SYNOPSIS

TITLE OF TRIAL: An open-label, single arm, phase II trial to investigate the safety and efficacy of Sym004 in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) who have failed anti-EGFR monoclonal antibody-based therapy
SPONSOR: Symphogen A/S
INVESTIGATORS: Coordinating Investigator Prof Jean-Pascal Machiels, Cliniques Universitaires St-Luc, Centre du Cancer, Avenue Hippocrate 10, 1200 Belgium, Brussels
TRIAL CENTERS: The trial was conducted at 10 sites in 3 countries: Belgium (3 sites), France (1 site) and Germany (6 sites).
PUBLICATIONS: Abstract presented at the 2013 ASCO annual meeting: J.-P. Machiels, P. Specenier, J. Krauß, A. Dietz, M.-C. Kaminsky, Y. Lalami, M. Henke, U. Keilholz, R. Knecht, N.J. Skartved, I.D. Horak, M. F. Flensburg and T.C. Gauler. Sym004, a novel strategy to target EGFR with an antibody mixture, in patients with advanced SCCHN progressing after anti-EGFR monoclonal antibody: A proof of concept study.

TRIAL PERIOD:	PHASE OF DEVELOPMENT:
First patient first visit was performed 15-Jul-2011 Last patient last visit was performed 08-Oct-2012 Last patient last survival follow-up contact (per defined cut-off) was performed 05-Dec-2012	Phase II

OBJECTIVES:

Primary Objective

To assess the efficacy of Sym004 in patients with recurrent and/or metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) who had disease progression during or within 12 weeks after treatment with an anti-Epidermal Growth Factor Receptor (EGFR) monoclonal Antibody (mAb)-containing regimen.

Secondary Objectives

- To assess the safety profile of Sym004
- To assess the biological activity in tumor and skin biopsies
- To determine overall survival
- To evaluate potential biomarkers
- To determine the Pharmacokinetic (PK) profile of Sym004

METHODOLOGY:

This was a multi-center, open-label, multiple dose, phase II trial in patients with advanced recurrent and/or metastatic SCCHN. Patients attended a screening visit, which took place within 14 days of Visit 2. At Visit 2, the first infusion with Sym004 was given and the patients then received weekly infusions with Sym004 until disease progression or withdrawal from treatment for other reasons. Sym004 was dosed at 12 mg/kg unless the body mass index of a patient exceeded 30 kg/m^2 or the dose had to be reduced due to skin toxicity.

During the trial, patients underwent clinical response evaluation by Computerized Tomography (CT) scans (or Magnetic Resonance Imaging (MRI) for neck including larynx) according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) at Visit 8 (Week 6), Visit 14 (Week 12) and subsequently every 8 weeks until disease progression or withdrawal for other reasons. Response was evaluated locally and used for eligibility and treatment decisions. Central response evaluation was utilized as basis for analysis of the primary and secondary endpoints. Follow up visits were performed 4, 8 and 12 weeks after the last administration of Sym004. After the follow-up visits, patients were followed for survival on a monthly basis.

During the course of the trial, an Independent Data Monitoring Committee (IDMC) evaluated safety according to the trial specific IDMC charter.

An overview of trial design is shown in the following figure:

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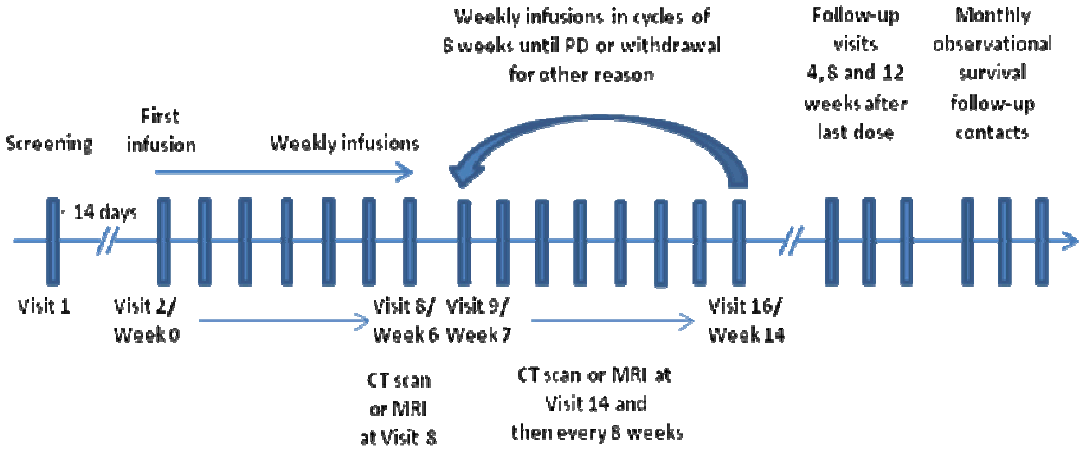

NUMBER OF PATIENTS (PLANNED AND ANALYZED):
Twenty-five patients were planned for the trial. Twenty-eight patients were screened and 26 patients were enrolled (1 extra patient was enrolled as 1 patient turned out to be not evaluable during the trial). All 26 patients received at least one dose of Sym004.
Of the 26 patients, 18 patients withdrew from treatment due to Progressive Disease (PD), 3 due to death, 2 due to Adverse Events (AEs) and 3 patients withdrew by their own decision.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:
Key inclusion criteria:

- Histologically confirmed diagnosis initially or at relapse of SCCHN of the oral cavity, oropharynx, hypopharynx or larynx
- Recurrent and/or metastatic SCCHN not amenable to curative treatment with surgery and/or (chemo)radiation
- Previous treatment with a marketed anti-EGFR mAb in the palliative setting either as monotherapy or in combination with chemotherapy or radiotherapy and showing
    a) Documented clinical benefit or response for at least 8 weeks (Partial Response (PR), Complete Response (CR) or Stable Disease (SD) verified by CT scan or MRI according to RECIST on the anti-EGFR mAb-based therapy
    and
    b) Documented disease progression (PD verified by CT scan or MRI according to RECIST) during or within 12 weeks following the last administration of anti-EGFR mAb
- Accessible tumor for biopsy and patient acceptance of repeat tumor biopsies
- At least one measurable lesion according to RECIST (version 1.1) at screening
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Normal organ or bone marrow function

Key exclusion criteria:

- More than 2 lines of prior chemotherapy in the palliative setting
- Expected survival <12 weeks
- Known brain metastases
- Chemotherapy or radiation therapy within 21 days prior to Visit 2 at the exception of palliative radiotherapy for bleeding or pain, which was allowed anytime, if not given on target lesions
- Anti-EGFR mAbs within 14 days prior to Visit 2
- Known previous grade >3 infusion related reactions with chimeric mAbs
- History of other malignancy within 5 years prior to Visit 2, with the exception of basal cell carcinoma of the skin and carcinoma in situ of the cervix or urinary bladder

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TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:
Sym004 was supplied in 10 mL glass vials and was formulated at 5 mg/mL, i.e. a total of 50 mg Sym004 per vial. Sym004 consists of a 1:1 ratio mixture of the two antibodies mAb992 and mAb1024. Sym004 (batch number CMC-E-0027/PD10121) was administered as an intravenous infusion through a peripheral line or indwelling catheter. Sym004 was diluted in saline before infusion. The volume of saline depended on the dose of Sym004 given: 1000 mL for 12 and 9 mg/kg, and 500 mL if the dose was reduced to 6 mg/kg.

DURATION OF TREATMENT:
Patients received weekly infusions of Sym004 until disease progression or withdrawal from treatment for other reasons.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:
N/A

CRITERIA FOR EVALUATION - EFFICACY:
For evaluation of efficacy endpoints, the following scans/locations were mandatory:

- CT scan or MRI of the neck (including larynx)
  and
- CT scan of the thorax and abdomen

During treatment, CT scans (or MRI for neck including larynx) were repeated at Visit 8, Visit 14 and subsequently every 8 weeks until PD. Responses were initially evaluated locally according to RECIST (version 1.1). Copies of the scans/images were sent to an imaging company for central review and assessment of efficacy endpoints.
When a patient showed signs of disease progression, a CT scan/MRI was performed as soon as possible (preferably within 2 weeks). In case of withdrawal from treatment for any reason, a CT scan/MRI was performed at the first follow-up visit 4 weeks after the last infusion of Sym004. If a scan had been performed at the time of withdrawal, it was not repeated.

Tumor and skin biopsies for assessment of biomarkers were obtained at Visit 2 (pre-dose), Visit 6 and at the first follow-up visit. Selected biomarkers were analyzed, mainly by immunohistochemistry.

CRITERIA FOR EVALUATION - PHARMACOKINETICS:
Blood samples for PK analysis of Sym004 were collected at the following time points:

- Visits 2 and 5: Pre-treatment, end of infusion, 1 hour, 2 hours, 4 hours, 8 hours, 24 hours and 48 hours (not Visit 5) after infusion
- Visits 3, 4, 6 and subsequent visits: Pre-treatment and end of infusion
- Follow-up visits 4, 8 and 12 weeks after last infusion: During the visit

CRITERIA FOR EVALUATION – SAFETY

- AEs were collected from Visit 2 and until the first follow-up visit. Serious Adverse Events (SAEs) were collected from Visit 1 and until the first follow-up visit. SAEs assessed as related to the trial drug or trial conduct occurring after the first follow-up visits were also collected.
- Examination of skin toxicity (rash) was performed at all visits from Visit 2 to the first follow-up visit
- Blood samples for analysis of Anti-Drug Antibodies (ADA) were taken at Visit 2 (pre-dose), Visit 7, Visit 12, every subsequent 8 weeks and at all follow-up visits
- Blood and urine samples for assessment of clinical chemistry, hematology and urinalysis were taken from Visit 1 to the first follow-up visit
- Physical examination, recording of vital signs and weight, and assessment of ECOG status were performed from Visit 1 to the first follow-up visit
- Electrocardiogram (ECG) was recorded at Visit 1, Visit 6, every subsequent 4 weeks and at the first follow-up visit

STATISTICAL METHODS:
EFFICACY ENDPOINTS AND ANALYSES:
Primary efficacy endpoint
The primary efficacy endpoint was Progression Free Survival (PFS), estimated by median PFS time and 24-week PFS proportions.

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PFS was defined as the time from first infusion of Sym004 until disease progression or death. The progression events were defined by verifiable imaging data. Patients who died without confirmed PD were considered as progressed. Patients who died or showed PD more than 21 days after last treatment were censored (i.e. were considered alive without progression on Day 21 after last treatment).
PFS time was listed and estimated using the Kaplan-Meier method, and was presented graphically. Estimated PFS, median time and quartiles was presented with corresponding two-sided 95% Confidence Intervals (CIs). Proportions still progression free at 24 weeks was calculated with corresponding 95% CI.
The primary efficacy analysis was made using the Full Analysis Set (FAS) and the Per Protocol (PP) analysis set. The FAS analysis was considered the primary.

Secondary efficacy endpoints
The secondary efficacy endpoints were the following:

- Objective tumor response (according to RECIST version 1.1) and derived endpoints (Objective Response Rate (ORR), disease control rate, best overall response)
- Time to Progression (TTP)
- Overall survival
- Skin and tumor biomarkers

Secondary efficacy analyses were primarily performed for the FAS. Objective tumor response (CR, PR, SD, or PD) was listed by visit. Best overall tumor response (from screening until disease progression/recurrence) was listed and summarized (including 95% CI for proportions). TTP was summarized using Kaplan-Meier plots and presentation of median time to event including 95% CI for median time. Similarly, the 24-week rate of progression freedom was estimated with 95% CI. Time to death (overall survival) was summarized using Kaplan-Meier plots and presentation of median time to event including 95%CI for median time and estimation of proportion dead/alive at 24 weeks.
The results from the biomarker analysis were mainly listed.

PHARMACOKINETIC ANALYSES:
Serum concentrations of Sym004, mAb992 and mAb1024 were listed by patient and visit. The non-compartmental PK parameters $AUC_{0\text{-}168h}$, $AUC_{0\text{-}inf}$, $T_{½}$, C_{max}, C_{min}, T_{max}, T_{min}, trough value, clearance and volume of distribution were calculated on mAb992, mAb1024 and Sym004 concentration-time profiles obtained following the first and fourth infusions of Sym004 (i.e. Visit 2 and Visit 5 data). Data were presented with summary statistics for the FAS and the PP analysis set and individual plasma concentration profiles were plotted.

SAFETY ENDPOINTS AND ANALYSES:
Safety endpoints consisted of:

- AEs
- Skin rash
- ADA
- Laboratory parameters (hematology, biochemistry, urinalysis)
- Other safety parameters (vital signs, ECG, physical examination, ECOG)

Safety endpoints were presented with summary statistics for the FAS.

DEMOGRAPHY OF TRIAL POPULATION:
The FAS included all 26 patients. The PP analysis set included 23 patients. Two patients were excluded from the PP analysis set as they had too low drug exposure and 1 patient was excluded due to violation of an inclusion criterion.

There were 23 male and 3 female white patients included in the trial. Mean age was 62.0 years and ranged from 42 to 87 years. Median disease duration was 3.0 years (range: 0.8 – 25.0 years).

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In line with the inclusion criteria, all 26 patients had received previous therapy with anti-EGFR mAbs. All 26 patients had also received cisplatin and 19 patients (73.1%) had received fluorouracil. Best response during at least 8 weeks of previous treatment with anti-EGFR mAb was CR for 1 patient (3.8%), PR for 9 patients (34.6%) and SD for 16 patients (61.5%). Mean time from disease progression was 87.8 days and ranged from 4 to 456 days. One patient did not have disease progression during or within 12 weeks from last administration of anti-EGFR mAb (20 weeks) and thus violated one of the inclusion criteria.

Five patients (20.0%) were current smokers and 20 patients (80.0%) were former smokers (N=25). For 1 patient, smoking status was missing. Fourteen patients (53.8%) had a history of tobacco abuse. Eight patients (36.4%) were current users of alcohol, 10 patients (45.5%) were former users and 4 patients (18.2%) had never used alcohol (N=22). For 4 patients, alcohol status was missing. Ten patients (38.5%) had a history of alcohol abuse or alcoholism.

EFFICACY RESULTS:

- Median PFS time was 82 days [95% CI: 41 ; 140] for the FAS based on central evaluation and 54 days [95% CI: 40 ; 138] based on supportive local evaluation.
- Proportion still progression free at 24 weeks was 12% [95% CI: 1% ; 39%] for the FAS based on central evaluation and 13% [95% CI: 2% ; 32%] based on local evaluation.
- The 95% CIs for the primary analyses based on the FAS and the PP analysis set were overlapping and very close to each other.
- Best overall response based on central evaluation was PD for 6 patients (23.1%) and SD for 13 patients (50.0%). No patient showed CR or PR.
- Proportion of patients with SD was 46.2% at Visit 8 and 15.4% at Visit 14 for the FAS based on central evaluation (N=26).
- Tumor shrinkage was observed in 8 patients. The percentage decrease in sum of the largest diameters for the patients were 6.5%, 7.1%, 9.6%, 10.2%, 11.3%, 13.6%, 16.7% and 27.1%, respectively.
- As no patient showed CR or PR based on central evaluation, it was not possible to estimate duration of overall response and the estimated rates of ORR were all 0%.
- Median TTP based on central evaluation was 85 days [95% CI: 42 ; 147] for the FAS. The proportion still progression free at 24 weeks was 15% [95% CI: 1% ; 46%]. The data were confirmed by the PP analysis and by the local evaluation as the 95% CIs were overlapping.
- In the analysis of overall survival, median time to death was 156 days [95% CI: 86 ; 202] for the FAS and the 24-week survival estimate was 42% [95% CI: 22% ; 60%].
- The exploratory biomarker analysis showed a Sym004 mediated down-modulation of EGFR in membrane (17/18 patients) and in cytoplasm (15/18 patients) in skin biopsies and a down-modulation of EGFR in membrane (9/11 patients) and in cytoplasm (8/11 patients) in tumor biopsies. A decrease in % Ki67 positive cells in tumor area was observed in 4 of 11 paired tumor biopsies. None of 21 evaluated patients had EGFRvIII mutation. High cMET polysomy was observed in 6 patients, but no true cMET gene amplification was observed. One patient was positive for human papilloma virus (out of 19 evaluated patients). An increase in HER3 cytoplasmic and membrane staining was observed in 5 of 11 paired tumor samples. It was not possible to conclude if expression of pEGFR and HER2 were modulated by Sym004 treatment.

PHARMACOKINETIC RESULTS:

- The measured serum levels of mAb992 and mAb1024 were close to a 1:1 ratio at each visit throughout the trial. Similar PK was indicated for the antibodies.
- AUC_{0-168h} for Sym004 increased 60% from Visit 2 (first infusion) to Visit 5 (fourth infusion).
- Similar C_{max} was observed at Visit 2 and Visit 5, while C_{min} increased 130% from Visit 2 to Visit 5.
- $T_{½}$ increased 50% from Visit 2 to Visit 5.
- Clearance decreased approximately 60% from Visit 2 to Visit 5.

SAFETY RESULTS:

- A total of 385 AEs were reported in the trial, of which 205 AEs were assessed as related to trial drug by the Investigators. All patients reported at least 1 AE and at least 1 related AE during the trial.

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- The event reported by the highest number of patients was hypomagnesemia (19 events in 17 patients (65.4%)). Of these events, 17 events in 16 patients (61.5%) were assessed as related to trial drug by the Investigators. Six events in 6 patients (23.1%) were of Common Toxicity Criteria for AEs (CTCAE) grade 3. Four events in 4 patients (15.4%) (all related) were of CTCAE grade 4 and were reported as SAEs.
- The other most frequently reported events were all within the System Organ Class (SOC) Skin and subcutaneous tissue disorders, i.e. dermatitis acneiform (20 events in 16 patients (61.5%)), pruritus (13 events in 13 patients (50.0%)), dry skin (14 events in 12 patients (46.2%)), erythema (15 events in 11 patients (42.3%)) and rash (9 events in 8 patients (30.8%)). Almost all of these events were assessed as related to trial drug. All events in this SOC were of CTCAE grades 1 to 3.
- Frequently reported AEs outside this SOC included fatigue (13 events in 10 patients (38.5%)), diarrhea (12 events in 9 patients (34.6%)) and nausea (15 events in 8 patients (30.8%)).
- Fifteen patients (57.7%) experienced AEs that led to interruption of trial drug and for 7 patients (26.9%), the dose was modified/reduced due to AEs. Six patients (23.1%) reported AEs for which action taken was dose withdrawn. Two of these patients discontinued treatment due to AEs according to the end of treatment page of the case report form.
- Most of the AEs recorded in the trial were of CTCAE grade 1 (161 AEs in 26 patients) or grade 2 (137 AEs in 26 patients). There were 72 AEs of CTCAE grade 3 reported by 23 patients (88.5%). AEs of CTCAE grades 4 and 5 were reported as SAEs.
- According to the trial database, 37 SAEs were recorded in 20 patients (76.9%). The most frequently reported SAEs were neoplasm malignant (6 SAEs in 6 patients (23.1%)), hypomagnesemia (4 SAEs in 4 patients (15.4%)) and sepsis (3 SAEs in 3 patients (11.5%)). The other SAEs were reported by 1 or 2 patients each.
- Seven SAEs in 7 patients (26.9%) were assessed as related to trial drug by the Investigators: 4 events of hypomagnesemia, 1 event of pneumonia, 1 event of herpes zoster ophthalmic and 1 event of death. Three of these events were reported as suspected unexpected serious adverse reactions (SUSARs) (pneumonia, herpes zoster ophthalmic and death).
- Five SAEs had fatal outcome: 2 events of neoplasm malignant and 1 event each of sepsis, general physical health deterioration and death.
- There were 2 SAEs in the safety database that were not included in the trial database (they were reported outside the AE reporting period): tumor hemorrhage and neoplasm malignant. Both SAEs were assessed as not related to trial drug by the Investigators and both events were fatal.
- With regards to clinical laboratory evaluation, there was no consistent change in the patterns for the laboratory parameters, except for lowered magnesium levels in the majority of patients (as also reflected by the AE profile).
- No ADA was detected in any patient in the trial.
- Skin rash was observed in 25 patients (96.2%). Eleven patients (42.3%) had skin rash with CTCAE grade 3 on at least one occasion during the trial. No skin rash with CTCAE grade 4 or 5 was observed.
- There were no clinically significant changes in ECG, vital signs or body weight during the trial.

CONCLUSION:
In summary, Sym004 is the first compound shown to induce tumor shrinkage in patients resistant to platinum based chemotherapy and cetuximab in recurrent/metastatic SCCHN. The median overall survival with Sym004 of around 5 months is similar to the reported median overall survival in less heavily pre-treated (cetuximab-naive), platinum-resistant recurrent/metastatic SCCHN patients treated with compounds such as methotrexate or cetuximab. Sym004 showed overall an acceptable safety profile with skin toxicities as the most frequently reported AEs. There were no unexpected safety findings in the trial.
The observed EGFR down-regulation in skin and tumor biopsies supports the novel mechanism of action suggested by the preclinical studies and suggests that Sym004 may target EGFR dependent tumors more efficiently than current anti-EGFR antibodies. Sym004 should therefore be tested in patients with less advanced disease as well as in cetuximab- and platinum-resistant SCCHN patients.

DATE OF THE REPORT: 18 Jun 2013

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The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice

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Investigators Brochure

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ELECTRONIC SIGNATURES

Signed By	Signature Meaning	Outcome	Date
Hanna Liedman	Approver: I approve the document as suitable and appropriate for use.	Approved	18-Jun-2013 01:38:08 PM GMT +02
Mimi Folden Flensburg	Approver: I approve the document as suitable and appropriate for use.	Approved	19-Jun-2013 10:18:35 AM GMT +02