2. SYNOPSIS

NAME OF SPONSOR/COMPANY: Genmab A/S	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Hx-EGFr NAME OF ACTIVE INGREDIENT: Zalutumumab	Volume: Page:	
Title of Trial: An Open-label, Multi-center, Phase I/II Trial Investigating the Pharmacokinetic Profile of Zalutumumab, a Human Monoclonal Epidermal Growth Factor Receptor Antibody in Non-curable Patients with SCCHN		
Investigators: Multicenter (7 principal investigators: 2 each in Hungary, Belgium, and Slovakia, and 1 in Great Britain)		
Trial Centers: Patients were enrolled at 5 sites in 4 countries: 2 sites in Belgium, and 1 site each in Hungary, Great Britain, and Slovakia.		
Publication (Reference): Not applicable		
Studied Period (years): 10 March 2010 to 31 October 2011 (date of first patient's informed consent to date of trial termination)		**Phase of development:** I/II

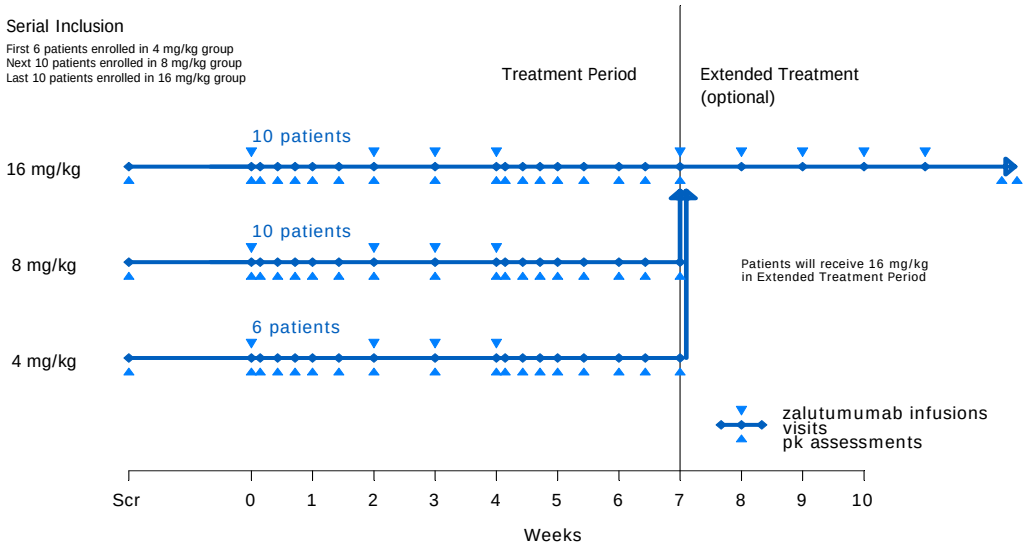
Objectives:

The primary objective of this trial was to determine key pharmacokinetic (PK) parameters for zalutumumab as monotherapy in patients with squamous cell carcinoma of the head and neck (SCCHN).

The secondary objectives of this trial were to investigate the safety and secondary PK parameters of weekly administrations of intravenous (IV) zalutumumab as monotherapy in patients with SCCHN.

Methodology:

This was an open-label, multicenter, uncontrolled, serial group, Phase I/II trial to investigate the PK profile of zalutumumab in patients with noncurable SCCHN. The planned total number of patients to be enrolled was 26. There were 3 dosing groups: 4, 8, and 16 mg/kg with a planned enrollment of 6, 10, and 10 patients, respectively. During the Treatment Period, patients received a single dose of zalutumumab followed by a 2-week infusion-free period and then 3 weekly infusions. Patients had the option of continuing into the Extended Treatment Period after completing the Treatment Period. During the Extended Treatment Period, patients received weekly infusions of zalutumumab at a dose of 16 mg/kg for as long as the investigator deemed that treatment was beneficial for the patient or until the patient experienced disease progression. The trial design is presented graphically below:



SYNOPSIS (CONTINUED)

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Number of Patients (planned and analyzed): The planned number of patients to be enrolled in this trial was 26. A total of 31 patients were enrolled, and 30 patients were included in the analyses presented in this trial report.

Diagnosis and Main Criteria for Inclusion: Patients aged 18 years or above who had histologically or cytologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx that was considered incurable with standard therapy and who had a World Health Organization (WHO) performance status of ≤ 2 and an expected survival rate of at least 3 months. Patients provided signed informed consent before any trial-related activity was performed.

Test Product, Dose and Mode of Administration, Batch No.:

Zalutumumab (Batch Numbers: GEHF01 and GEKC01) was administered as an IV infusion at a dose of 4, 8, or 16 mg/kg.

Duration of Treatment: Patients were administered a total of 4 infusions of zalutumumab during a 7-week Treatment Period. After completing the Treatment Period, patients may have entered the Extended Treatment Period until they experienced disease progression. During the Extended Treatment Period, patients received weekly infusions of zalutumumab.

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Criteria for Evaluation: All patients who had received at least 1 dose of trial drug were evaluable for PK, safety analysis, and host immune response.

Pharmacokinetics: The primary PK endpoints were exposure (area under the concentration-time curve from start of first and last infusions to 7 days [$AUC_{0-\tau}$, where τ represents the 7-day dosing interval]) and maximum concentration of zalutumumab in plasma (C_{max}) after a single dose (first infusion) and after multiple doses (fourth infusion) of zalutumumab during the Treatment Period.

Secondary PK endpoints were:

- Area under the concentration-time curve from the start of the first infusion (time 0) to 14 days (AUC_{0-14d})
- Area under the concentration-time curve from the start of the fourth infusion (time 0) to 21 days (AUC_{0-21d})
- Area under the concentration-time curve from the start of the first infusion (time 0) extrapolated to infinity using concentration data collected up to Day 14 ($AUC_{0-\infty}$)
- Concentration of zalutumumab immediately before the next infusion (C_{trough})
- Half-life ($t_{1/2}$)
- Clearance (CL)
- Apparent volume of distribution during the terminal phase (V_z)
- Apparent volume of distribution at steady-state (V_{ss})

Safety: The safety, immunogenicity, and other endpoints were:

- Extent of exposure
- Adverse events
- Laboratory test results
- Vital signs
- Physical examination findings
- Skin rash
- Concomitant medications
- Host immune response: human antihuman antibodies (HAHA)
- Overall survival

Efficacy: None

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Statistical Methods:

Analysis population: The full analysis set (FAS) comprised all patients who were exposed to trial drug irrespective of their compliance to the planned course of treatment. This was the primary analysis population and was used for evaluation of all PK and safety endpoints. Because the trial was an open-label, dose-ranging trial, there was no requirement to lock the database before determination of the primary analysis population.

Statistical analysis: Categorical data are summarized by using the number of patients in each category and the total number of patients in the corresponding treatment group, while continuous data are presented by using the number of patients (n), mean, standard deviation, median, and minimum and maximum values.

Analysis of primary PK endpoints:

- The $AUC_{0-\tau}$ and C_{max} were log-transformed and compared, by using noncompartmental methods, within each treatment group between the first and fourth infusions to address accumulation. These 2 endpoints were analyzed separately by using an analysis of variance (ANOVA) model with the number of infusion as a fixed effect and patient as a random effect.
- The $AUC_{0-\infty}$, $AUC_{0-\tau}$, and C_{max} were analyzed for dose-proportionality by pairwise comparisons, which compared the differences between the 4 and 8 mg/kg treatment groups and between 8 and 16 mg/kg treatment groups. Log-transformed $AUC_{0-\infty}$/dose, $AUC_{0-\tau}$/dose, and C_{max}/dose were each analyzed separately for dose proportionality by an ANOVA with treatment group included as a fixed effect. The variance-covariance matrix structure used in the model was diagonal. No adjustments for multiple testing were made.

Analysis of secondary PK endpoints:

- Secondary PK endpoints were derived for the first and fourth infusions based on a noncompartmental model and are summarized by treatment group and infusion.

Analysis of safety endpoints:

- Adverse events are coded by using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 12.1. All AEs are included in listings. The number of events and number of patients reporting these events are summarized by treatment group, system organ class (SOC), and preferred term (PT) for:
  - All treatment-emergent AEs (TEAEs)
  - Serious TEAEs
  - TEAEs related to zalutumumab
  - Serious TEAEs related to zalutumumab
  - Fatal TEAEs
  - TEAEs by intensity (Common Toxicity Criteria for Adverse Events [CTCAE] grade)
  - TEAEs of grade 3 or 4
  - TEAEs occurring on any infusion day
  - TEAEs occurring on any infusion day judged to be related to zalutumumab
  - TEAEs related to infusion occurring on any infusion day
  - TEAEs leading to withdrawal of zalutumumab
  - TEAEs leading to interruption of zalutumumab
  - TEAEs related to infusion
- A summary of the absolute value, absolute change from Baseline, and percent change from Baseline for all hematology and biochemistry variables is provided by visit and treatment group by using summary statistics for continuous variables. Shift tables of range flags (High/Low) from Baseline to each visit in the Treatment Period are provided showing the number of patients in each category by treatment group for all hematology and biochemistry variables.
- For vital sign measurements, a summary of the absolute value, absolute change from Baseline, and percent change from Baseline is provided by visit and treatment group by using summary statistics for continuous variables.
- Skin rash graded according to the CTCAE is presented based on the skin examination performed before

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administration of zalutumumab. The number of patients in each grade category (CTCAE grades 1 to 5) for the highest CTCAE grading recorded across all visits is summarized by treatment group.

- All values for the HAHA titers are listed and tabulated by treatment group, including the number of patients with HAHA concentrations less than 0.5 mg/L.
- Overall survival was defined as the time (in months) from the date of the first infusion until the date of death from any cause. Overall survival was censored if the patient was lost to follow-up or refused to continue the trial. For patients alive at the time of data cut-off (ie, 8 weeks after the last dose of zalutumumab), overall survival was censored. In any case of censoring, the date of censoring was the last time point documenting survival (ie, the last date the patient was known to be alive). Overall survival was assessed by using Kaplan-Meier estimates. The number of deaths and the number of censored observations are presented together with the quartile and median survival times with corresponding 2-sided 95% confidence intervals (CIs) based on the Kaplan-Meier estimates.

SUMMARY - CONCLUSIONS

DISPOSITION OF TRIAL POPULATION: A total of 38 patients were screened for enrollment in this trial. Of the 31 patients who were enrolled, 1 patient died before receiving the first infusion and is not included in the FAS population. A total of 24 patients (80%) completed the Treatment Period (Visits 1-18) and 6 patients were withdrawn from the trial. Reasons for withdrawal from the trial during the Treatment Period were death for 3 patients (2 patients in the 8 mg/kg treatment group and 1 patient in the 16 mg/kg treatment group), disease progression for 2 patients in the 4 mg/kg treatment group, and an AE for 1 patient in the 8 mg/kg treatment group. Eighteen patients (60%) entered the Extended Treatment Period. During the Extended Treatment Period, 18 patients were withdrawn from the trial. Reasons for withdrawal were disease progression for 13 patients; trial terminated by sponsor for 2 patients; and AE, withdrawal by patient, and "other" (patient decision) for 1 patient each.

DEMOGRAPHICS OF TRIAL POPULATION: Patients were enrolled at 5 sites in 4 countries: 20 patients at 2 sites in Belgium, 5 patients at 1 site in Great Britain, 4 patients at 1 site at Slovakia, and 2 patients at 1 site in Hungary.

The majority of patients were male (87%) and all were white. The overall median age was 59.0 years (range: 45 to 83 years) and the median body mass index was 20.95 kg/m^2 (range: 15.7 to 29.8 kg/m^2).

A diagnosis of SCCHN had been made for these patients a median of 33 months before Screening (range: 2 to 218 months), with the primary tumor most commonly located in the oral cavity (43% of patients). The majority of patients (53%) had Stage IVa cancer at the time of diagnosis.

PHARMACOKINETIC RESULTS: Analysis of the PK data for 3 dose levels of zalutumumab (4, 8, and 16 mg/kg) confirmed accumulation of zalutumumab in plasma after 4 infusions of zalutumumab on Days 0, 14, 21, and 28 by comparing $AUC_{0-\tau}$ and C_{max} after the first and last infusion for each treatment group. Mean C_{trough} values of zalutumumab in plasma also appeared to show accumulation across the 3 treatment groups and increased from Day 21 to Day 28 and to Day 35. Dose-proportionality was revealed in $AUC_{0-\infty}$ after a single infusion and $AUC_{0-\tau}$ after multiple infusions and in C_{max} values after single and multiple infusions.

Saturation of one or more processes with increasing dose level was suggested by an increase in elimination $t_{1/2}$, an increased in apparent volume of distribution, and a decrease in CL after the first and fourth infusions. Geometric mean CL was similar for the 16 mg/kg treatment group after the first infusion and for the 8 and 16 mg/kg treatment groups after the fourth infusion.

SAFETY RESULTS: During the Treatment Period, the majority of patients (87%) received 4 infusions of zalutumumab as specified by the protocol. The median total dose of zalutumumab administered ranged from 928.5 mg in the 4 mg/kg treatment group to 4098.5 mg in the 16 mg/kg treatment group. During the Extended Treatment Period, 18 patients continued to receive zalutumumab for up to 16 additional infusions, and the median total dose of zalutumumab was 8413.0 mg.

Most of the TEAEs reported during the trial were expected effects during treatment with zalutumumab. Approximately one-third of the TEAEs were judged by the investigator to be related to zalutumumab and included rash, dermatitis acneiform, headache, stomatitis, fatigue, hypomagnesemia, and infusion-related reactions. Of the related TEAEs, events of rash and dermatitis acneiform were most commonly reported for patients in the 8 and 16 mg/kg treatment groups. During

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the Extended Treatment Period, the most commonly reported TEAE that was judged by the investigator to be related to zalutumumab was hypomagnesemia. The incidence of this expected effect of zalutumumab treatment indicates that monitoring for and treating low magnesium levels becomes more important in long-term treatment with zalutumumab.

Most TEAEs reported during the trial were CTCAE grade 1 or 2. There were a total of 21 CTCAE grade 5 (fatal) TEAEs reported during the trial. No CTCAE grade 4 TEAEs were reported during the trial. Of the 10 infusion-related TEAEs reported during the Treatment Period, 1 event was assessed as CTCAE grade 3 and was also reported as an SAE.

During the trial, a total of 21 patients experienced fatal (CTCAE grade 5) SAEs. Onset of the fatal SAEs occurred during the Treatment Period for 10 patients and during the Extended Treatment Period for 11 patients. The cause of death was predominantly related to disease progression, and none of the deaths was considered to be related to zalutumumab. During the Treatment Period, the overall incidence of SAEs was 50%, and during the Extended Treatment Period, 16 of 18 patients experienced an SAE. Of the 48 SAEs reported during the trial, only 8 events were judged by the investigator to be related to zalutumumab.

No patients developed positive HAHA titers during the trial. Overall, there were no remarkable safety signals in clinical laboratory results, physical examination findings, and vital sign measurements. The exception was the observation of hypomagnesemia during the Extended Treatment Period.

Overall survival was estimated for the 21 patients (70%) who died during the course of the trial. The remaining 9 patients (30%) were censored from the analysis, predominantly because they were lost to follow-up. The median Kaplan-Meier point estimate was 5.6 months (median 95% CI: 3.64, 7.51).

CONCLUSION: The results presented in this trial report furthered the understanding of key PK parameters for zalutumumab as monotherapy in patients with noncurable SCCHN. The PK profile of zalutumumab shows accumulation of zalutumumab in plasma after multiple infusions and dose-proportionality after single and multiple infusions. In addition, $t_{1/2}$, CL, and the apparent volume of distribution appeared to be dose-dependent.

In this Phase I/II trial, zalutumumab was administered as a weekly infusion to patients with noncurable SCCHN. The regimen was generally well tolerated, and the safety profile was manageable for doses up to 16 mg/kg. Events of hypomagnesemia, which were expected adverse effects of treatment with zalutumumab, were predominantly seen in the Extended Treatment Period and underlined the need for careful long-term monitoring of magnesium levels in patients undergoing ongoing and previous treatment with zalutumumab.

Date of the report: 11 April 2012