SYNOPSIS

Name of Sponsor: medac Gesellschaft fuer klinische Spezialpräparate mbH Fehlandtstrasse 3, 20354 Hamburg, Germany	
Name of finished product:	
Name of active ingredient: pegylated recombinant asparaginase	
Title of study:	A randomised, multi-centre, parallel-group, open label, Oncaspar controlled dose ranging trial of three doses of pegylated recombinant asparaginase in adult patients with newly diagnosed acute lymphoblastic leukaemia
Investigators:	Coordinating Investigator: [redacted] Principal Investigators: [redacted]
Study centre(s):	The clinical study was performed in 30 centres in Germany.
Publication (reference):	None.
Studied period (years):	date of first enrolment: 20-Jan-2011 date of last completed: 02-Oct-2012
Phase of development:	Phase I / II
Objectives:	The objective of this trial was the assessment of efficacy and safety of three different doses of pegylated recombinant asparaginase (PEG-rASNase) in comparison to Oncaspar during treatment of adults with *de novo* acute lymphoblastic leukaemia (ALL). This study was to provide first data for determining specific asparaginase (ASNase) doses to yield various durations of asparagine (ASN) depletion which are required within different treatment phases of ALL therapy.
Primary:	Primary objective of this trial was to compare the rate of patients with ASN depletion three weeks after infusion of three different doses of PEG-rASNase in comparison to Oncaspar in the induction treatment of adults with *de novo* ALL.
Secondary:	- To compare the rate of patients with ASN depletion between the treatment arms 1, 2, 4, 5, 6, 7 and 9 weeks after study drug administration - To compare the rate of patients with ASNase activity levels in serum >100 U/L between the treatment arms at defined time points within nine weeks after study drug administration - To compare the duration of ASNase activity levels in serum >100 U/L and its variability after study drug administration between the treatment arms - To compare the following pharmacokinetic (PK) parameters between the treatment arms after study drug administration: maximum plasma concentration (C_{max}), half-life ($t_{½}$), total clearance (CL_{total}), constant of elimination (K_{el}), area under the ASNase serum activity versus time curve of ASNase calculated (AUC_{0-t}) and area under the drug concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) and to assess dose proportionality of different PEG-rASNase dosages

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	- To compare the time profiles of ASNase activity and amino acid levels (ASN, aspartic acid [ASP], glutamine [GLN] and glutamic acid [GLU]) in serum between the treatment arms after study drug administration - To compare the incidence of increased bilirubin Grade III/IV according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0 between the treatment arms within seven weeks after study drug administration - To compare the incidence of all other adverse events (AEs) between the treatment arms within seven weeks after study drug administration - To determine ASNase activity and amino acid levels in cerebrospinal fluid (CSF) before study drug administration and on German Multicentre Trial for Adult Acute Lymphoblastic Leukaemia (GMALL) protocol Days 28, 35 and 42 of the induction phase - To compare anti-ASNase and anti-pegylated L-asparaginase (PEG-ASNase) antibodies in serum within nine weeks after study drug administration - To determine the complete remission (CR) rate and minimal residual disease (MRD) status after the induction phase
Methodology:	Randomised, open label, Oncaspar controlled dose-ranging, multicentre study in parallel groups.
Number of patients (planned and analysed):	planned: 52 enrolled: 48 (due to premature study termination) withdrawn: 2 (before treatment) completed: 46 analysed (safety): 46 analysed (efficacy): 46
Diagnosis and main criteria for inclusion:	Inclusion criteria 1. Previously untreated ALL (pro-B, common, pre-B, early T, thymic T, mature T) 2. Age ≥ 18 years and ≤ 55 years 3. Treatment according to the GMALL 07/2003 protocol or subsequent GMALL protocols for patients with *de novo* ALL 4. Written informed consent 5. Women of child-bearing potential or partners of men with child-bearing potential had to use a highly effective method of contraception (pearl index <1%) such as complete sexual abstinence, combined oral contraceptive, hormone intrauterine contraceptive device, vaginal hormone ring, transdermal contraceptive patch, contraceptive implant or depot contraceptive injection in combination with a second method of contraception like a condom or a cervical cap / diaphragm with spermicide or surgical sterilisation (vasectomy) in male patients or male partners during the study and at least six months thereafter 6. Negative pregnancy test for women of child-bearing potential Exclusion criteria 1. Patients with Philadelphia chromosome (breakpoint cluster region – Abelson murine leukaemia [BCR-ABL]) positive ALL 2. Severe comorbidity or leukaemia-associated complications 3. Known hypersensitivity to ASNase 4. History of severe pancreatitis 5. History of thrombosis or pulmonary embolism 6. Pre-existing clinically relevant coagulopathy 7. Liver dysfunction (e.g. acute or current hepatitis, alcohol or drug abuse) or history of clinically relevant liver disease 8. Bilirubin >1.5 x upper limit of normal (ULN)

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	9. Other current malignancies 10. Severe psychiatric illness or other circumstances which may have compromised the cooperation of the patient or the ability to give informed consent 11. Body mass index >30 kg/m² 12. Known pregnancy, breast feeding
Test products, dose and mode of administration, batch number:	PEG-rASNase (500 U/m², 1000 U/m² or 1500 U/ m²) was administered on Day 0, which corresponded to Day 20 of the induction phase of the GMALL 07/2003 or subsequent protocols. The total dose needed per patient was diluted in 100 mL sterile physiological saline (0.9% NaCl) and administered by intravenous infusion over 1 – 2 hours. The batch number of PEG-rASNase administered during this clinical study was F100412.
Duration of treatment:	After registration the patients were randomly assigned to one of four treatment groups and received the study medication on Day 0 which was equivalent to Day 20 of the induction phase of the GMALL 07/2003 protocol. Blood samples were taken until Day 62 after administration of study medication and CSF samples until GMALL study Day 42. On Day 62 a Final Examination took place. In subsequent treatment phases of the GMALL 07/2003 or subsequent study protocols patients were treated with Oncaspar. Those treatment phases were not a part of this clinical study.
Reference therapy, dose and mode of administration, batch number:	Oncaspar (2000 U/m^2) was administered on Day 0, which corresponded to Day 20 of the induction phase of the GMALL 07/2003 or subsequent protocols. The total dose needed per patient was diluted in 100 mL sterile physiological saline (0.9% NaCl) and administered by intravenous infusion over 1 – 2 hours. The batch numbers of Oncaspar administered during this clinical study were E110136E and F100374A.
Criteria for evaluation:	
Efficacy:	- the rate of patients with ASN depletion between the treatment arms 1, 2, 4, 5, 6, 7 and 9 weeks after study drug administration - the rate of patients with ASNase activity levels in serum >100 U/L between the treatment arms at defined time points within nine weeks after study drug administration - the duration of ASNase activity levels in serum >100 U/L and its variability between the treatment arms after study drug administration - PK parameters C_{max}, $t_{½}$, CL_{total}, K_{el}, MRT, AUC_{0-t} and $AUC_{0-\infty}$ between the treatment arms after study drug administration and to assess dose proportionality of different PEG-rASNase dosages - time profiles of ASNase activity and amino acid levels (ASN, ASP, GLN and GLU) in serum measured at day 0, 1 or 2, 4, 7, 10, 14, 17, 21, 28, 35, 42, 49 and 62 after study drug administration between treatment arms - ASNase activity and amino acid levels in CSF before study drug administration and on GMALL protocol Days 28, 35 and 42 of the induction phase - CR rate and MRD status after induction phase.
Safety:	- AEs were captured beginning from the time point of study drug administration until seven weeks afterwards. Serious adverse reactions were documented until Day 62 of the study - antibodies: anti-ASNase, anti-PEG, anti-Oncaspar and anti-PEG-rASNase antibody titres in serum were determined whenever a blood sample collection was scheduled - laboratory parameters: following standard laboratory parameters had to be determined between Day -5 and Day -1 before PEG-rASNase/Oncaspar administration. They had to be followed up at least once weekly for seven weeks after administration of the study medication (i.e. until Day 49). clinical chemistry: creatinine, bilirubin, aspartate aminotransferase/glutamate oxaloacetate transaminase (AST/GOT), alanine aminotransferase/glutamate pyruvate transaminase (ALT/GPT),

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	gammaglutamyltransferase (GGT), lactate dehydrogenase (LDH), lipase, triglycerides, serum glucose, total serum protein; coagulation: fibrinogen, antithrombin III (AT III), D-dimer; haemogram: haemoglobin, haematocrit, leucocytes, platelets. Any abnormal laboratory result fulfilling the criteria for a serious adverse event (SAE) was reported as such.
Statistical methods:	The statistical evaluation was carried out by medac's Department of Biometrics and Data Management. Data were analysed using SAS software package v9.3 on Windows platform. Ordinal data were summarised with minimum, 1st quartile (Q1), median, 3rd quartile (Q3) and maximum. Continuous data were summarised with – dependent on the specific analysis – the following parameters: Number of patients with non-missing observations, arithmetic mean, standard deviation (SD), 90% confidence interval (CI) for the arithmetic mean, coefficient of variation, minimum, 1st quartile (Q1), median, 3rd quartile (Q3) and maximum. For descriptive analysis of ASNase activities and amino acid concentrations geometric mean, geometric SD, 90% CI for geometric mean and geometric coefficient of variation were additionally provided. Categorical data were presented in contingency tables with frequencies and percentages. Efficacy: The number of patients and the rate of patients with ASN depletion were described stratified by treatment arm. Two-sided exact 90% CIs for difference between ASN depletion rates were provided. For the analysis of duration of ASNase activity levels >100 U/L, start of infusion was determined as the beginning of duration and end was determined by a linear interpolation approach utilising a log-linear scale, fixing the time point when the line connecting the last observation >100 U/L and the next observation ≤100 U/L crossed the threshold of 100 U/L. PK parameters were calculated from the individual serum ASNase activity levels following single dosing assuming a non-compartment model. Descriptive statistics and listing of model-independent PK characteristics for serum ASNase activity within nine weeks after infusion stratified by treatment were provided. Semi-logarithmic box-whisker diagrams with geometric means of model-independent PK characteristics were provided. For further statistical analysis PK parameters AUC_{0-t}, AUC_{0-inf}, C_{max}, CL_{total}, k_{el}, mean residence time (MRT) and $t_{1/2}$ were log-transformed (natural logarithms). Analysis of variance (ANOVA) procedures were applied for comparison of PK parameters between different PEG-rASNase dosages and Oncaspar. For each dose level, back transformed estimates and 90% CIs were presented. The associated 90% CIs were derived using the least-squares (LS)Means and the root of the total between-subject variance from the ANOVA of log-transformed data with subsequent exponential transformation. For assessment of dose-proportionality the power model on a natural logarithm-transformed PK characteristic as well as the CI approach based on dose normalised PK parameters were be applied. Furthermore, diagrams showing the individual profiles of ASNase activity and ASN level over the time were provided. Safety: Descriptive statistics (frequency and summary tables) were used for the safety evaluation. Associated AE tables present the total number of patients reporting at least one specific event and the maximum toxicity Grade.

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	Safety Analysis Set The Safety Analysis Set included all randomised patients who were treated with study medication (PEG-rASNase or Oncaspar). Full Analysis Set The Full Analysis Set included all randomised patients who received PEG-rASNase/Oncaspar without serious deviations (i.e. more than 50% missing blood samples per ASNase concentration profile, two or more consecutively missing blood samples whose sampling times were prior to the time of the first quantifiable concentration above lower limit of quantification [LLoQ]). This population was used for efficacy and pharmacodynamic analyses. Valid PK Population The Valid PK population comprised all patients of the Full Analysis Set, if no accelerated ASNase inactivation (AAI) occurred.
SUMMARY OF RESULTS	
EFFICACY RESULTS:	The primary objective of this study was to compare the rate of patients with ASN depletion three weeks after infusion of PEG-rASNase or Oncaspar in the induction phase. With Oncaspar complete ASN depletion was achieved in all patients at week 3. In the time between week 3 and week 5 the ASN level increased above LLoQ in all patients and at time point week 5 no patient was depleted any more. In contrast, complete depletion at time point 3 weeks after infusion was achieved in 91%, 83% and 75% of patients in the 500 U/m^2, 1000 U/m^2 and 1500 U/m^2 PEG-rASNase treatment groups, respectively. In the PEG-rASNase treatment groups, an unexpected phenomenon of AAI accompanied by ASN level elevation occurred. Seven out of 35 (20%) patients treated with PEG-rASNase (one, two and four patients in 500, 1000 and 1500 U/m^2 treatment arms, respectively) showed accelerated ASNase activity inactivation 7-28 days after study drug administration, compared to none (0/11) in the Oncaspar group. Due to this phenomenon, the rate of patients with complete ASN depletion in the 1500 U/m^2 treatment group already decreased to 92% at week 1. Patients without AAI in the PEG-rASNase treatment groups had a long-lasting ASN depletion, partly 9 weeks after infusion. The serum activity-time profile of Oncaspar following single dose infusion showed well-known increase of clearance with time. In contrast, dose proportionality and linear PK was shown for PEG-rASNase in patients without AAI. ASNase activity correlated with ASN depletion in serum under both treatments. ASN was reliably depleted also with ASNase activity level considerably below the desired threshold of 100 U/L. No remarkable differences between treatment groups in ASNase activity, ASP, GLN and GLU concentrations or significant changes in CSF of study patients were observed. The patients in all treatment groups responded to treatment.
SAFETY RESULTS:	Adverse reactions, observed in PEGASP.1 study, are known side events of ASNase treatment and chemotherapy. No relevant difference between overall frequency and intensity or onset of AEs, SAEs or related AEs between treatment groups was observed. Safety laboratory parameters showed no relevant differences between treatment groups. Low levels in blood cell counts were attributed to the underlying disease and treatment. Most of the patients showed elevated transaminases and hyperbilirubinaemia, which reflected the side effects of toxic polychemotherapy in these patients. In most patients, the coagulation parameters fibrinogen and AT III decreased after the study drug treatment, which is a well-known effect of ASNase therapy. PEG-rASNase showed a similar safety profile as marketed Oncaspar.
CONCLUSION:	Study results showed that PEG-rASNase is a well-tolerated new ASNase preparation. In the majority of study patients, treated with this substance, dose dependent long-lasting ASN depletion was observed, in

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	some cases nine weeks after treatment. Seven out of 35 (20%) patients treated with PEG-rASNase showed accelerated ASNase activity inactivation 7-28 days after study drug administration, compared to none (0 of 11) in the Oncaspar group. The reasons for this phenomenon could not be identified despite of additional analyses. No deaths occurred during the study. No relevant difference between overall frequency and intensity or onset of AEs or SAEs was observed. It can be concluded, that PEG-rASNase is an effective and safe ASNase preparation with dose dependent linear PK. However, due to occurrence of unexpected AAI phenomenon, the anticipated expectations of medac on PEG-rASNase have not been fulfilled. For the identification of causes for AAI further basic investigations are necessary.
Date of the report:	12-May-2014