SYNOPSIS

Name of Sponsor/Company: Chugai Pharma Europe **Name of Finished Product:** TP300 **Name of Active Ingredient:** CH4556300-000	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*
Title of Study: A phase IIa, open-label, multi-centre study of TP300 as a single agent first line therapy in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma		
Investigator(s): 1. Professor Jeffry Evans 2. Dr Alan Anthoney 3. Dr Was Mansoor 4. Dr Daniel Ford 5. Dr David Propper 6. Dr Martin Eatock 7. Dr Roshan Agarwal		

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Name of Finished Product:	**Dossier**	
TP300		
Name of Active Ingredient:	**Volume:**	
CH4556300-000	**Page:**	

Study Centre(s):

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3. Dept Medical Oncology
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   Wilmslow Road, Withington
   Manchester, M20 4BX
4. Cancer Research Clinical Trials Team
   Old Clinical Investigations Building
   City Hospital
   Dudley Road
   Birmingham, B18 7QH
5. Centre for Experimental Cancer Medicine
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   London, EC1M 6BQ
6. Northern Ireland Cancer Clinical Trials Unit
   Belfast City Hospital
   East Podium,C Floor
   Belfast, BT9 7AB
7. West London Cancer Research Network
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   1st Floor Mint Wing
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   Praed St
   London, W2 1 NY

Name of Sponsor/Company: Chugai Pharma Europe **Name of Finished Product:** TP300 **Name of Active Ingredient:** CH4556300-000	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*

Publication (Reference):
Not applicable.

Study Period: 29 October 2009 to 22 November 2010	**Phase of Development:** IIa

Objectives

Primary:

To assess the objective response (OR), defined as complete or partial response (CR/PR), assessed in accordance with the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Secondary:

- To assess progression-free survival (PFS), which is defined as the time of the first dose of TP300 until the date of disease progression or death whichever occurs first.
- To assess the time to progression (TTP), defined as the time from first dose to first progression of disease.
- To assess the safety and tolerability of TP300.
- To further assess pharmacokinetic (PK) characteristics of TP300 active form and active metabolite.

Methodology:

This was a phase IIa, open-label, multicentre study in the United Kingdom. Male and female patients with histologically or cytologically confirmed diagnosis of gastric or gastro-oesophageal junction (Siewert type II, III) adenocarcinoma were screened, including disease assessment (CT scan), within a maximum of twenty eight days before the scheduled start of TP300 administration. All other screening assessments were performed within 14 days of study entry.

TP300 was administered as a 60-minute intravenous infusion every 3 weeks, for up to 6 cycles. Patients who, in the opinion of the investigator, benefited from the treatment could continue with TP300 beyond 6 cycles.

Patients were assessed for tumour response after every 2 cycles of treatment and at the end of the study. Patients with evidence of disease progression (PD) after 2 cycles of treatment were withdrawn. Patients responding (CR or PR) or patients with stable disease (SD) continued treatment up to 6 cycles. Safety was assessed before each treatment cycle and adverse events (AEs) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In addition, clinically relevant changes in vital signs and laboratory parameters from baseline were assessed.

Blood samples were collected for laboratory safety tests, for PK analysis and biomarker assay. In addition, an optional blood sample was taken from each consented patient for pharmacogenetic research. Urine samples for laboratory safety tests were collected if indicated.

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Number of Patients (Planned and Analysed):

It was planned to recruit 43 evaluable patients in total. A modified Simon's two-stage design was used for this study. In the 1st stage 18 patients were to be recruited and analysed. If less than 2 patients had a response, then the study would not progress to the stage 2. This was based on a response rate of 25%, a one-sided alpha error of 5%, and power of 80 % to reject the null hypothesis of a response rate of 10%. Ultimately 20 patients were enrolled in the study but only 19 were dosed and included in the analysis; of these 16 were available for final evaluation.

Diagnosis and Main Criteria for Inclusion:

Male and female patients, aged at least 18 years, with histologically or cytologically confirmed diagnosis of gastric or gastro-oesophageal junction (Siewert Type II and III) adenocarcinoma, ECOG performance status of 0 or 1, and life expectancy $\geq$ 3 months.

Test Product, Dose and Mode of Administration, Batch Number:

TP300 was supplied in vials containing 5 mL of TP300 at a concentration of 4 mg/mL. The starting dose was 8 mg/m^2 and than increased to 10 mg/m^2 from Cycle 2 onwards in the absence of dose-limiting toxicity. The mode of administration was intravenous infusion.

Batch Number: TP6B01

Duration of Treatment:

TP300 was administered once every 3 weeks and patients received up to 6 cycles.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Not applicable.

Name of Sponsor/Company: **Chugai Pharma Europe Ltd** **Name of Finished Product:** **TP300** **Name of Active Ingredient:** **CH4556300-000**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*(For National Authority Use only)*

Criteria for Evaluation:

Efficacy:

Tumour response was assessed in accordance with the RECIST version 1.1.

Safety:

Safety was assessed using clinical laboratory results, physical examinations, electrocardiograms, and reporting of AEs. AEs were graded according to the NCI CTCAE version 3.0.

Pharmacokinetics:

Summary statistics were calculated for nominal time points for the plasma concentrations of CH0793076 (TP3076) and CH0793011 (TP3011). Nonlinear mixed effects modeling (with software NONMEM®) was used to analyze the dose-concentration-time data of TP3076 and TP3011. The data was pooled with the data from the Phase I study, TP101EU. TP101EU contained full profile PK analysis, whilst in TP103EU, samples were collected at a limited number of timepoints.

Statistical Methods:

The overall response rate was reported with exact 95% confidence interval. Median TTP and PFS was estimated by Kaplan-Meier method, with 95% confidence interval. Kaplan-Meier curve for TTP and PFS was shown.

Adverse Events were analysed by presenting frequency and percentage of patients with adverse events in each system organ and preferred term. Laboratory variables and vital signs were reported using descriptive statistics.

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SUMMARY – CONCLUSIONS

Twenty patients were enrolled into stage 1 of the study. Nineteen patients received study medication, of which sixteen received at least 2 cycles of treatment and were evaluated for tumour response. The efficacy required to progress to stage 2 of the study was not achieved. Therefore, this study was concluded following the completion of the stage 1.

Efficacy Results:

A total of 18 patients were evaluated by CT scan at the time of screening, at the end of every 2 cycles and at the end of the treatment. The RECIST version 1.1 criteria were applied. The final assessments were performed by IRC. Two out of the eighteen dosed patients were excluded from the per protocol set due to difficulty in defining clearly measurable lesions. Best overall response of the 16 evaluated patients were 12 stable diseases and 4 progressive diseases. There were no complete or partial responders.

Safety Results:

There were 20 SAEs reported from 12 patients; 10 of them were DLTs. Haematological toxicities included seven cases of neutropenia, 3 grade 3 and 4 grade 4.

Pharmacokinetic Results:

Blood samples (3 mL) were taken on day 1 of cycle 1 at the following time points: before infusion (0 hours) and 1, 5 (± 1), and 24 (± 5) hours after the start of TP300 infusion. This was repeated on day 1 of cycle 2 for the patients who escalated to 10 mg/m^2. The plasma concentration profile from the present study was comparable with the results of the Phase I study at 8 and 10mg/m^2 dose, and showed a consistent correlation between the exposure to the active metabolite of TP300 and decrease in neutrophil count, as well as low inter-patient variability for the pharmacokinetic variables calculated.

Conclusions:

The primary objective in sage 1 to obtain 3 ORs (confirmed after 4 cycles of treatment) was not achieved.

Date of the Report: 31 May 2011