Clinical Study Report Synopsis

Drug Substance	ICI35,868
Study Code	D0092C00001
Edition Number	1
Date	31 August 2011

A multi-centre, single-blind, randomised, parallel group, phase IIb dose rate range finding study to find maintenance dose rate range of ICI35,868 for the minimal-to-moderate sedation on gastrointestinal endoscopic tests (including endoscopic polypectomy)

Study dates:	First subject enrolled: 23 August. 2010 Last subject last visit: 17 November. 2010
Phase of development:	Dose finding study (late-stage phase II clinical trial)
International Co-ordinating Investigator:	
Sponsor's Responsible Medical Officer:	

This study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents

Medical center for the study

This study was conducted at two medical centers in Japan.

Publication

None

Study objectives and endpoint

Study objectives and endpoints are shown in Table S1.

Table S1 Primary, secondary objective and endpoint

Objective	Endpoint	Category
Primary objective	**Primary Endpoint**	
To find maintenance dose rate range of ICI35,868 to control the levels of sedation to be minimal-to-moderate (comfortable and calm) for diagnostic gastrointestinal endoscopy (including endoscopic polypectomy).	Sedation levels by MOAA/S score in maintenance period	Efficacy
Secondary objectives	**Secondary Endpoints**	
1. To find initiation dose rate range of ICI35,868 to initiate minimal-to-moderate sedation (comfortable and calm) for diagnostic gastrointestinal endoscopy (including endoscopic polypectomy).	• Sedation levels by MOAA/S score in initiation period • Sedation levels by MOAA/S score from the start to the end of maintenance period.	Efficacy
2. To measure the blood concentration, at the end of administration for initiation period and during maintenance period.	Blood concentrations of propofol	PK
3. To evaluate the patient satisfaction with sedation using Patient Satisfaction with Sedation Instrument (PSSI) questionnaire	PSSI	Efficacy
Safety objective	**Safety Endpoints**	
To evaluate the safety of ICI35,868 for the minimal-to-moderate sedation (comfortable and calm).	• AE • Laboratory safety assessment • ECG • Oxygen desaturation (SpO_2), breathing rate pulse and blood pressure • Other safety assessments 1. Incidences of cardiovascular and respiratory adverse episodes 2. Rescue interventions 3. Dose reduction, interruption and discontinuation of investigational product	Safety
Exploratory objective	**Exploratory Endpoints**	
To evaluate endoscopist satisfaction with sedation using Clinician Satisfaction with Sedation Instrument (CSSI) questionnaire.	CSSI	Efficacy

Study design

This study was designed as a multi-centre, single-blind, randomised, parallel group, placebo controlled study.

The initiation and maintenance dose rate range of ICI35,868 to control the levels of sedation to be minimal-to-moderate (comfortable and calm) for diagnostic gastrointestinal endoscopy (including endoscopic polypectomy) was explored.

Target subject population and sample size

Adult subjects (more than 65 years old or less than 65 years old) of ASA physical status I and II during non-emergent EGD and colonoscopy procedure.

Total number of subjects: 120 subjects

A total of 120 subjects with EGD and colonoscopy were randomised to six ICI35,868 Groups (Group 2-7) or placebo group (Group 1). Twenty subjects for each of Groups 1-5, 10 subjects for each of Groups 6-7 were randomised, and the subjects with EGD and colonoscopy were randomised in the ratio of 1:1 in each group.

Out of 20 subjects in each of Groups 1-5, six elderly subjects who were 65 years of age or over (3 subjects on EGD and colonoscopy each) were enrolled and only adults under 65 years of age were enrolled in Groups 6-7.

Blood concentrations (for PK) of propofol were measured in 6 of 20 subjects (2 adults (under 65 years of age) and 1 elderly (65 years of age or over) for each EGD and colonoscopy group of Group 1-5) and 4 of 10 subjects (2 adults for each EGD and colonoscopy of Group 6-7).

Doses and treatment regimens and Lot No.

Details of investigational product and other treatments are shown in Table S2 and a list of Infusion Rate is shown in Table S3.

6 maintenance dose rate groups of ICI35,868, 25, 50, 75, 120μg/kg/min (1.5, 3, 4.5, 7.2 mg/kg/hour) and one placebo group. As maintenance dose rate ICI35,868 were given at infusion rate of 25, 50, 75, 120μg/kg/min. A vehicle was given as placebo at infusion rate of 25μg/kg/min, minimal rate.

Anaesthesiologist administrate investigator product for ICI35,868 and placebo groups.

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form and strength	Lot No.	Expiration Date
ICI35,868 (Propofol Intravenous injection 1%)	propofol 200 mg/20 mL emulsion for injection or infusion (20 mL ampoule)	X10078A	30 APR 2012
Placebo (Intralipid)	The vehicle of Diprivan emulsion for injection or infusion (100 mL bag)	10DD1722	29 FEB 2012

Table S3 List of infusion rate

Group	Subjects	Initiation		Maintenance Infusion Rate (μg/kg/min)
		Dose (mg/kg)	Period (minutes)	
Group 1	20	Same with Group 2		
Group 2	20	0.17	3	25
Group 3	20	0.33	3	50
Group 4	20	0.5	3	75
Group 5	20	0.8	3	120
Group 6	10	0.5	1	75
Group 7	10	0.5	5	75

Duration of treatment

1day (Initiation period and maintenance period)

Statistical method

- Primary variable

The number of subjects and its proportions for each MOAA/S score classified as 0-1, 2-4, 5 at 2 and 4 minutes from the beginning of the maintenance period and arithmetic mean of proportions for each categorized MOAA/S score at 2 and 4 minutes in maintenance period will be calculated by treatment group.

Subject population

A total of 123 subjects out of 129 consented subjects were randomised in the treatment groups (Group 1-7), and 120 subjects (20 subjects in Group 1-5, 10 subjects in Group 6-7) of them received the study drug. Six subjects were withdrawn from the study before randomisation. Additionally, other 3 subjects were withdrawn before administration of the study drug. A total of 117 subjects were completed the study, and 3 subjects were discontinued by the occurrence of adverse event.

There were no apparent trends in demographic and other baseline characteristics.

Summary of efficacy results

In Groups 2-5 (with same length of initiation period of 3 min), the proportion of subjects with MOAA/S scores of 2-4 after 2 and 4 min of the beginning of maintenance period increased generally in a dose-dependent manner. The proportion of subjects with MOAA/S scores of 0-1(excessive sedation) was highest in Group 5.

At the end of initiation period, proportion of subjects with MOAA/S score 2-4 in Groups 2-5 (with same length of initiation period of 3 min) increased generally in a dose-dependent manner. MOAA/S score 0-1 (excessive sedation) was reported in 1 subject in Group 5.

In Groups 4, 6 and 7 (with same maintenance dose rate of 75 μg/kg/min, but different length of initiation period), the proportion of subjects with MOAA/S score 2-4 was highest in Group 4 (with length of initiation

period of 3 min). In Group 6 (with length of initiation period of 1 min), all subjects were classified to MOAA/S score 5. With this result, the possibility was suggested that the drug level at the effect sites in brain did not become sufficient to attain the sedation of MOAA/S score 2-4 during the initiation period of 1 min.

The mean of PSSI score of subjects with MOAA/S score 5 at all time points increased in a dose-dependent manner in Groups 2-4, therefore, it suggested that subject survey results showed a high level of satisfaction in subjects with MOAA/S score 5 and there were minimal sedation in those subjects.

The means of CSSI score were highest in Group 4 among Groups 2-7, however, there was no apparent tendency in a dose-dependent manner.

Summary of PK results

The means of blood concentrations of ICI35,868 in Group 2-5 (with same length of initiation period of 3 min) increased generally in a dose-dependent manner, however, blood concentrations of ICI35,868 varied among subjects in each group.

The means of blood concentrations of ICI35,868 was the highest in initiation period in Group 4 among Groups 4, 6 and 7 (the maintenance dose rate of 75μg/kg/min, and the maintenance dose periods are different). The means of blood concentrations of ICI35,868 was the lowest in maintenance period in Group 7 among Groups 4, 6 and 7.

Although, there were no apparent relation between plasma concentrations of ICI35,868 and MOAA/S score nor SpO_2, PSSI in maintenance period showed apparent tendency of increase as increase of plasma concentrations of ICI35,868.

Summary of safety results

The incidence of AE and AE related to study drug were the highest in Group 5 (ICI35,868 group, maximum dose in all treatment groups) among Group 2-7.

Blood pressure increased were reported in only Group 1 (placebo group, 4/20 subjects, 20%). It was considered that the TEAE was occurred with stress by endoscopy, and suggested that the TEAE could be suppressed by the administration of ICI35,868.

There were no severe AEs and SAEs include death in all treatment groups.

There were 4 TEAEs leading to study discontinuation in 3 subjects with colonoscopy. These TEAEs leading to study discontinuation were moderate oxygen saturation decreased (Group 5), mild restlessness (Group 5), mild ventricular extrasystoles and mild blood pressure decreased (Group 7, one and the same subject). All of these TEAEs were considered related to study drug and the subjects recovered.

Abnormal change of clinical laboratory test that was considered as AE was only C-reactive protein increased (1 subject in Group 5).

Cardiovascular and respiratory adverse episodes (vital alarm) that were reported as TEAE were increased blood pressure (2 subjects in Group 1), high pulse (1 subject in Group 1), no breath (1 subject in Group 5) and decreased blood pressure (1 subject in Group 7).

In Group 5 (maximum dose), the incidence of AEs was higher than the other treatment groups and AE of oxygen saturation decreased was reported, so it was suggested that study drug administration of 120μg/kg/min was less tolerated than that of the 25 to 75μg/kg/min.