CLINICAL STUDY PROTOCOL

A Study Designed to Determine the Gastro-Retentive and Modified Release Properties of Memantine Hydrochloride Prototype Capsule Formulations in Healthy Subjects

Quotient Study Number: QCL117924
EudraCT Number: 2017-000982-61

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SPONSOR/QUOTIENT CLINICAL CONFIDENTIAL

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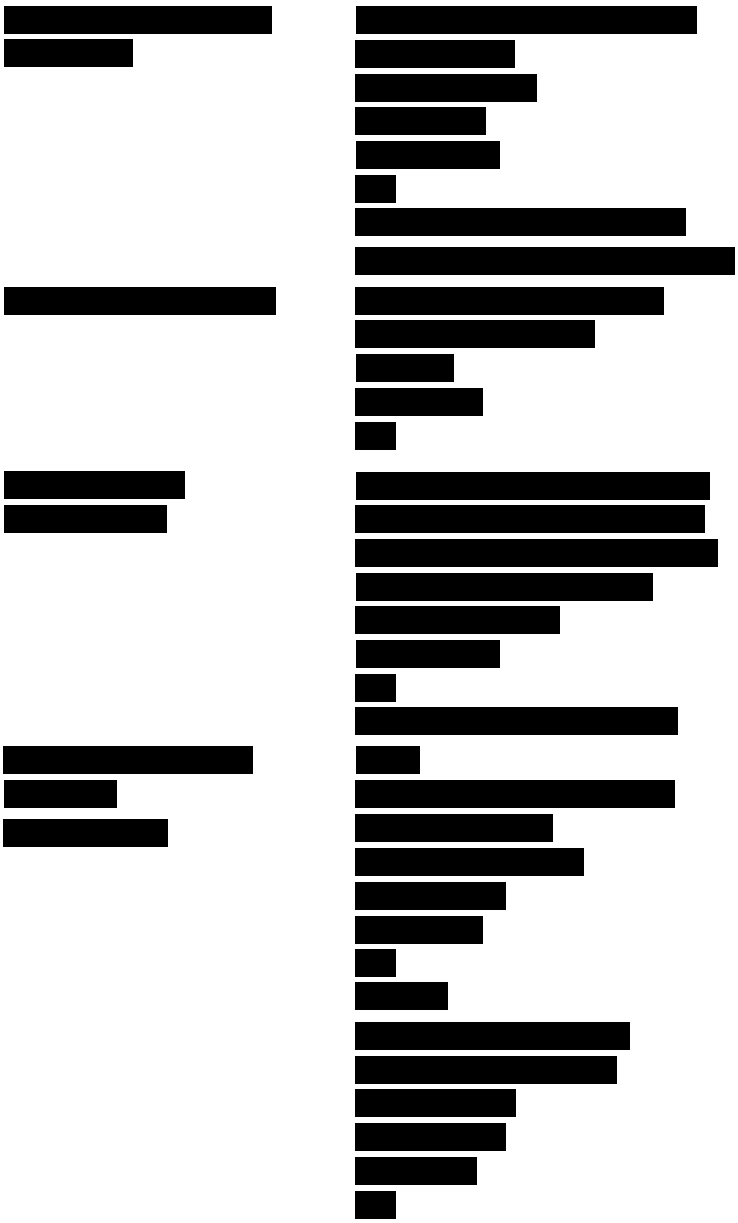

Signatures for Quotient

CONFIDENTIALITY AND GCP COMPLIANCE STATEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 16.3 of this protocol.

Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of the sponsor.

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3 Synopsis

Sponsor: Lyndra Inc.	Investigational Medicinal Product: Memantine Hydrochloride Modified Release Prototype Capsule	EudraCT No.: 2017-000982-61

Title of Study:

A Study Designed to Determine the Gastro-Retentive and Modified Release Properties of Memantine Hydrochloride Prototype Capsule Formulations in Healthy Subjects

Principal Investigator:

P Evans MBChB, MRCS (Ed)

Study Centre:

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Objectives:

Primary:

- To assess the gastro-retentive (GR) properties of memantine hydrochloride modified release (MR) prototype capsules as determined by magnetic resonance imaging (MRI).

Secondary:

- To determine the pharmacokinetics (PK) of memantine hydrochloride when administered as the MR prototype capsules.
- To provide additional safety and tolerability information for memantine hydrochloride MR prototype capsules.
- To assess the impact of dosing in the fed state on the PK properties of a selected memantine hydrochloride MR prototype capsule (optional).
- To assess the impact of dosing in the fed state on the GR properties of a selected memantine hydrochloride MR prototype capsule (optional).

Exploratory:

- To assess the impact of diurnal differences and food consumption on the PK of memantine hydrochloride MR prototype capsule(s) on Days 3 and/or 5 of selected regimen(s).
- To use abdominal X-ray to confirm the elimination of the elastomeric core of the memantine hydrochloride MR prototype formulations from the body by Day 21 where the formulation contains radiopacifier.

Methodology:

This is a single centre, open-label, single dose, 5-period study in 24 healthy male and female subjects, with an optional Period 6, if required. It is expected the study will be executed in 3 cohorts of 8 subjects, with each cohort participating in up to 2 study periods (total of up to 6 study periods). Cohort 3 may be conducted in parallel with Cohort 2.

Subjects will be dosed in a sequential manner, as appropriate. Each subject will be administered up to 2 regimens across 2 study periods as follows:

Cohort	Regimen	Investigational Medicinal Product Dose
1	A	50 mg Memantine Hydrochloride MR Prototype Capsule as Formulation 1
	B	50 mg Memantine Hydrochloride MR Prototype Capsule as Formulation 2
2	C	50 mg Memantine Hydrochloride MR Prototype Capsule as Formulation 3
	D	50 mg Memantine Hydrochloride MR Prototype Capsule as Formulation 4
3	E	50 mg Memantine Hydrochloride MR Prototype Capsule as Formulation 5 or a previously dosed MR Prototype Capsule
	F (optional)[a]	50 mg Memantine Hydrochloride MR Prototype Capsule as Formulation 6 or a previously dosed MR Prototype Capsule

MR, modified release

[a] Regimen F will be administered to Cohort 3 in Period 2, if required, either in the fasted state or after a breakfast (meal composition to be confirmed [tbc])

Regimens A to E: planned dose administration will be in the fasted state following an overnight (minimum 10 h) fast; however, food status for Regimens B to E may be changed (e.g., administered with a meal composition [tbc]) based on emerging GR properties and PK data from previous regimens

Details of the IMP are provided in the IMP section

There will be a minimum 35-day interval between each dose administration. If at Day 14 of Period 1 plasma PK levels are >20 ng/mL, subjects will not progress to a second treatment period.

An interim decision will take place after each regimen to decide on the memantine hydrochloride MR prototype capsule to dose in the next regimen, prandial status and food composition for dose administration in the subsequent period, and after Regimen E to decide if Regimen F is required. Selection of the MR prototype capsule formulations will only be made after a complete review of all data collected from the previous cohort(s). For selection to occur, data must be available from a minimum of 6 subjects in each regimen who have completed the planned safety, PK and MRI assessments up to 312 h (Day 14). Where the desired GR properties have not been achieved for any dosed formulation the dose decision can select any previously tested formulation to dose again in the fed state during the next study period since it is known that dosing in the fed state can improve gastroretention of oral dosage forms. For all regimens, blood samples will be collected for PK analysis up to Day 35 and there will be the option to increase the number of PK samples over a 24-hour period on Days 3 and/or 5 to assess the impact of diurnal differences and food consumption during the regimen on the PK profile (details provided in PK Assessments section).

Study Design:

Subjects will be screened for inclusion in the study in the 28 days before dosing. Each period will follow the same study design. Subjects will be admitted to the clinical unit in the evening prior to product administration (Day -1). It is planned that subjects will be dosed in the morning of Day 1, in a standing position, following an overnight fast (minimum of 10 h) or after a breakfast (light, medium or high fat breakfast to be confirmed) for optional Regimen F. However, the food status for Regimens B to E may be changed (e.g., administered with a meal composition to be confirmed) based on emerging GR properties and PK data from the previous regimens.

There will be an appropriate interval between dosing of subjects based on logistics. In Cohort 1, sentinel dosing of Regimen A will be performed for the first subject, who will be dosed 7 days prior to the remaining 7 subjects in the cohort. The decision to progress with dosing of the remaining subjects in the cohort will be decided by the investigator or delegate and the sponsor's medical monitor based on the available safety data and MRI images up to Day 6.

Subjects will remain in the clinical unit until 168 h post-dose (Day 8) and will return on Days 10, 14, 21, 28 and 35 for PK blood sample collection. MRI scans (at the University of

Nottingham, to assess the GR properties of the capsule formulations) will be performed as described below. X-ray imaging (at Woodthorpe Hospital, to confirm elimination of the elastomeric core from the body by Day 21) may be performed, as described below.

Faecal samples may be collected until 168 h post-dose in order to retrieve the formulation components (2 drug polymer arms, 4 inactive polymer arms and elastomeric core). If faecal analysis shows all formulation components have been retrieved, no further MRI imaging or faecal sample collections will be performed (see below).

Follow-up procedures will take place on Day 35 post-final dose to ensure the ongoing wellbeing of the subjects.

MRI scans

Subjects will have an MRI scan performed on Days 2, 4, 7, 10 and 14 of each period to assess the GR properties of the capsule formulations. During periods of residency in the clinic, subjects will be given a light snack the evening before the scheduled MRI scan. During the outpatient phase of the study, subjects will be asked to fast from approximately 23:00 prior to attending the clinic.

After the overnight fast, subjects will receive 50.4 g of carbohydrate as a drink (2 x 200 mL drinks) at least 2 h before the MRI procedure in order to reduce the increased gastric motility resulting from prolonged periods of fasting (in the clinic on Days 2, 4 and 7, and at home on Days 10 and 14), and will then drink at least 500 mL of potable water immediately before the MRI scan. If the MRI confirms that the MR prototype formulation is not resident in the stomach, additional MRI images of the small intestine may be performed on that day to confirm its location. No further MRI scans will be performed on subsequent days if stomach residency is not confirmed.

If complete gastric emptying (all stellate components) is not confirmed on Day 14, subjects will be asked to return for a follow-up MRI scan between Day 14 and Day 25 (allowing a minimum 10-day window before admission to Period 2) to confirm complete gastric emptying of the stellate components. If any MR prototype is still present at this follow-up MRI scan, subjects will not progress to Period 2 and will be managed in accordance with best clinical practice.

X-Rays

The elastomeric core will be identifiable for some of the formulations tested and can be detected by X-ray. Where a radiopaque formulation is being tested, 2 abdominal X-ray per subject may be performed during the study (1 per treatment period) in the non-fasted state to to confirm elimination from the body by Day 21.

Number of Subjects Planned:

A total of 24 healthy male and female (women of non-childbearing potential [WONCBP]) subjects are planned to ensure a minimum of 6 evaluable subjects per regimen. Subjects withdrawn or discontinuing the study prematurely because of an investigational medicinal product (IMP)-related AE or termination of the study will be considered to have completed the study and will not be replaced. Subjects withdrawing for other reasons may be replaced at the discretion of the investigator and sponsor. Up to 4 replacement subjects may be dosed in each cohort to ensure 6 evaluable subjects per regimen.

Subjects will not be allowed to progress to Period 2, but may be replaced if:

- Their plasma level on Day 14 is >20 ng/mL
  Or
- MRI scans show complete gastric emptying (all stellate components) has not occurred by Period 1, Day 25 (see Study Design section).

Duration of Study:

Single dose administration on up to 2 occasions in 3 separate cohorts of subjects (Cohorts 1, 2 and 3).

The estimated time from screening to the end of the study for each subject is approximately 14 weeks.

Main Inclusion Criteria:

- Healthy male and female (WONCBP only) subjects aged 18 to 60 years.
- Body mass index 18.0 to 32.0 kg/m^2 or, if outside the range, considered not clinically significant by the investigator.
- Male subjects must agree to the use of an adequate method of contraception for up to 35 days post-dose. No methods of contraception are required for female (WONCBP) subjects.
- Willingness to undergo serial MRI scans and abdominal X-rays.
- Subject is aware of the specific risks around MRI scans (including claustrophobia and rarely, tingling or burning at tattoo sites).
- Subject must agree to remove all piercings prior to MRI imaging.
- Subjects must demonstrate their ability to swallow a size 000 empty white opaque capsule at screening.
- Must agree not to drive or to operate heavy machinery for up to 17 days post dose (Day 18) due to possible adverse effects of memantine (e.g., somnolence, dizziness, confusion, hallucinations, balance disorders etc).
- Subject must have a negative screening faecal occult blood test

Investigational Medicinal Product, Dose and Mode of Administration:

The IMP, memantine hydrochloride MR prototype capsule (50 mg) will be used in this study, and will be administered as Memantine Hydrochloride MR Prototype Capsule Formulations 1 to 6.

The intermediate formulation consists of 4 primary components; an elastomeric core (which ensures deployment of the dosage form), 2 drug polymer arms (which contain and release the drug), 4 inactive polymer arms (which maintain the structural integrity of the stellate formulation), and 6 disintegrating matrices on the arms (which are intended to control gastric exit and gastrointestinal safety). The intermediate formulation is encapsulated into a Size 00 EL capsule. Once the capsule dissolves in the stomach, the formulation opens to form a 6-arm stellate structure. The elastomeric core can also incorporate a radiopacifier so that the location can be identified by X-ray after oral administration.

Administration will be by the oral route. The memantine hydrochloride MR prototype capsules will be administered with a total of 340 mL of water (consisting of 40 mL given immediately prior to dosing and 200 mL given with the IMP) while subjects are standing. A further 100 mL of water (bolus wash) will be given immediately after dosing. Each volume of water given will be swallowed in one go and will not be sipped.

Pharmacokinetic Assessments:

Venous blood samples for PK analysis will be collected at regular time intervals.

Up to an additional 10 PK samples may be taken over a 24-h period on Days 3 and/or 5 if the option is taken to assess the impact of diurnal differences and food consumption during the regimen on the PK profile (see Study Design section). During Regimen A of Cohort 1, these additional samples will be collected at 4-h intervals throughout Days 3 and/or 5. In subsequent cohorts and/or regimens, this schedule may be adjusted based on emerging PK data from previous regimens, subject to the restriction that up to 10 additional samples may be taken in total over a 24-h period on Days 3 and/or 5 for this purpose. If the MRI imaging on Days 2

and/or 4 shows that the MR prototype formulation is no longer resident in the stomach, the additional PK sampling will not be performed on the subsequent day.

The plasma concentration data for memantine, provided by York Bioanalytical Sciences, will be analysed by Quotient Clinical using Phoenix WinNonlin v6.3 or a more recent version (Certara USA, Inc., USA).

The following PK parameter estimates will be obtained, where possible and appropriate:

Cmax, AUC(0-t), AUC(0-168) and AUC(0-inf).

Relative bioavailability (Frel) of the selected memantine hydrochloride MR prototype capsule in the fed state compared to the fasted state (if tested).

Additional PK parameters and/or comparisons may be calculated, which will be detailed in the Reporting and Analysis Plan (RAP).

MRI and X-Ray Assessments:

Analysis of MRI data will be performed on Days 2, 4, 7, 10 and 14 to inform if the stellate formulation is retained in the stomach. If complete gastric emptying (all stellate components) is not confirmed on Day 14, subjects will be asked to return for a follow-up MRI scan between Day 14 and Day 25 (allowing a minimum 10-day window before admission to Period 2) to confirm complete gastric emptying of the stellate components. If any MR prototype is still present in the stomach at this follow-up MRI scan, subjects will not progress to Period 2 and will be managed in accordance with best clinical practice.

X-ray imaging (up to 2 abdominal X-ray per subject during the study; 1 per treatment period) may be performed in the non-fasted state to confirm elimination of the elastomeric core of the memantine hydrochloride MR prototype formulation by Day 21.

Safety Assessments:

Safety will be assessed by the following:

Vital signs, 12-lead electrocardiograms, clinical laboratory evaluations (clinical chemistry, haematology and urinalysis), faecal occult blood tests and monitoring of AEs.

Statistical Methodology:

Descriptive summaries for safety data by regimen will be provided, including changes from baseline, as required.

Descriptive summaries for MRI assessments by regimen will be provided. The percentage and number of subjects with gastric retention at Days 2, 4, 7, 10 and 14, will be presented. Summary plots will also be provided.

Descriptive summaries will be provided for all PK concentration and parameter data by regimen, including plasma concentrations on Days 3 and/or 5 at all additional time points taken, if applicable.

Formal statistical analysis will be performed on the PK parameters AUC(0-t), AUC(0-168), AUC(0-inf) and Cmax to assess relative bioavailability. The PK parameters will undergo a natural logarithmic transformation and will be analysed using a mixed effects model with terms for regimen as a fixed effect and subject as a random effect. Adjusted geometric mean ratios (GMRs) and 90% confidence intervals for the GMR will be provided for each relevant comparison between MR prototype capsule formulations. In addition comparisons of formulations dosed in the fed and fasted state will be made, as appropriate.

Sample Size and Power:

The study is exploratory and no formal sample size calculation was performed. For a study of this type, a sample size of 8 subjects enrolled in each cohort to achieve a minimum of 6 evaluable subjects per regimen is considered sufficient to meet the objectives of the study. A subject is considered to be an evaluable subject for the study if they have received one

dose of memantine hydrochloride MR prototype capsule and have PK data (AUC0-168) and safety data up to Day 8.