Clinical Study Report Synopsis

Drug Substance ICI35,868
Medical Device EES0000645/A
Study Code D0092C00002
Edition Number 1.0
Date 16 Sep 2014

A multi-centre, double-blind (partially single-blind), randomized, parallel-group, placebo-controlled, phase III confirmatory study to assess efficacy and safety of the moderate sedation of ICI35,868 with and without EES0000645/A on gastrointestinal endoscopy and gastrointestinal endoscopic polypectomy

Study dates: First subject enrolled: 15 Oct 2013
Last subject last visit: 25 Mar 2014

Phase of development: Phase III (confirmatory study)

International Co-ordinating Investigator: NA

Sponsor's Responsible Medical Officer:

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

Study centers

Four centers

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Details of the objectives and criteria for evaluation were shown in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	The primary objective of the study was to evaluate the efficacy and safety of the moderate sedation with ICI35,868 administered by GI physician/nurse using EES0000645/A or by an anesthesiologist as compared to no sedation (administration of placebo), in subjects who were to undergo gastrointestinal diagnostic endoscopy or gastrointestinal endoscopic polypectomy.	Achievement of target sedation Target sedation is defined as MOAA/S score of 2 to 4 for ≥50% of all MOAA/S measurements from scope-in to scope-out.
Secondary	Efficacy	The secondary objective was to evaluate subject satisfaction with sedation using the Patient Satisfaction with Sedation Instrument (PSSI) questionnaire.	Subject satisfaction (based on PSSI questionnaire)
Safety	Safety	The safety objective was to evaluate the safety of ICI35,868 with and without EES0000645/A as well as placebo without EES0000645/A.	AE Laboratory tests Physical examination Electrocardiogram (ECG) Vital signs Other safety variables 1. Cardiovascular and respiratory episodes 2. Rescue interventions 3. Dose interruption or discontinuation of investigational products

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Efficacy	The exploratory objective was to evaluate GI endoscopist satisfaction with sedation using the Clinician Satisfaction with Sedation Instrument (CSSI) questionnaire.	GI physician satisfaction (based on CSSI questionnaire)

Study design

This study was a multi-centre, double-blind (partially single-blind), randomized, parallel-group, placebo-controlled, phase III confirmatory study.

The efficacy and safety of ICI35,868 (propofol) with and without investigational medical device (EES0000645/A) for moderate sedation for diagnostic gastrointestinal endoscopy and gastrointestinal endoscopic polypectomy were evaluated using placebo as a control.

Target subject population and sample size

The study included subjects who were to undergo a non-emergency routine esophagogastroduodenoscopy (EGD) or colonoscopy that was to be completed within 1 hour.

Target number of subjects: 250

Subjects who were to undergo EGD or colonoscopy (target number of subjects, 250) were randomly assigned to either a placebo group, Group 1 (50 subjects), or the ICI35,868 groups, Groups 2 and 3 (100 subjects each), in a 1:2:2 ratio. Subjects for EGD and those for colonoscopy were included in each group in a 1:1 ratio. GI endoscopic polypectomy was planned to be performed on 1 or more subjects in Group 1, and 2 or more subjects each in Groups 2 and 3.

Investigational product and comparator: dosage, mode of administration and batch numbers

Details of the investigational products and infusion rates were shown in Table S2 and Table S3, respectively.

For Groups 1 and 2, the investigational product (ICI35,868 or placebo) was administered by the anesthesiologist in a double-blinded manner. For Group 3, the GI physician or the nurse as directed by the GI physician operated EES0000645/A and administered ICI35,868 in a single-blinded manner.

Table S2 Details of investigational products

Investigational product	Dosage form and strength	Manufacturer	Batch number	Expiration date
ICI35,868 (Propofol, Intravenous injection 1%) [a]	Propofol 200 mg/20 mL emulsion for injection or infusion (20 mL vial)	AstraZeneca KK	R13028C	February 2015
Placebo (Intralipid) [b]	The vehicle of Diprivan emulsion for injection or infusion (100 mL bag)	Fresenius Kabi AB, Sweden	10FH1820 10GG4934	January 2014 December 2014

a: ICI35,868 was stored at 25°C or less and were not frozen.
b: Intralipid was stored at 2°C to 8°C in a dark place.

Table S3 List of infusion rates

Group	Subjects (planned) [a]	Initiation [b]		Maintenance infusion rate (μg/kg/min) [c]	Intermittent bolus/PRN dose
		Dose (mg/kg)	Period (minutes)		Dose (mg/kg)
1 (placebo)	50	Same as Group 2			
2	100	0.5	3	75 (initial rate) 120 (maximum rate)	0.25
3 (EES0000645/A)	100	0.5	3	75 (initial rate) 120 (maximum rate)	0.25

a: Number of subjects who were to undergo GI endoscopy or endoscopic polypectomy.
b: Initiation period was defined as a period between the initiation of the infusion of investigational product and scope-in.
The infusion rate was 0.5 mg/kg dose per 3 minutes (0.167 mg/kg/min) during the initiation period.
After 3 minutes from the initiation of the administration of investigational product, the infusion rate was set to be 75 μg/kg/min (0.075 mg/kg/min), ie, the initial maintenance infusion rate. If the target sedation level (MOAA/S score 2-4) was not achieved at this point, the anesthesiologist (Groups 1 and 2) or GI physician/nurse (Group 3) was to increase the infusion rate or administer bolus/PRN dose until the target sedation level was achieved. Then, the GI physician was to start GI endoscopy (scope-in).
c: Maintenance period was defined as a period between scope-in and scope-out (end of the infusion of investigational product). Maintenance infusion rate was to be adjusted to maintain the target sedation level (MOAA/S score 2-4).

Investigational medical device (EES0000645/A) (used only in Group 3)

The EES0000645/A is the investigational medical device developed and manufactured by Ethicon Endo-Surgery Inc. and consists of the components described below.

- Main units

1. Procedure room unit (PRU)
2. Umbilical cable
3. Bedside monitoring unit (BMU)
4. Power adapter for BMU
5. Oxygen supply adapter

- Single Patient Use (SPU)

6. Drug infusion cassette
7. Oral/nasal cannula
8. Bite block

- Multiple Patient Use (MPU)

9. Pulse oximeter probe
10. Non-invasive blood pressure (NIBP) cuff
11. Electrocardiogram (ECG) lead set
12. Automatic Response Monitor (ARM) handset

The BMU is designed to monitor the subject continuously from the time prior to the procedure, during the procedure and through post-procedural recovery. The BMU displays the subject's SpO_2, blood pressure and heart rate when it is used alone.

The PRU is designed to be used in the procedure room. When connected to the BMU, the PRU becomes the primary interface between the physician and EES0000645/A during the procedure. Through this interface, the PRU monitoring screen displays all the subject physiological parameters (SpO_2, $EtCO_2$, blood pressure, heart rate, breathing rate, ECG and ARM responsiveness) and O_2 administration, allowing physicians to adjust the ICI35,868 infusion rate to control the level of sedation.

Duration of treatment

One day

Statistical methods

Primary efficacy variable

The proportion who achieved target sedation in each group was calculated along with its exact 95% confidence interval using the Clopper-Pearson method.

Subject population

Of the 272 enrolled subjects, 54 were randomly assigned to Group 1, 107 to Group 2 and 111 to Group 3. Of these, 261 subjects (51 subjects in Group 1, 101 subjects in Group 2 and 109 subjects in Group 3) received the investigational product. All the 261 subjects who received the investigational product completed the study. After randomization, 11 subjects were withdrawn before receiving the investigational product.

Summary of efficacy results

Primary Endpoint (achievement of target sedation)

- Overall, the proportion of subjects who achieved target sedation was statistically significantly higher in Group 2 and Group 3 than in Group 1. This result indicates that ICI35,868, with or without the EES0000645/A, can be used to achieve and maintain moderate sedation in subjects undergoing colonoscopy and EGD procedures (with and without polypectomy).

Secondary Endpoints

- Overall, PSSI total score was statistically significantly higher in Group 2 and Group 3 than in Group 1. This result indicates that subjects who received moderate sedation with ICI35,868 had higher level of satisfaction.

Exploratory endpoint

- Overall, CSSI total score was statistically significantly higher in Group 2 and Group 3 than in Group 1. This result indicates that GI physicians had higher level of satisfaction when subjects received moderate sedation with ICI35,868.

Other variables

- Overall, no noticeable difference was observed for the time from start of administration of the investigational product to scope-in between Group 2 and Group 3.

- Overall, the total dose (sum of initiation dose and maintenance dose, including PRN dose) of the investigational product was slightly lower in Group 3 than in Group 2. This result was consistent with cumulative distribution of maintenance infusion rates for Groups 2 and 3.

- The proportion of subjects with titrations was higher in Group 2 and Group 3 than in Group 1. The purpose for a titration was mostly to maintain the target sedation level.

- During both the initiation period and maintenance period, the number of bolus/PRN doses were less in Groups 2 and 3 than in Group 1. During initiation, the use of bolus/PRN doses for any group was mostly due to subjects still having a MOAA/S = 5', whereas in the maintenance period this use was mostly to relieve transient increases in discomfort.

Summary of safety results

- Incidence rate of subjects with TEAEs and TEAEs related to investigational product were comparable between three groups. All of the TEAEs reported in this study were mild in intensity, except for 4 moderate TEAEs reported in 4 subjects.
- Death, other SAEs, TEAEs leading to study discontinuation, TEAEs leading to medical intervention were not reported in this study.
- TEAEs leading to discontinuation of investigational product were reported for one colonoscopy subject in Group 1 (bradycardia and oxygen saturation decreased) and for one EGD subject in Group 3 (apnoea). These TEAEs were mild in intensity and not considered investigational product related. Outcome of these TEAEs were recovered/resolved.
- There were several abnormal values in laboratory test and vital signs reported as TEAEs. Except for blood urine present (one subject in Group 3) reported as moderate in severity, all TEAEs were considered as mild in severity.
- Accounting for differences in setting of patient monitors used between groups in the study, the number and incidence rate of subjects with cardiovascular and respiratory episodes between groups were not considered substantive difference.
- There were no AEs related to investigational medical device. Device failures were not reported in this study.