A Phase 2, Multicenter, Randomized, Double-Blind, Comparator-Controlled Study of the Efficacy, Safety, and Pharmacokinetics of Intravenous Ulimorelin (LP101) in Patients with Enteral Feeding Intolerance

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Primary Efficacy Objective:To evaluate the effect of multiple daily intravenous (IV) doses of ulimorelin on the proportion of the daily protein prescription (DPP) received through enteral nutrition by mechanically ventilated and tube-fed patients...

Ethical review	Approved WMO
Status	Pending
Health condition type	Food intolerance syndromes
Study type	Interventional

Summary

ID

NL-OMON47313

Source
ToetsingOnline

Brief title
LP101-CL-201

Condition

- Food intolerance syndromes

Synonym
Enteral feeding intolerance

Research involving

Human

Sponsors and support

Primary sponsor: Lyric Pharmaceuticals Inc.
Source(s) of monetary or material Support: Lyric Pharmaceuticals;Inc.

Intervention

Keyword: daily protein prescription, Enteral Feeding Intolerance, tube fed mechanically ventilated, Ulimorelin

Outcome measures

Primary outcome

Primary Efficacy Endpoint

The daily average (mean) percentage of daily protein prescription (DPP)

received through enteral nutrition by mechanically ventilated and tube-fed

patients with EFI, Efficacy Phase Days 1 through 5

Secondary outcome

Secondary Efficacy Endpoint

The daily average (mean) percentage of daily caloric prescription (DCP)

received through enteral nutrition by mechanically ventilated and tube-fed

patients with EFI, Efficacy Phase Days 1 through 5

Safety:

• SAEs and AEs, summarized by treatment group and Medical Dictionary for

Regulatory Activities (MedDRA) system organ class (SOC) and preferred term.

• Vital signs, ECG results, and clinical laboratory tests, summarized by

treatment group

• 30-day hospital mortality rates (Efficacy Phase only)

Pharmacokinetics:

The following PK parameters for total and free ulimorelin will be calculated at minimum:

• Maximum plasma concentration (Cmax) on Efficacy Phase Day 1 and Day 4

• Accumulation factor (Rac) for Cmax on Efficacy Phase Day 4

• The area under the plasma concentration-time curve over the dosing interval, tau (*) (AUC0-t) on Efficacy Phase Day 4 will be calculated pending sufficient terminal phase data

• An assessment of achieving steady state by Efficacy Phase Day 5 will be performed pending sufficient trough data

Pharmacodynamics:

• Liquid gastric emptying by paracetamol AUC0-60, AUC0-120, Cmax, concentration at 60 minutes (C60), and time to maximal concentration (tmax) on Efficacy Phase Day 4 compared to baseline

• The exposure-response relationship between ulimorelin free Cmax and paracetamol parameters of gastric emptying on Efficacy Phase Day 4

• 60 minutes post-dose GH and IGF-1 concentrations on Efficacy Phase Days 1 and 4 compared to baseline

• CRP, IL-6, IL-10 and IL-6 to IL-10 ratio on each study day compared to baseline

Study description

Background summary

Ulimorelin is an intravenous (IV) synthetic agonist of the human ghrelin receptor originally discovered and developed by Tranzyme Pharma, Inc., for the management of postoperative ileus (POI) and diabetic gastroparesis, two hypomotility disorders of the gastrointestinal (GI) tract. Ulimorelin is a small molecule macrocycle and a potent, selective agonist at the cloned human growth hormone secretagogue receptor (hGHS-R1a; ghrelin receptor). It demonstrated prokinetic activity in animal models of GI hypomotility and anti-catabolic effects in a mouse xenograft model of cancer cachexia. Because of its dual prokinetic and anabolic properties, ulimorelin is now being developed by Lyric Pharmaceuticals for the treatment of enteral feeding intolerance (EFI) in critically ill patients. By both improving GI motility and mitigating the loss of lean body mass (LBM), ulimorelin may significantly impact the clinical outcomes of these patients.

Ghrelin is a 28-amino-acid peptide that was identified as the natural ligand for the hGHS-R1a. In addition to the stimulation of growth hormone (GH) secretion, ghrelin is a potent stimulant of appetite and GI motility [1 ,2]. The prokinetic effects of ghrelin, including stimulation of gastric emptying, are thought to represent both direct effects on ghrelin receptors and up-regulation of vagal tone. Mechanistic studies in isolated tissues indicate that ghrelin stimulates and coordinates electrical signaling in the GI tract via hGHS-R1a and vagal stimulation to promote gut motility [3 4,5]. This is confirmed in a number of pharmacological assays of GI motility in rats and dogs [6 ,7 ,8]. A series of investigator-initiated trials in humans demonstrated that ghrelin peptide exerts significant prokinetic effects in healthy subjects and in patients with diabetic and idiopathic gastroparesis [2,9,10].

Ghrelin has been termed the *feeding hormone*, because it both stimulates appetite and gastric emptying and enables the anabolic effects of GH and insulin-like growth factor 1 (IGF-1) on protein tissue stores [11]. Because of these properties, ghrelin has been advocated as a pharmacological treatment for conditions associated with deficiencies in LBM [12]. Native ghrelin administration was shown to increase handgrip strength and breathing capacity in chronic obstructive pulmonary disease [13]. It has been proposed as a potential therapy to improve lung function and prevent LBM loss in patients in the Intensive Care Unit (ICU) [14,15], as well as to promote nutritional rehabilitation after ICU discharge [16]. Ghrelin agonists have also been under development for the loss of LBM in cancer patients and elderly patients with hip fracture [17].

Growth hormone has been proposed for ameliorating catabolic wasting in critically ill patients [18,19,20,21,22], but after several successful trials [23,24,25,26,27,28], development came to a halt when a significant increase in mortality was observed in two similarly designed companion trials [29]. These

studies were criticized on the grounds that supratherapeutic (20-fold replacement) slow-releasing subcutaneous (SC) doses were administered, inducing high peak GH secretion (estimated ~200 ng/mL, normal 0-10) and sustaining these levels throughout the day [30,31,32]. This is said to have led to uncontrolled hyperglycemia, cardiotoxicity, inflammatory stress, and metabolic imbalances [33,34,35,36,37]. Natural counter-regulatory mechanisms at the level of the pituitary and hypothalamus were bypassed, and pulsatile GH secretion was suppressed [14,15,31]. Since that time, recombinant GH or IGF-1 analogues have been administered safely and successfully in several trials [34,38,39]. Ghrelin analogs have been proposed as a safer means to achieve protein sparing in critically ill patients, because they preserve pulsatile GH secretion and counter-regulatory mechanism at the level of the pituitary-hypothalamic axis [14,15,34].

Ghrelin also has anti-inflammatory properties that could be beneficial to patients with critical illness [40,41,42], in whom high levels of pro-inflammatory cytokines exert deleterious effects [43]. Ghrelin down-regulated TNF-a and interleukin (IL)-6 activity [44] and protected against endotoxin-induced acute kidney injury [45] in animal models of sepsis. Ghrelin also improved tissue perfusion via down-regulation of endothelin-2 [46] and NF-*B [44]. High levels of circulating cytokines may be responsible for the devastating loss of LBM in critical illness [47,48]. The anti-inflammatory effects of ghrelin have been postulated to be the result of up-regulation of vagal and down-regulation of sympathetic tone [43,49]. In a clinical study of 154 patients with hospital-acquired sepsis, sympathetic inhibition with the beta-blocker esmolol resulted in a 50% reduction in mortality [50], suggesting the potential benefit of invoking the same autonomic mechanism through use of a ghrelin agonist.

Enteral nutrition (EN) refers to the delivery of a nutritionally complete enteral formula into the gut via a nasogastric, nasoenteric, orogastric, or percutaneous feeding tube in patients who cannot eat or attain adequate oral intake from food and/or oral nutritional supplements. Enteral nutrition is associated with improved protein turnover, improved wound healing, reduced septic complications, decreased bacterial translocation across intestinal mucosa, and decreased catabolic response to injury [51,52]. Enteral nutrition is recommended as soon as possible following admission to the ICU in order to minimize the protein-calorie deficit developing early in critical illness [53,54]. Protein and calorie deficits have been associated with increased organ failure, infection, hospital length of stay, and complications [55,56]. In observational studies, randomized controlled trials, and meta-analyses, infection rates, hospital length of stay and mortality were inversely correlated with the level of enteral nutritional support [53,57,58,59,60,61,62,63].

Treatment of EFI is the target indication for the current study. EFI is defined as the inability to deliver adequate EN to critically ill patients due to

delayed gastric emptying in the absence of mechanical obstruction. EFI is the predominant GI complication during a course of EN in critically ill patients [64,65,66,67]. Observational studies and meta-analyses have revealed that more than 30% of critically ill patients experience intolerance to enteral feeding [68,69]. This incidence may be as high as 85% in patients with polytrauma, traumatic brain injury, and sepsis [70,71]. Compared with patients without EFI, patients with EFI have longer ICU stays and higher ICU mortality [68,69,72]. These are expected outcomes of highly catabolic critically ill patients who fail to achieve acute nutritional needs [16].

Enteral feeding intolerance is typically diagnosed by the presence of high gastric residual volume (GRV). While the value of GRV was questioned in recent clinical trials [73,74], the conclusions of these studies were confounded by the bias of unblinded treatment intervention, the confounding effects of concomitant use of prokinetic agents in most study participants, and the failure to adjust the volume of tube feeding administered for loss due to vomiting. Despite controversies regarding the use of GRV to determine feeding intolerance, it remains the standard for monitoring EN in ICU patients in most ICUs worldwide [75,76]. Elevated GRV (150 to 250 mL) has been shown to predict delayed gastric emptying [77,78] and poor ICU outcome [68,75,76]. While controversy remains [72,76], 250 to 500 mL is typically employed to identify EFI in most hospital ICUs [76], and 500 mL is recommended in the most recent US guidelines [54]. The guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN) are silent on this issue [79].

It is recommended that prokinetic agents be employed to promote GI motility and facilitate enteral feedings in patients with EFI [53,54]. However, no drugs are approved for this indication and metoclopramide and erythromycin, the most commonly used prokinetic agents, rapidly lose effectiveness and are marginally safe in the ICU setting. Metoclopramide is associated with serious central nervous system side effects, and erythromycin can lead to critical drug-drug interactions, QT prolongation, and super infection with multiple drug-resistant organisms. A safer and more effective prokinetic agent with synergistic anabolic effects could improve outcomes in critically ill patients with high catabolic rates and nutritional needs.

The purpose of this trial is to evaluate the efficacy and safety of ulimorelin in enabling the delivery of nutrition to critically ill patients with intolerance to enteral feedings.

For reference please see the study protocol.

Study objective

Primary Efficacy Objective:
To evaluate the effect of multiple daily intravenous (IV) doses of ulimorelin on the proportion of the daily protein prescription (DPP) received through

enteral nutrition by mechanically ventilated and tube-fed patients with EFI

Secondary Efficacy Objective:
To evaluate the effect of multiple daily IV doses of ulimorelin on the proportion of the daily caloric prescription (DCP) received through enteral nutrition by mechanically ventilated and tube-fed patients with EFI

Safety Objective:
To evaluate the safety and tolerability of multiple daily IV doses of ulimorelin in mechanically ventilated and tube-fed patients with EFI.

Pharmacokinetic Objectives:
To evaluate the relationships between α-1-acid glycoprotein (AAGP) levels, pharmacokinetic (PK) endpoints, and pharmacodynamic (PD) endpoints following multiple daily IV doses of ulimorelin in mechanically ventilated and tube-fed patients with EFI

Pharmacodynamic Objectives:
To evaluate the effect of ulimorelin on gastric emptying in mechanically ventilated and tube-fed patients with EFI.

Observational Phase Objective: To explore factors associated with the progression of at-risk patients to EFI.

Study design

This is a multicenter, randomized, double-blind, comparator-controlled study with a lead-in Observation Phase. The study consists of 2 parallel-dose treatment groups consisting of ulimorelin and metoclopramide.

Intervention

The study will consist of two parallel-dose treatment groups consisting of ulimorelin (600 µg/kg) or metoclopramide (10 mg) administered 3 times daily as a 50 mL IV infusion over 30 minutes for 5 days. Patients will continue to receive study drug 3 times daily Q8H for 5 days (15 doses total).

Study burden and risks

The flow chart of the study is described on pages 56 - 60 of the protocol. The duration of the study is as follows:
The Observation Phase will take in total 72 hours. The Efficacy Phase; screening period on the first day, treatment period of 5 days. Follow-up period from day 6 to day 8. And a 30 day follow-up by review of medical records. Patients will be in the ICU during the whole study period (screening to day 8). Screening assessments will not take more than 2 hours, thereafter from Efficacy

Phase day 1 to day 5 study related procedures including but not limited to study drug administration (3 times daily, 30 minutes each), Gastric emptying determination and additional blood and urine sampling will take approximately 3 hours. The total of blood sample volume collected is 136 ml in the Efficacy Phase.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Observation Phase
•Men and non-pregnant women aged 18 years and above
•Intubated and mechanically ventilated in the ICU
•Receiving continuous nasogastric, orogastric, or percutaneous gastric tube feedings
•A 12-Fr or larger nasogastric, orogastric, or percutaneous gastric feeding tube, with its distal

tip at least 10 cm below the gastroesophageal junction and visible in the stomach on a routine radiographic examination within 24 hours of screening
•At risk for the development EFI, with risk defined as GRV between 300 mL and 499 mL on one or more measurements
•Expected to remain intubated, mechanically ventilated, and receiving nasogastric orogastric or percutaneous feeding for at least 48 hours
Efficacy Phase
•Men and non-pregnant women aged 18 years and above
•Intubated and mechanically ventilated in the ICU
•Receiving continuous nasogastric, orogastric, or percutaneous gastric tube feeding
•A 12-Fr or larger nasogastric, orogastric, or percutaneous gastric feeding tube, with its distal tip at least 10 cm below the gastroesophageal junction and visible in the stomach on a routine radiographic examination within 24 hours of screening
•Enteral feeding intolerance, defined as a GRV of >= 500 mL on one or more measurements
•Expected to remain intubated, mechanically ventilated, and receiving nasogastric orogastric or percutaneous feeding for at least 48 hours.

Exclusion criteria

Observation Phase:
• Inability to obtain written informed consent to participate in the study from the patient or legally authorized representative.
• Weight prior to ICU admission exceeding 150.0 kg.
• Suspicion or confirmation of active bowel obstruction, perforation, or leakage.
• History of esophageal or gastric surgery prior to or during the current hospital admission.
• Patient*s clinical condition is deteriorating rapidly, or the Investigator does not consider there to be a reasonable expectation that the patient will complete the study.
• Childs C cirrhosis (ALT elevations are not excluded in the Observation Phase, as these can resolve on follow-up);Efficacy Phase:
• Inability to obtain written informed consent to participate in the study from the patient or legally authorized representative.
• Weight prior to ICU admission exceeding 150.0 kg.
• Suspicion or confirmation of active bowel obstruction, perforation, or leakage.
• History of esophageal or gastric surgery prior to or during the current hospital admission.
• Use of any of the following prokinetic medications is allowed until 48 hours before randomisation but prohibited from 48 hours prior to randomisation through the 5 days of treatment with study drug: domperidone, cisapride, neostigmine, or opioid antagonists, including alvimopan, naloxone, naltrexone, or analogs of naloxone or naltrexone; erythromycin or azithromycin. [N.B., azithromycin is permitted for treatment of pulmonary infections up to 48 hours before randomization, but not thereafter through Day 5. Up to 2 doses of metoclopramide are permitted within 48 hours of randomisation, provided that metaclopramide is not administered within 10 hours of the first dose of study drug or at any time through Day 5. If a patient receives metoclopramide during the screening period, a radiologic examination must confirm that the feeding tube remains visible in the stomach after the final dose of drug during screening and prior to the start of baseline gastric

emptying measurements and has not migrated to the duodenum. Use of clarithromycin for any indication is not excluded.].
• QT interval corrected using Fridericia*s formula (QTcF) > 480 msec on a 12-lead ECG during screening.
• Patient*s clinical condition is deteriorating rapidly, or the Investigator does not consider there to be a reasonable expectation that the patient will complete the study.
• Childs C cirrhosis or ALT >= 1000 U/L

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	13-11-2016
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ulimorelin.HCl.monohydrate
Generic name:	Ulimorelin

Ethics review

Approved WMO

Date:	31-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-08-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

(Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000723-94-NL
CCMO	NL57626.078.16