Phase 3, Multi-Center Randomized, Placebo-Controlled, Double-Blind Study to Confirm the Reversal of Hepatorenal Syndrome Type 1 With Lucassin® (Terlipressin) (REVERSE Trial)

IRB#: TBA

Trial Status: Preparing for enrollment

Phase: III

Sponsor: Ikaria Holdings

Why is this study being done?

This study is designed to evaluate the efficacy and safety of intravenous Lucassin® (terlipressin) versus placebo for the treatment of type 1 hepatorenal syndrome (HRS) in subjects receiving standard of care albumin therapy.

Who is eligible to participate in the study?

Inclusion Criteria:

1. Written informed consent by subject or legally authorized representative
2. At least 18 years of age
3. Cirrhosis and ascites
4. Rapidly progressive reduction in renal function characterized by:
   - SCr ≥ 2.5 mg/dL
   - Doubling of SCr within 2 weeks (or for observations of shorter duration, SCr values over time meeting slope-based criteria for proportional increases likely to be representative of at least a doubling within 2 weeks)
5. No sustained improvement in renal function (< 20% decrease in SCr and SCr ≥ 2.25 mg/dL) 48 hours after both diuretic withdrawal and the beginning of plasma volume expansion with albumin:

Note: Albumin doses recommended by the IAC are 1 g/kg on the first day (Maximum 100 g) and 20 - 40 g/day thereafter as clinically indicated. It is recommended (if clinically appropriate) that the albumin dose is kept constant during the study drug administration period.

Note: The qualifying SCr value is the SCr value at least 48 hrs after both diuretic withdrawal (if applicable) and the beginning of albumin fluid challenge. The qualifying SCr value must be ≥ 2.25 mg/dL AND at least 80% of the diagnostic (pre-fluid challenge) SCr value.

Exclusion Criteria:

1. Serum creatinine > 7 mg/dL
2. Shock Note: Hypotension (MAP < 70 mm Hg or a decrease > 40 mm Hg in systolic blood pressure from baseline) with evidence of hypoperfusion abnormalities despite adequate fluid resuscitation.
3. Sepsis or systemic inflammatory response syndrome (SIRS)
Note: SIRS: Presence of 2 or more of the following findings:

Temperature > 38°C or < 36°C; heart rate > 90/min; respiratory rate of > 20/min or a PaCO2 of < 32 mm Hg; white blood cell count of > 12,000 cells/µL or < 4,000/µL.

Note: Sepsis: Documented infection and systemic inflammatory response syndrome.

4. < 2 days anti-infective therapy for documented or suspected infection
5. Proteinuria > 500 mg/day
6. Hematuria or microhematuria (> 50 red blood cells per high power field)
7. Clinically significant casts on urinalysis, including granular casts

Note: Urine sediment examination is required to exclude presence of granular casts and other clinically significant casts (e.g., red blood cell [RBC] casts).

8. Evidence of intrinsic or parenchymal renal disease (including acute tubular necrosis)
9. Obstructive uropathy or other renal pathology on ultrasound or other medical imaging
10. Current or recent treatment (within 4 weeks) with nephrotoxic drugs, e.g., aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAID) Note: Up to 3 doses of an NSAID within the prior month (prescription or over the counter) is acceptable Note: Use of short-term (< 2 weeks) oral neomycin for acute encephalopathy is acceptable.
11. Current or recent (within 4 weeks) renal replacement therapy
12. Superimposed acute liver failure/injury due to factors other than alcoholic hepatitis, including acute viral hepatitis, drugs, medications (e.g., acetaminophen), or other toxins (e.g., mushroom [Amanita] poisoning)
13. Current or recent treatment (within 48 hours) with octreotide, midodrine, vasopressin, dopamine or other vasopressors
14. Severe cardiovascular disease as judged by investigator
15. Estimated life expectancy of less than 3 days
16. Confirmed pregnancy
17. Known allergy or sensitivity to terlipressin or another component of the study treatment
18. Participation in other clinical research studies involving the evaluation of other investigational drugs or devices within 30 days of randomization.

**Minimum age:** 18

**What is involved in the study?**

| Terlipressin: Experimental | Drug: terlipressin
Blinded terlipressin reconstituted with 5 mL of sterile 0.9% sodium chloride solution for injection will be administered intravenously as a slow bolus injection over 2 minutes at a dose of 1 mg (1 vial) every 6 hours (4 mg/day). |
|---------------------------|------------------------------------------------------------------------------------------|
| Placebo: Placebo Comparator lyophilized mannitol | Drug: Placebo
Lyophilized mannitol reconstituted with 5 mL of sterile 0.9% sodium chloride solution administered intravenously as a slow bolus injection over 2 minutes at a dose of 1 mg (1 vial) every 6 hours (4 mg/day). |
**Detailed Description:**

Hepatorenal syndrome is a rare syndrome of marked renal dysfunction in patients with cirrhosis, decompensated liver disease, and portal hypertension. Hepatorenal syndrome type 1 is characterized by a rapid progressive renal impairment and has a very poor prognosis with > 80% mortality within 3 months. At present, there are no approved drug therapies for HRS type 1 in the US, Australia, or Canada. The only curative treatment for HRS type 1 and the underlying end-stage cirrhosis is liver transplantation. However, many patients will not survive long enough to receive a liver transplant and therapy, which may provide a bridge to transplantation, is badly needed. Increased understanding of the pathophysiology of HRS type 1 has demonstrated that vasoconstrictive drug therapy may reverse HRS type 1. Substantial data available from many published clinical investigations in the literature provide compelling evidence suggesting that administration of terlipressin improves renal function in patients with HRS.

**How long will the study run?**

February 2012

**Who can I contact to find out more about this trial?**

Name: Melissa Cohen
Phone #: (612) 624-6649

**What are the locations of this trial?**

Not provided by study sponsor