This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

1.0 TITLE PAGE

Reference P04722
Reports of Efficacy and Safety Studies Study Reports of Uncontrolled Clinical Studies

CLINICAL STUDY REPORT

SCH 717454 A DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF SCH 717454 (ROBATUMUMAB) IN COMBINATION WITH DIFFERENT TREATMENT REGIMENS IN SUBJECTS WITH ADVANCED SOLID TUMORS

Generic Name:	Robatumumab
Protocol:	P04722
EudraCT Number:	2009-011101-16
Dosage Form:	Intravenous
Phase:	1B/2
Indication:	Advanced solid tumors
Study Design:	Non-randomized, dose-escalation, multicenter, open-label trial
Sponsor Name:	Schering-Plough Research Institute, a division of Schering Corporation, a Subsidiary of Merck & Co., Inc. (hereafter referred to as Merck)
Clinical Monitor:	[redacted]
Study Initiation Date (FPE):	23 OCT 2009
Study Early Termination Date (if applicable):	07 JUN 2011
Study Completion Date (LPLV):	
Investigator Name/Affiliation:	[redacted] USA.

[redacted]

GCP Compliance:	This study was conducted in conformance with Good Clinical Practice standards and applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.
DocID:	5029928
Interim CSRs for the same Protocol:	None
Questions about the clinical study report should be directed to the individual listed on the accompanying correspondence.	

CSR Template Approval Date: 25 JUL 2011

2.0 SYNOPSIS

SCHERING-PLOUGH RESEARCH INSTITUTE, A DIVISION OF SCHERING CORPORATION, A SUBSIDIARY OF MERCK & CO., INC. (hereafter referred to as Merck) SCH 717454 (robatumumab), intravenous, in advanced solid tumors	**CLINICAL STUDY REPORT SYNOPSIS**
PROTOCOL TITLE/NO.: A DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF SCH 717454 (ROBATUMUMAB) IN COMBINATION WITH DIFFERENT TREATMENT REGIMENS IN SUBJECTS WITH ADVANCED SOLID TUMORS	#P04722
PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with Good Clinical Practice (GCP) standards and applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. [redacted]	
INVESTIGATOR [redacted] **STUDY CENTER:** [redacted]	
PUBLICATION(S): None.	
PRIMARY THERAPY PERIOD: 23 OCT 2009 to 07 JUN 2011	**CLINICAL PHASE:** 1B/2
DURATION OF TREATMENT: Screening phase lasted approximately 28 days. Treatment Phase: subjects received treatment until any withdrawal criterion had been met. [redacted] Post Study Visit 1 was to be performed approximately 30 days after the final dose of SCH 717454 or the standard treatment assigned (whichever was last) for safety assessment. Post Study Visit 2 was to be performed at approximately 4 months after the last dose of SCH 717454.	
OBJECTIVE(S): Primary Trial Objectives: **Part 1:** To determine a safe and generally well-tolerated dose of SCH 717454 to be administered in combination with different treatment regimens in subjects with advanced solid tumors. **Part 2:** To determine tumor response rate for SCH 717454, as defined by Response Evaluation Criteria in Solid Tumor (RECIST), in combination with different treatment regimens. **Secondary Trial Objectives (Part 1 and Part 2):** • To evaluate the adverse event (AE) profile of SCH 717454 administered in combination with different treatment regimens in subjects with advanced solid tumors; • To evaluate the pharmacokinetic (PK) parameters of SCH 717454 when administered in combination with other treatment regimens; • To determine the incidence of anti-SCH 717454 antibodies; • To evaluate peripheral blood levels of: o Insulin-like growth factor-1 (IGF-I) and Insulin-like growth factor-2 (IGF-II), and o Insulin-like growth factor binding protein-2 (IGFBP-2) and insulin-like growth factor binding protein-3 (IGFBP-3).	
STUDY STATUS: Due to the fact that the program with SCH 717454 was terminated, the trial was ended prematurely. All subjects that had already been enrolled by the time this decision was made were allowed to continue with the protocol. Since only fifteen subjects participated in the trial, results are reported in this aCSR.	

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STUDY DESIGN: This was a Phase 1B/2, non-randomized, dose-escalation, multicenter, open-label trial designed to evaluate the safety and tolerability of SCH 717454 in combination with standard treatment in subjects with advanced solid tumors.

Six different treatment regimens were to be investigated in combination with SCH 717454: [redacted]

The study was to be divided into two parts. Part 1 consisted of an initial safety evaluation and dose-finding of SCH 717454 in combination with each treatment regimen. Part 2 consisted of an expansion of each SCH 717454 regimen at a newly established dose level, to better define safety, tolerability, and initial efficacy in specific target populations. [redacted]

SUBJECT/PATIENT DISPOSITION: [redacted]

DOSAGE/FORMULATION NOS.: For Part 1, SCH 717454 was to be administered intravenously (IV) over 1 hour at a dose of either 10 mg/kg, 15 mg/kg (for Regimens B and C), or 20 mg/kg together with the assigned standard treatment. For Part 2, SCH 717454 was to be administered at the dose selected during Part 1, based upon the maximum tolerated dose (MTD) or maximum administered dose (MAD), PK, and pharmacodynamic (PD) data.
Subjects were to be assigned to 1 of the 6 treatment schedules. [redacted]

All subjects received SCH 717454 from the same batch (Batch # [redacted]

DIAGNOSIS/INCLUSION CRITERIA: Subjects with a diagnosis of advanced solid tumor were selected to participate in the study for Part 1, and subjects with specified advanced solid tumors were to be selected to participate in the study for Part 2. Subjects were to be ineligible for curative therapy options or have either failed, progressed, or relapsed after curative therapy.

Key Inclusion Criteria

1. Each subject was ≥18 years of age, of either sex and of any race/ethnicity;
2. **Part 1:** Each subject had a histologically or cytologically confirmed advanced malignant solid tumor;

   Part 2: Each subject had a histologically or cytologically confirmed, with measurable disease (as defined by RECIST), advanced, malignant solid tumor type as specified below for which treatment in the given regimen was appropriate [redacted]
   - **Regimen A:** Colorectal Adenocarcinoma;
   - **Regimen B:** Non-small Cell Lung Cancer;
   - **Regimen C:** Gastric Adenocarcinoma;
   - **Regimen D:** Her2+ Breast Cancer;
   - **Regimen E:** Renal Cell Cancer;
   - **Regimen F:** Pancreatic Adenocarcinoma.

[redacted].

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EVALUATION CRITERIA:
Primary Efficacy Endpoint (Part 2):
[redacted]
Primary Safety Endpoint (Part 1)
[redacted]
Secondary Safety Endpoint (Part 1 and Part 2)
[redacted]
PK Endpoints (Part 1 and Part 2), PD endpoints (Part 1 and part 2), and Other Endpoints.
[redacted]

STATISTICAL PLANNING AND ANALYSIS:
Data Sets to be Analyzed:
- **All Treated Set:** All subjects who received at least one dose of study medication. Safety and efficacy analysis were to be based on this dataset.
- **Per Protocol Set:** Subjects who received assigned treatment, who met key eligibility and evaluability criteria. Efficacy analysis was to be based on this dataset.

Primary Efficacy Analysis:
The primary analysis was to be conducted on the All Treated Set and the Per Protocol Set. Overall best response was to be tabulated by treatment regimen. Listings of tumor response for each subject were to be provided.
Safety Analysis:
All commonly occurring AEs were to be tabulated by dose cohort and treatment regimen. Summary statistics and incidence rates were to be provided for the Descriptive Safety Endpoints.
Primary Safety Analysis (Part 1): Summaries of dose-limiting toxicities (DLTs), all AEs and laboratory results were to be provided for the MAD.
Secondary Safety Analysis (Part 1 and Part 2): Adverse events and laboratory results were to be tabulated by dose level for each regimen. Electrocardiograms were to be summarized. In addition, CD4 levels were to be summarized by treatment using descriptive statistics.
PK Analysis (Part 1 and Part 2): Serum SCH 717454 concentrations were to be determined using a validated electrochemiluminescence (ECL) assay. Using noncompartmental analysis, the derived PK parameters for SCH 717454 were to include, but were not to be limited to, time to maximum observed concentration (Tmax), maximum observed concentration (Cmax), and AUC (area under the curve). Drug concentrations and PK parameters for SCH 717454 were to be listed and summarized using means, standard deviations, and percent coefficients of variation.
PD Endpoints (Part 1 and Part 2): Absolute levels and changes in PD measurements were to be compared among each other and with clinical outcome, in terms of both toxicity and efficacy.
Other Endpoints (Part 1 and Part 2): The incidence of anti-SCH 717454 antibodies was to be assessed.

RESULTS: Due to the fact that the program with SCH 717454 was terminated, the trial was ended prematurely. Given the small number of subjects in each regimen, it was not possible to determine the MTD of SCH 717454 to be administered with each combination treatment.
Subject characteristics: A total of 15 subjects were enrolled with 2,3,2,4, and 4 subjects in Regimens A, B, D, E, and F, respectively. All were treated with the initial dose of SCH 717454 at 10 mg/kg. [redacted] All 15 subjects discontinued from the trial. The primary reason for discontinuation was disease progression.
PK results:
The PK analysis was not performed due to the small number of subjects. [redacted]

[redacted]

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Efficacy: Twelve subjects were evaluable for response. Two of them achieved an overall best response of partial response, eight had stable disease, and two had progressive disease. [redacted]. The Dose escalation phase was not completed due to the early termination of the study. Thus, a formal assessment of potential MTD could not be performed.

Safety:

All 15 subjects reported one or more treatment emergent adverse event (TEAE). Fourteen of them had at least one TEAE of Grade 3 or 4. The most common TEAEs were hyperglycemia and nausea (both reported in 7 subjects each). Anemia, diarrhea, and hypomagnesemia were each reported in 6 subjects. Myalgia and fatigue were both reported in 5 subjects each. The most common TEAEs reported as Grade 3 or 4 were hyperglycemia (6 subjects), neutropenia (4 subjects), and thrombocytopenia (3 subjects). [redacted]

Thirteen subjects experienced treatment-related TEAEs. The most frequently reported treatment-related TEAEs were hyperglycemia (7 subjects), nausea (5 subjects), fatigue (5 subjects), diarrhea (5 subjects), myalgia (5 subjects), and neutropenia (4 subjects). Treatment-related TEAEs reported as Grade 3 or 4 were hyperglycemia (5 subjects), neutropenia (4 subjects), and thrombocytopenia (2 subjects). [redacted].

A total of 7 subjects reported at least one serious adverse event (SAE). Six subjects had SAEs that were considered Common Terminology Criteria (CTC) Grade 3 or 4. None of the SAEs reported were deemed to be related to SCH 717454.
[redacted]

Three subjects reported AEs leading to study discontinuation. These AEs were: performance status decreased, hepatic failure, and fatigue. None of them were deemed to be related to SCH 717454. [redacted]

No subjects died within 30 days following end of treatment [redacted]. Five subjects died during the study: one subject died due to an AE of declining performance status, not considered to be drug-related by the investigator, and four subjects died due to disease progression [redacted].

[redacted]

[redacted]

For immunogenicity assessment, only subjects who had a negative pre-treatment sample and a post-treatment sample were considered to be evaluable. If a subject had a single sample considered positive in the anti-SCH 717454 antibody assay (with the exception of pre-treatment positive subjects), then they would be counted as positive in the immunogenicity assessment. In this study, 3 subjects were considered evaluable. None of the 3 evaluable subjects had any post treatment samples that were positive in the anti-SCH 717454 antibody assay [redacted]

[redacted]

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CONCLUSIONS:

Given that only 15 subjects were enrolled in the study, no formal analyses or conclusions can be drawn from the data.

- Twelve subjects were evaluable for response. Two of them achieved an overall best response of partial response, eight had stable disease, and two had progressive disease.
- All 15 subjects reported one or more TEAEs. The most common TEAEs were hyperglycemia, nausea, anemia, diarrhea, and hypomagnesemia. The most frequent TEAEs reported as Grade 3 or 4 were hyperglycemia, neutropenia, and thrombocytopenia.
- Thirteen subjects experienced treatment-related TEAEs. The most frequently reported treatment-related TEAEs were hyperglycemia, nausea, fatigue, diarrhea, myalgia, and neutropenia. Treatment-related TEAEs reported as Grade 3 or 4 were hyperglycemia, neutropenia, and thrombocytopenia.
- A total of 7 subjects reported at least one SAE. Six of them had SAEs considered Grade 3 or 4. None of the SAEs were considered related to SCH 717454.
- Three subjects reported AEs leading to study discontinuation. None of them were considered related to SCH 717454.
- Five subjects died during the study. Four of them died due to disease progression, and one died due to an AE of declining performance status, not considered to be related to SCH 717454.