect to deaths, there was no shift towards a specific SOC.

During the course of the study, in total 752 laboratory values for 32 patients were classified as being abnormal with clinical significance. 58 values for 20 patients were observed at screening (n=38), 53 values for 19 patients at baseline (n=29), 621 values for 32 patients during the treatment phase (n=37) and 20 values for eight patients during the subsequent FU phase (n=29).

At screening, most of the abnormal clinical chemistry values with clinical significance were observed for liver enzymes gamma-GT, ALT, AST and alkaline phosphatase (AP). Also at baseline, these laboratory parameters showed highest incidence rates of abnormal values with clinical significance. Beside these laboratory parameters, also triglyceride-values were often abnormal with high frequency.
During the treatment phase most patients were affected by abnormal total cholesterol values with clinical significance, followed by triglyceride-, gamma-GT-, ALT-, AST-, total glucose-, alkaline phosphatase- and LDL-values. During the treatment phase more than half of the patients showed at least one clinical abnormal laboratory value for total cholesterol, triglycerides and gamma-GT.
In the follow-up phase, clinical significant laboratory values were reported only occasionally, with highest frequencies reported for gamma-GT.
All other abnormal clinical chemistry values with clinical significance affected less than 15% of the evaluated patients during a particular study period.

Abnormal hematology values with clinical significance were reported occasionally at screening, baseline and during follow-up. During the treatment phase most patients (30%) were affected by abnormal values for platelets.

All other abnormal hematology values with clinical significance affected less than 15% of the evaluated patients during a particular study phase.

The number of patients for which a new abnormality of clinical significance compared to previous visits was reported varied from 6.9% to 47.4% of the assessed patients. No temporal trend in respect

to an increase or decrease of the percentage of patients with new abnormalities could be observed from baseline to EoS.

The relative incidences and type of adverse events observed in this study reflect the safety information provided in the SmPCs of everolimus and prednisone. Most of the SAEs were assigned to different medical concepts affecting only one particular patient. However, three out of 33 SAEs were diarrhoea.
Four deaths (11.1%) occurred during the study run-time, which is considerably more than in the study CRAD001A2309 in which about 2.5% to 3.2% deaths (1.5 mg and 3.0 mg everolimus) after twelve months were observed. Two of the four fatal SAEs in this study were assumed to be related to the study medication (everolimus and/or prednisone). Due to the limited number of treated patients, the incidence rates might not be representative and have to be taken with caution.
No safety signals emerged from other safety assessments.

Summarizing, no new safety signals or safety concerns emerged from the safety data obtained within this study.

Conclusion

In the primary analysis two patients out of 36 patients which were deemed screening failure retrospectively were not regarded as screening failures in the primary analysis set by the statistic vendor. In addition, for one patient allocation of secondary treatment was not correct and classification of treatment failure and treatment success by the statistic vendor was not conclusive; besides, the statistic vendor did not provide patient listings showing reasons for classification as treatment failure.
Thus, the primary and secondary endpoints were reanalysed with a revised Analysis Set in which these aspects were considered. In general, results did not differ significantly between the two analysis sets. However, time to treatment failure was significantly shorter for the revised Analysis Set.
For the discussion of the results, only results derived from the revised Analysis Set were regarded.

The primary endpoint, treatment success at six months was observed for 55.9% of the study patients. Six out of 34 patients (16.7%) received secondary treatment between month 6 and month 12.
For comparison, recently, results of a randomized phase II/III study by Carpenter et al. were published who evaluated the efficacy of prednisone (PDN) and sirolimus (SRL) vs. prednisone (PDN), sirolimus (SRL) and CNI in 138 patients with cGvHD (study code: BMT CTN 0801; NCT NCT01106833) [Carpenter et al., 2018]. As for this study, the primary endpoint of the study was the proportion of patients being alive with CR or PR and without relapse or secondary therapy at month 6. In that study, 48.6% (PDN/SRL) and 50.0% (PDN/SRL/CNI) showed CR or PR at month 6. Of note, about 20%-30% of patients receiving PDN/SRL and 11%-24% receiving PDN/SRL/CNI received secondary treatment between month 6 and month 12.
In a different study, Inamoto et al. used a novel composite endpoint, i.e. failure-free survival (FFS) which was defined as absence of second-line treatment, non-relapse mortality and recurrent malignancy. This endpoint deviates from the primary endpoint defined in this study, as it did not directly addresses response (CR/PR) and furthermore there was no direct predefined procedure to handle disease progression, in terms of second-line treatment initiation, as second-line treatment initiation was at the discretion of the investigator. Four hundred patients receiving initial systemic treatment for moderate to severe cGvHD were included. The FFS rate was 68% after six months and 54% after twelve months, respectively [Inamoto et al., 2014].
Already in 2009, Martin et al. conducted a study to evaluate a beneficial effect of the addition of MMF to the standard treatment regimen with CNI or SRL and (for most of the patients) PDN at initial

doses of 1.0 mg/kg/day [Martin et al., 2009]. The primary endpoint was the rate of patients with treatment success after two years. Deviating from the definition of treatment success within this study, Martin et al. defined treatment success as withdrawal of all systemic treatment, including the study drug, after resolution of all reversible manifestations of cGVHD with no secondary systemic therapy. Martin et al. observed treatment success rates after two years of 15% for patients receiving the standard treatment plus MMF, and 13% for patients receiving only the standard treatment, respectively. The cumulative incidence of success for the primary endpoint was 23% among 74 patients in the MMF arm and 18% among 77 patients in the control arm. However, cumulative incidences of treatment success after six months were about 80% for the control arm and 60% for the MMF arm.

Recently, Martin et al. published results of another study in which they analysed outcomes in a cohort of 328 patients that were enrolled within three months after diagnosis of cGvHD [Martin et al., 2017]. Patients received initial treatment for cGvHD including PRD with or without CNI (58%), PRD with or without CNI and other agents (29%), and other agents without PRD (13%). The study aimed to narrow down an endpoint that is associated with clinical benefit after initial treatment of cGvHD. They found that CR or PR at one year without secondary systemic treatment provides clinical benefit in patients with cGVHD. However, success as defined by that novel endpoint was reported to be currently observed for less than 20% of patients with cGvHD. Furthermore, conclusions made from results obtained at six months were found in that study to be less striking, especially as about 45-55% of the patients in that study received secondary systemic treatment between six months and one year [Martin et al., 2017].

Thus, the significance of the primary endpoint in this study might also be limited the time point (month 6) for assessing treatment success. However, one of the secondary endpoints of this study was to access the time to treatment failure. At 1 year, treatment failure was observed in 63% of the patients indicating a treatment success rate of 37%, which appears to be higher than reported by Martin et al (less than 20%).

In respect to the overall survival (OS) rate of patients treated with PDN and everolimus for cGvHD, 79.5% of the patients were alive until study completion. For comparison, Carpenter et al. observed OS rates at two (one[1]) years of 81.5% (87%) for PRD/SRL and 74% (78%) with PRD/SRL/CNI, respectively [Carpenter et al., 2018]. Similar rates were also observed by Martin et al, who reported survival rates of 87% of the patients in the control arm and for 74% in the MMF arm, respectively [Martin et al., 2009].

In respect to the relapse rate of underlying malignancies of patients treated with prednisone and everolimus for cGvHD, 5.9% of the patients experienced a relapse until study completion. These values are similar to results observed in other studies [Inamoto et al., 2014; Martin et al., 2017], in which values of about 10-20% (81/400 and 32/328) of patients with recurrent diseases after twelve months were observed.

In respect to safety monitoring, incidence rates of thrombotic microangiopathy (TMA), non-infectious pneumonitis (NIP) and avascular osteonecrosis were assessed, as these events were known side effects of cGvHD treatments, in particular treatment with CNIs, SRL/everolimus and corticosteroids, respectively. Thrombotic microangiopathy (TMA) is a known side effect of CNIs. In this study none of the patients experienced TMA. This is quite similar to low proportions observed in other studies that range from about 1% to about 5% [Couriel et al., 2005; Carpenter et al., 2018].

In this study, one patient (2.6%) suffered from non-infectious pneumonitis (NIP). NIP is a known side effect of SRL and everolimus and values reported in literature show broad range of about 1% up to about 17% [Lee et al., 2012; Lopez et al., 2014; Baas et al., 2014; White et al., 2010; Carpenter et al., 2018]. Even higher incidence rates of 50% were reported in a phase II study of everolimus plus oral prednisone with eight patients with metastatic renal cell cancer [Lolli et al., 2017]. The value observed in this study is similar to the values observed in other studies.

[1] *One year-values were not given in the publication but approximated from a survival plot.*

Corticosteroids are considered a risk factor for the development of avascular osteonecrosis (AVN). none of the patients in this study showed AVN. Incidence rates reported in literature range from about 2% to 10% [Tauchmanovà et al., 2003; McAvoy et al., 2010]. The study published by McAvoy et al. investigated the corticosteroid dose dependent risk for avascular osteonecrosis risk; it revealed a 4.0 to 8.6 fold cumulative prednisone dose-dependent increased risk for patients receiving PDN [McAvoy et al., 2010]. Of note, in that study the median time from HCT to AVN was depending on the transplant type 15 (4-41) to 21 (1-80) months. Thus, significance of values observed in this study might be limited by the shorter time of observation.
Overall, despite the differences in the concrete definition of endpoints and the time point for assessing the (primary) endpoint(s) between the various studies, the data did not indicate beneficial effects from addition of everolimus to the prednisone treatment regimen in terms of improvement of the primary endpoint (treatment success at six months). Addition of everolimus to prednisolone did not increase risk of relapse of underlying malignancy and was not associated with an increased risk of other side effects such as TMA and NIP or AVN. Notably the rate of treatment failure at one year was 63%, meaning 37% rate of treatment success, which appears higher than previously reported rates (Martin et al., 2017). This is of particular importance because this endpoint is associated with clinical benefit (Martin et al., 2017).

Date of report
31-Mar-2019

Substantial protocol amendments
After initial approval by the health authorities and the ethics committee, the protocol was amended twice.
Subject of the first amendment was to simplify clinical trial routines as well as to correct minor inconsistencies in the protocol. A Data Safety Monitoring Board (DSMB) was created to ensure the safety of the participants, details concerning dose modification and concomitant medication were added, and visit schedule was amended by safety visits for additional physical examination, clinical lab tests and concomitant medication. Adaption of assessment of skin manifestation of cGvHD biopsy which was allowed to be organized as per local routine (a central review could still be arranged by each site), and adaption of adverse event documentation.
Subject of the second amendment was also to simplify clinical trial routines as well as to correct minor inconsistencies in the protocol. The number of centers was increased, the duration of the study was prolonged by one year, exclusion criteria 11 was clarified and calcineurin inhibitor tapering was prolonged from 1 - 3 to 1 - 4 weeks.