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Brief Title: **The Impact of Ibutamoren on Nonalcoholic Fatty Liver Disease**

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Institutional Review Board
Intervention/Interaction Detailed Protocol

[redacted]

Project Title: The Impact of Ibutamoren on Nonalcoholic Fatty Liver Disease (NAFLD): A Pilot Study

[redacted]

[redacted]

For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

SIGNIFICANCE OF THE PROBLEM:

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease, with a global prevalence of 25%.[1] Nonalcoholic steatohepatitis (NASH) cirrhosis is the second leading indication for liver transplantation in the U.S. and will be the top indication by 2025.[2, 3] Despite the significant morbidity and mortality, the molecular mechanisms that lead to the development of NAFLD and progression to NASH are poorly understood, and there are no FDA-approved treatments. **As a long-acting, oral ghrelin mimetic, ibutamoren is a direct immunomodulator and effective growth hormone (GH) secretagogue.** GH, which is reduced in obesity, is a critical stimulator of lipolysis,[4] regulator of abdominal fat depots and an important mediator of inflammation[5] and immune cell populations.[6, 7] ***Thus, investigation of ibutamoren administration in NAFLD/NASH could lead to insights into the development of NAFLD, progression to NASH, and identification of novel therapeutic targets.***

A2. IBUTAMOREN HAS DIRECT IMMUNOMODULATORY EFFECTS:

Ibutamoren regulates T cell populations involved in the pathogenesis of NAFLD/NASH directly through the ghrelin receptor (GHSR1a). One of the characteristic findings in NASH is imbalanced CD4 T cell helper activity with a dominance of Th17 signaling compared to regulatory T cells,[8] and targeting this balance is a new approach in the treatment of NAFLD.[9] Ghrelin has been shown to directly inhibit the differentiation of Th17 cells through the GHSR1a and downstream inhibition of mTOR/STAT3 signaling[10, 11] and has the potential to improve this T pathological cell imbalance.

Ibutamoren has the potential to prevent disease progression in NAFLD/NASH through additional anti-inflammatory effects via GHSR1a activation in immune cells.[12-14] Ghrelin and the GHSR1a receptor are expressed in human T cells and monocytes, and ghrelin activates the GHSR1a in these cells to reduce inflammatory cytokines such as IL-6 and TNF-α.[12] Additionally, RNA interference-mediated reduction in ghrelin production in human T cells was shown to increase production of pathological inflammatory cytokines.[15] The anti-inflammatory effects of ghrelin and ghrelin mimetics like ibutamoren have been demonstrated in animal models of acute[16-18] and chronic[19-24] inflammation and small human studies of chronic[23,25] and post-operative inflammatory conditions.[25] Ghrelin has also been shown to reduce inflammation with

chronic high-fat feeding.[26, 27] Ghrelin reduced inflammation, oxidative stress and apoptosis in a mouse model of NAFLD, with activation of AMPK and PI3K/Akt pathways as proposed mechanisms that have been implicated in NAFLD/NASH.[27] Finally, ghrelin administration not only reduced inflammatory markers but also hepatic triglycerides in a mouse model of high fat feeding, suggesting multiple beneficial effects of GHSR1a activation.

A3. IBUTAMOREN AUGMENTS GH RELEASE, WHICH HAS IMMUNE AND LIPOLYTIC EFFECTS:

Ibutamoren also regulates T cell populations indirectly through downstream effects of GH augmentation. Ibutamoren is also a potent GH secretagogue, and GH is an important regulator of Th17 and regulatory T cells. Transgenic overexpression of GH reduces pathogenic TH17 responses in animal models of rheumatoid arthritis[6] and type 1 diabetes,[7] delaying disease onset and severity. Thus, ibutamoren, indirectly via GH, has an additional mechanism for amelioration of the pathological Th17 response characteristic of NASH.[8, 9]

GH is also an anti-inflammatory cytokine[28] and an important mediator of inflammation, and ibutamoren may have additional indirect anti-inflammatory effects through GH augmentation. The GH receptor is a member of the cytokine receptor family, and GH has cytokine-like effects. GH administration decreases hsCRP, a marker of systemic inflammation, and other cytokine levels, including IL-6 and TNF-α, in patients with GH deficiency due to both pituitary disorders and obesity.[5, 29-31] This may have critical implications for the progression of simple steatosis to NASH, as inflammation is a hallmark of disease progression. TNF-α, IL-6 and hsCRP have been implicated in the inflammatory milieu causing this progression to NASH,[32] and inflammation on initial histology has been associated with a 2.5-fold risk of advanced fibrosis.[33]

GH is a critical stimulator of lipolysis,[4] and preclinical data suggest that GH axis augmentation has the potential to reduce hepatic steatosis and prevent progression of NAFLD. GH signals via the JAK2/STAT5 pathway in hepatocytes.[34] Multiple mouse models have demonstrated that hepatocyte-specific knockouts of the GH receptor, JAK2 or STAT5 result in a NAFLD phenotype.[35-38] These models demonstrate that loss of GH receptor/JAK2/STAT5 signaling leads to an increase in PPAR-gamma, which drives the NAFLD phenotype through increased hepatic lipid uptake (via increasing CD36, a fatty acid transporter) and upregulation of *de novo* lipogenesis.[38, 39] These data suggest that GH suppresses hepatic lipid uptake and *de novo* lipogenesis in the normal state, and that GH axis augmentation could be a potential therapeutic target in NAFLD.

A4. OBESITY IS A STATE OF RELATIVE GH-DEFICIENCY AND POTENTIAL THERAPEUTIC TARGET IN NAFLD:

In obesity, pulsatile GH production is reduced by 75%, primarily due to reduced GH pulse amplitude, and visceral adiposity is a strong negative determinant of GH secretion.[40, 41] In the normal state, hypothalamic growth hormone releasing hormone (GHRH) stimulates the pulsatile release of GH by the pituitary gland, leading to hepatic production of insulin-like growth factor-1 (IGF-1). Clinical GH replacement is delivered via daily injection, while GH secretagogues like ibutamoren restore the endogenous pulsatility and feedback loops, restoring the GH/IGF-1 axis in a more physiologic manner.

Administration of GH to patients with severe GH deficiency due to hypopituitarism improves NAFLD, consistent with an etiopathologic role of GH deficiency. Studies of hypopituitary patients with profound GH deficiency have demonstrated a higher rate of NAFLD compared to sex, age- and BMI-matched controls (77% versus 12%, respectively, $p<0.001$), in a group where the mean BMI was just above normal (25±4.9 kg/m^2). Additionally, administration of physiologic GH replacement decreased ALT, AST, hsCRP and markers of fibrosis in a group of hypopituitary individuals with GH deficiency, more than half of whom had NAFLD. Histologic steatosis score and fibrosis stage improved in a subset (n=5) with pre- and post-GH biopsies.[42]

Studies of otherwise healthy, overweight and obese individuals *without pituitary disorders* also implicate relative GH deficiency in the pathophysiology of NAFLD/NASH, and preliminary clinical data suggest that restoration of the GH axis in the obesity. In the cross-sectional Aim of the K23 study, I demonstrated that overweight and obese subjects with NAFLD have lower peak stimulated compared to non-NAFLD controls of similar age, BMI and sex. Additionally, lower peak stimulated GH was associated with higher intrahepatic lipid content (IHL) by proton magnetic resonance spectroscopy (1H-MRS), independent of age, BMI, sex and visceral adipose tissue (data in preparation for publication).

Preliminary clinical data suggest that restoration of the GH axis in obesity is a potential therapeutic strategy in NAFLD. Our group demonstrated that once daily GH administration by subcutaneous injection with an increase in IGF-1 levels to the upper-normal range reduced IHL by 1H-MRS in overweight/obese individuals unselected for NAFLD.[29] Of importance, only a subset of study subjects would have qualified as having NAFLD. Despite this, we detected a decrease in IHL. These pilot data are exciting with regard to the potential for GH augmentation as an effective therapeutic strategy in NAFLD. **However, studies demonstrate that GH pulsatility may be particularly important for effective lipolysis,*[43]* and that a more continuous (versus pulsatile) administration of GH may downregulate GH signaling pathways.*[44]*** *Thus importantly, in contrast to once daily GH administration, restoration of endogenous GH pulsatility via a GH secretagogue like ibutamoren may enhance the lipolytic effects of GH[43, 44] while preserving endogenous feedback loops, enhancing both efficacy and safety profiles.*

[redacted]

[redacted]

[redacted]

A6. SCIENTIFIC PREMISE AND HYPOTHESIS:

The proposed intervention, ibutamoren, is an orally administered, long-acting ghrelin mimetic that has direct immune effects that target specific areas of known immune dysregulation in NAFLD/NASH, physiologically restores endogenous GH pulse amplitude, and has a strong safety profile with prior administration in over 1,200 individuals (adults and children).[45-53] ***Our overarching hypothesis is that oral ibutamoren administration will improve steatosis, inflammation and fibrosis in subjects with overweight/obesity and NASH.*** [redacted]

[redacted]

2. Specific Aims and Objectives

A. **SPECIFIC AIM 1:** We hypothesize that GH augmentation by oral ibutamoren for 6 months in subjects NAFLD compared to an historically studied placebo group subjects for 6 months will:

Aim 1A: Decrease hepatic steatosis, as measured by 1H-MRS **(primary endpoint)**

Aim 1B: Decrease hepatic inflammation and fibrosis, as measured by [redacted] **(primary endpoint)**

[redacted]

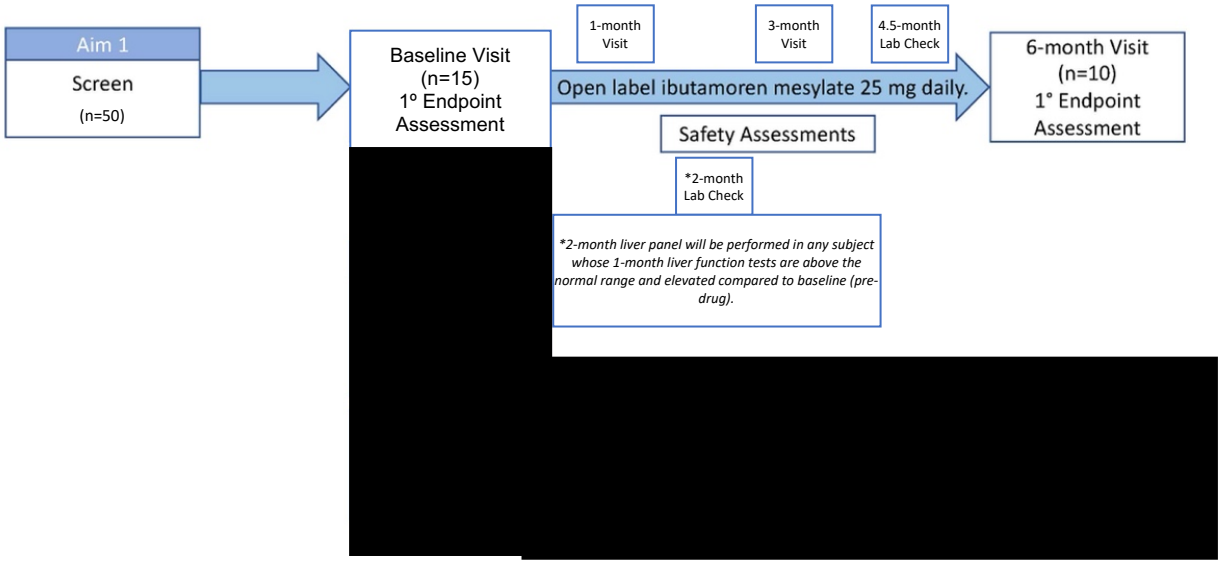
3. General Description of Study Design

Overview of Study Design (Figure 1, Table 1)

An overview of the study design is provided in Figure 1. Aim 1 examines the effect of Ibutamoren mesylate administration on intrahepatic lipid accumulation in 10 men and women with NAFLD and relative IGF-1 deficiency. [redacted]

This study also investigates potential mediators of GH-induced decrease in intrahepatic lipid accumulation, including insulin/glucose and lipids, as well as body composition parameters. Ibutamoren will be dosed at 25 mg daily after completion of all baseline tests.

Figure 1 Study Design: 6-month, open-label administration of ibutamoren mesylate 25 mg daily in subjects with NAFLD.



Aim 1A investigates the 6-month change in intrahepatic lipid content by 1H-MRS *(primary endpoint)* and **AIM 1B** investigates the 6-month change in hepatic inflammation and fibrosis [redacted] *(primary endpoint)* with GH augmentation by ibutamoren versus historical placebo-treated controls studied under identical procedures. Additional endpoints include change in NAFLD Fibrosis score and body composition by DXA.

[redacted]

Participants from the Protocol [redacted] will be used to formulate a control group for analysis.

4. Subject Selection

III. SUBJECT SELECTION

A. Inclusion/Exclusion Criteria

- **Aim 1:** Subjects: N=15 (goal of 10 completers) with NAFLD/NASH.
  - **Inclusion Criteria:**
    - Age 21-60yo and generally healthy
    - BMI≥25 kg/m^2
      - *BMI≥23 kg/m^2 for subjects whose background is South Asian, Chinese, Middle Eastern, Black African, or African-Caribbean.*

- Radiographic or histologic diagnosis of NAFLD / NASH
- IGF-1 level <3rd quartile of normal for age.

- **Exclusion Criteria:**
  1. Contraindications to MRI imaging (primary endpoint)
  2. Diabetes mellitus, defined as fasting glucose ≥ 126 mg/dL or hemoglobin A1C ≥6.5 or use of any medications prescribed to treat hyperglycemia is exclusionary for Aim 1.
     a. Subjects whose fasting glucose result at the screen visit is ≥ 126 mg/dL and who do not have a prior history of diabetes mellitus will be offered an optional retest with inclusion if subsequent repeat fasting glucose is < 126 mg/dL. Subjects with repeat glucose ≥ 126 mg/dL will be excluded from the study.
  3. History of cancer/malignancy of any organ system other than previously fully resected basal cell carcinoma of the skin
  4. Significant renal disease.
  5. Unwilling or unable to perform age- and sex-appropriate cancer screening such as mammogram, PAP and/or colonoscopy
  6. Decompensated or unstable cardiovascular disease (for example, heart failure, unstable coronary disease, uncontrolled arrhythmias) at the discretion of the study physician
  7. Active carpal tunnel syndrome
  8. Significant alcohol use, defined as >2 drinks/day (14/week) in women or >3 drinks/day (or 21/week) in men
  9. Aspartate or aminotransferase levels >300 U/L, suggesting liver disease other than NAFLD/NASH.
  10. Other known liver disease, for example, autoimmune or viral hepatitis, hemochromatosis or alcoholic fatty liver disease.
  11. Evidence of hepatobiliary and hepatic impairment such as:
      a. INR >1.3
      b. TB >1.5 mg/dL (with exception of Gilbert's with elevation of indirect bilirubin in the presence of direct bilirubin of < 0.4 mg/dL)
      c. Albumin <3.5 g/dL
      d. Platelet count <150,000 /uL
      e. Historical or screening biopsy consistent with cirrhosis
      f. Imaging suggestive of cirrhosis (e.g., splenomegaly, varices, nodular appearance of liver, radiographic evidence of ascites)
      g. History of clinical events of liver decompensation such as variceal bleeding, presence of ascites, etc.
  12. Pregnancy or breastfeeding.
  13. Known pituitary or hypothalamic disease affecting the growth hormone axis
  14. Regular use of drugs causing hepatic steatosis in the past 12 months (chronic oral steroids, methotrexate, tamoxifen)
  15. Use of medications that may impact study endpoints, such as pioglitazone or Vitamin E.
  16. Treatment with medications without acceptable alternative that may interact with ibutamoren, including:
      a. Moderate or strong inhibitors of CYP3A/4.

b. Moderate or strong inducers of CYP3A4.
c. Medications known to act as strong inhibitors of P-glycoprotein (P-gp).

17. Unsuitable for study per investigator discretion
18. Known HIV Diagnosis

[redacted]

B. Source of Subjects and Recruitment Methods

Recruitment will be performed by study personnel, including research coordinators, nurse practitioners and physician staff. To maximize enrollment of subjects, subjects will be recruited from a large population of patients with NAFLD through the following locations and the following resources:

1) Prior participants with overweight/obesity who have participated in Neuroendocrine Unit research studies [redacted]
2) MGH Fatty Liver and GI Clinics [redacted]
3) MGH NAFLD Cohort [redacted]
4) [redacted] Research Patient Data Registry (RPDR) [redacted]

[redacted]

5. Subject Enrollment

A. Enrollment

Subjects responding to the initial recruitment advertisements will undergo initial prescreening by phone, and if potentially eligible for participation, will be invited to participate in screening visits to determine study eligibility**.** For **Specific Aim 1 (main study)**, we expect to screen 50 radiographically-proven NAFLD subjects and enroll 12 NAFLD subjects, 6 women and 6 men, with NAFLD, in order to obtain 10 completers. [redacted]

B. Consent

All subjects will receive the written consent form or virtual eConsent form via MGB-approved eConsent platform (REDCap) for the study as well as the Human Subject's Bill of Rights. These documents will be read by the study subjects and also reviewed by the study subject with a

clinician or licensed nurse practitioner prior to participating in the study. Any questions, concerns, or ambiguities will be clarified by a licensed physician investigator or licensed nurse practitioner prior to the patient signing consent. Potential study subjects will sign informed consent and only then will begin participation in the study. If new information is ascertained during the study, we will modify our consent and re-consent our patients. [redacted]

C. Study Drug Start
Aim 1 participants who qualify and are enrolled in this study will start the medication after baseline testing is complete (as described below). This is an open-label pilot study.

6. STUDY PROCEDURES

Table 1. Aim 1 Schedule of Procedures

Open label ibutamoren mesylate (oral 25 mg daily) with be administered to 12 subjects (goal 10 completers) with comparison to identically-studied, historical placebo-group controls.

Visit Components	Screen	Baseline	1 month	2 month lab check	3 month	4.5 lab check	6 month
COVID-19 Screening Phone Call	x	x	x	x	x	x	x
Liver Ultrasound	x						
NAFLD Fibrosis Score		x					x
DXA		x					x
MRI/MRS		x					x
Waist-Hip Ratio		x					x
Endocrine/Misc. Labs							
Blood: TSH	x						
Blood: HCV Antibody	x						
Blood: HBV Surface AG	x						
Peripheral Blood Mononuclear Cells (PBMCs)		x					x
Ibutamoren Stimulation Test		x					
Blood: Insulin, lipids		x					x
Safety Evaluation							
Physical Exam***	x	x	x		x		x
Blood: INR	x						
Blood: Creatinine	x						
Bood: CBC	x						x
Blood: Liver function tests	x	x	x	x	x	x	x
Blood: Fasting Glucose	x	x	x		x		x
Blood: HbA1c	x				x		x
Blood: IGF-1	x		x		x		x
Urine pregnancy test	x	x	x		x		x

*** *Optional, limited physical exam will be performed at the discretion of the study provide*

A. Study Visits for Specific Aim 1:

1. **Screening Visit :** (n=50, approximately 50% women)
   After informed consent, subjects will be evaluated for eligibility with:
   - A basic metabolic panel, INR, CBC, TSH, fasting glucose, hemoglobin A1c (HbA1c), hepatic function panel, and IGF-1 will be performed.
   - Records of cancer screenings appropriate for the age and gender of the participant will also be requested.
   - Height and weight will be measured, and BMI will be calculated.
   - A history and physical will be performed.
   - A pregnancy test will be performed in all premenopausal women with childbearing potential.
   - A liver US or liver ultrasound elastography [redacted] will be performed in study subjects who do not have a known diagnosis of NAFLD.
     - Due to limited ultrasound sensitivity for screening for fatty liver, subjects will be invited to a screening MRI for assessment of NAFLD if the subject otherwise qualifies for the study but has a negative screen ultrasound for NAFLD.
   - Individuals will be queried regarding alcohol use as well as for history of other chronic liver disease.
   - Hepatitis C antibody and Hepatitis B surface antigen tests will be performed in study subjects who have not had this as a part of their clinical care.
   - Serum and plasma samples will be drawn and stored frozen for future testing.

Remote Blood Draws for Screening [redacted]*:* to allow maximum flexibility with our subject's schedules, the blood tests listed above can be drawn at [redacted] facility close to the subject's home location. Screen aliquots will not be obtained during a remote blood draw.

2. Baseline and 6-month visit: (n=15 at baseline, n=10 completers: approximately 50% women)
   The baseline visit will occur within 12 weeks after the screening visit. The following assessments will be made during the baseline visit, which will occur within a 30-day period and can occur in one session or over multiple days depending on schedules and patient preference. The 6-month visit will be performed during a +/- 3 week interval around the indicated return time to allow for potential scheduling conflicts. The order of the tests may vary depending on the subject and TCRC availability.
   - Interview to determine whether any changes in medical history since the screening visit has occurred
   - BMI, waist-hip-ratio measured
   - In the fasting state, a blood sample will be obtained to determine glucose, insulin, GH, IGF-1 (6 mo only), CBC (6 mo only), HbA1c (6 mo only), lipids, triglycerides, and liver function tests. Note: Pre-treatment HbA1c, IGF-1, CBC will have already been performed at the screening visit and are not repeated at baseline.
   - Fasting glucose will be performed at baseline and 6-month visits. Aliquots for insulin measurements will be taken at these time points as well.
   - A fasting GH-stimulation test will be performed at the baseline visit only using ibutamoren 25 mg oral dose with GH levels measured at 0, 30, 60, and 90 and

120 minutes. All hormones will be measured using gold standard techniques (including IGF-1 by LC/MS).
- Serum and plasma samples will be drawn and stored frozen for future testing.
- [redacted]
- MRI: 1H-MRS of the right hepatic lobe will be performed at the baseline and 6-month visits to quantify hepatic lipid content and other fat depots[redacted] sequences will also be performed for noninvasive analysis of hepatic iron content, inflammation and fibrosis. Sequences will also be performed to assess pancreatic fat, inflammation and fibrosis as well as renal inflammation and fibrosis. The entire protocol will be scheduled for one 45 minute MRI slot.
    - A baseline MRI will be acquired if the screen MRI occurred more than 6 weeks prior to baseline procedures. Otherwise, the MRI procedure at baseline is not required.
- Dual-energy x-ray absorptiometry (DXA) scan will be performed at the baseline and 6-month visits to determine body composition.

3. **Drug Start:** Ibutamoren will be started at a dose of 25 mg orally daily, starting after baseline procedures are complete. All subjects receive drug in this open label study.

4. 1-month follow up visit: (n=15, approximately 50% women): These visits will be performed between 3-6 weeks to allow for potential scheduling conflicts.
    - Study subjects will be assessed for interim medical history and side effects to study drug. An optional physical exam will be performed as indicated per the discretion of the study clinician.
    - IGF-1 will be measured as a safety lab
    - Pregnancy tests will be checked for all premenopausal women [redacted]
    - Fasting glucose and liver function tests will be measured as safety labs
    - If the visit is on-campus (MGH), serum and plasma samples will be drawn and stored frozen for future testing.

5. 2-month lab draw: If 1 month transaminases (ALT or AST) are above the normal range and elevated compared to the baseline values, a 2-month (+/- 2 week interval) liver function panel will be measured. This blood draw can be performed remotely at [redacted] location or at MGH at the preference of the subject.

6. 3-month follow-up visit: (n=15, approximately 50% women)

These visits will be performed during a +/- 2 week interval around the indicated return time to allow for potential scheduling conflicts.
- Study subjects will be assessed for interim medical history and side effects to study drug. An optional physical exam will be performed as indicated per the discretion of the study clinician.
- IGF-1 will be measured as a safety lab at all follow-up visits
- Pregnancy tests will be checked for all premenopausal women
- Fasting glucose, HbA1c and liver function tests will be measured as safety labs
- If the visit is on-campus (MGH), serum and plasma samples will be drawn and stored frozen for future testing.

Either the 1-month or 3-month visit may be performed remotely per the discretion of the

study investigator; at least one of these visits will be performed in person. [redacted]

7. 4.5-month lab draw:
   [redacted]A 4.5-month (+/- 2 week interval) fasting glucose and liver function tests will be measured as safety labs. [redacted]

Dosing for Aim 1: Ibutamoren mesylate will be dosed at 25 mg daily. Dosing may be reduced to 18 mg daily for an IGF-1 level above the normal range or GH-related side effects, but this is not expected based on prior studies of ibutamoren. Ibutamoren can be taken with or without food.

1 Month Post-Study Follow Up Call:
A study provider will attempt to contact subjects four weeks after study completion to document subject status at that time, which will be approximately one month after study drug discontinuation. Any remaining study results will be reviewed with the subject at that time.

REMOTE CONSENT AND VISIT PROCEDURES:
Virtual Consent and Screen Medical History:
In order to minimize potential COVID-19 exposures for study staff and subjects, consent and partial screening procedures may be performed virtually (via phone or MGB approved video platform) prior to an in-person portion of the visit. We will follow all MGB eConsent procedures. After consent via an MGB approved e-consent platform (via REDCap), the study provider will perform the screen medical history. The subject will also be instructed on how to fill out screen-related forms electronically. The subject will be told immediately via phone if the provider determines by history alone that they would be ineligible for the study. If the subject otherwise appears to be eligible based on history, they will be invited for an in-person portion of the screen visit that includes the limited physical exam, vital signs, blood draw and ultrasound or liver ultrasound elastography [redacted] as needed for diagnosis of NAFLD. [redacted]

[redacted]

[redacted]

Payment for Study Procedures

[redacted]

We will provide parking at MGH garages free of charge and will additionally reimburse [redacted] for travel to/from MGH for each visit.

ADDITIONAL REIMBURSEMENT: Subjects will be reimbursed [redacted] each additional blood draw related to glucose monitoring procedures or study discontinuation.

Communication Via Text Messages (SMS)
Following MGB policy regarding text messages, if subjects agreed to be contacted via text

messaging, study staff will send text reminders to notify and/or remind subjects of their upcoming visits.

C. DEVICES AND PROCEDURES

MR Spectroscopy: We will perform proton MR spectroscopy (1H-MRS) of the right hepatic lobe to determine intrahepatic lipids (IHL) using a 3Tesla MRI device (Siemens Vida, Siemens Medical Systems, Erlangen, Germany) as we have previously described. [56] Advantages of higher magnetic field strength are an increase in signal-to-noise ratio resulting in improved spatial resolution and increased chemical shift dispersion, potentially improving assessment of other fat resonances. Subjects will be positioned head-first in the magnet bore. A body matrix phased array coil will be positioned over the abdomen. A voxel measuring 20×20×20 mm (8 mL) will be placed within the right and then left lobe of the liver, avoiding vessels or artifact. Breath-hold single-voxel 1H-MRS data will be acquired using PRESS pulse sequence without water suppression. Liver lipid estimates will be automatically scaled to unsuppressed water peak (4.7 ppm) and expressed as lipid to water ratio. This ratio will be converted to percent fat using validated equations.[57] Measurement of IHL by 1H-MRS is recommended as a trial endpoint by the American Association for the Study of Liver Diseases (AASLD).[58]

[redacted] Transient elastography [redacted] a rapid non-invasive technique that measures liver stiffness by the transmission of mild amplitude and low frequency (50Hz) through the intercostal space using a vibrator at the skin surface. The vibration induces a shear wave velocity through the hepatic tissue, which is directly related to tissue stiffness and is expressed in kilopascals (kPa). Transient Elastography is an inexpensive, reproducible, painless, rapid (<10 minutes), and easy-to-perform tool. It has been proven in many studies to correlate well with the degree or severity of fibrosis and or cirrhosis. It has sensitivity and specificity of greater than 95% for predicting cirrhosis with liver stiffness value of 14.1kPa. It is an ideal tool not only for assessing the degree of fibrosis/cirrhosis but can also be used to monitor disease progression and treatment efficacy. If the traditional liver ultrasound machine is unavailable, the [redacted] will be performed at the screening visit to diagnose NAFLD using the controlled attenuation parameter (CAP).

[redacted]

[redacted]

[redacted]

[redacted]

Dual-energy X-ray-absorptiometry (DXA): Each subject will undergo a DXA scan at baseline and 6 month. DXA will be completed using Hologic QDR-Horizon A, Holigic Inc. Marlborough, MA.

Dynamic Endocrine testing: A fasting GH-stimulation test will be performed using ibutamoren 25 mg oral dose with GH levels measured at 0, 30, 60 and 90 and 120 minutes. All hormones will be measured using gold standard techniques (including IGF-1 by LC/MS). [redacted]

Other laboratory testing:
Liver function tests: A standard liver function test panel consisting of ALT, AST, GGT, alkaline phosphatase, total bilirubin, direct bilirubin, indirect bilirubin, ferritin and albumin will be measured using a standard clinical platform. *Lipids and Lipoproteins:* A fasting lipid profile, including total cholesterol, LDL, HDL and triglycerides, will be measured via clinical platforms. [redacted]

Liver Fibrosis Assessment:
The NAFLD fibrosis score: This score predicts the probability of fibrosis in patients with NAFLD using a score that uses the patient's age, body mass index, blood glucose levels, aminotransferase levels, platelet count, and albumin. A high NAFLD fibrosis score of >0.676 is associated with a probability of advanced fibrosis (F3-F4) of 82 percent (sensitivity 43 percent, specificity 96 percent), and a score of <-1.455 is associated with a negative predictive value of 88 percent (sensitivity 77 percent, specificity 71 percent) based on prior studies. [59, 60]

[redacted]

7. Risks and Discomforts

A. Risks to the Subjects

Human Subjects Involvement and Characteristics: This study will enroll a total of 50 (50 for Aim 1, and 10 Aim 1 participants for Aim 2) obese, otherwise healthy, individuals ages 21 to 60 (approximately 50% women). Subjects must be healthy, with no history of cardiovascular disease, renal impairment, diabetes or malignancy. Rationale for exclusions is discussed in the study protocol; in brief, these exclusions are designed to 1) exclude men and women at greatest risk for significant adverse events and 2) avoid confounding effects of medical conditions and medications. We exclude children and young adults through age 20 because GH administration in children prior to growth plate fusion causes linear growth, and GH administration could cause an increase in height.

Dose Rationale: The ibutamoren mesylate 25 mg oral daily dosing was selected due to evidence for both effective augmentation and safety in the adult target population. The proposed dose of 25 mg oral ibutamoren daily effectively augments IGF-1 levels by approximately 40-84%, which is within the range of normal.[53, 56] Fixed dose ibutamoren mesylate at 25 mg daily has been shown to augment IGF-1 levels by 40% in healthy obese men[56], which is comparable to or slightly below the 50% increase in IGF-1 levels we achieved (targeting upper-normal IGF-1 levels) with daily, subcutaneous GH administration at 6 weeks in a similar population.[29] Additionally, this is within the range of IGF-1 augmentation seen in patients with HIV-associated

NAFLD with the subcutaneously administered GHRH analogue tesamorelin, which augmented IGF-1 by approximately 59% with a net treatment effect of a 2.9% decrease in liver fat.[57] There is additional direct evidence with ibutamoren that this GH augmentation leads to effective GH-related augmentation of metabolism and body composition. This includes studies of the 25 mg dose of ibutamoren mesylate that have demonstrated an increase in fat free mass in healthy, older adults (ages 60-81 years) at 12 months[46] and a transient increase in basal metabolic rate and an increase in fat free mass in healthy adults with obesity at 2 months.[56] These investigations are promising regarding safe and effective GH-augmentation by 25 mg daily ibutamoren mesylate and impacts on fat-free mass, and we now propose to study the impact of this dose of ibutamoren on hepatic steatosis, inflammation and fibrosis, endpoints which were not assessed in prior trials of ibutamoren mesylate at this dose.

[redacted]

[redacted]

[redacted]

Risks of each aim are outlined below.

Potential Risks of Aim 1:

[redacted] ***The FDA's confidence in the safety of ibutamoren (LUM-201) stems from a very large non-clinical safety package that provides a large safety window at doses proposed for the pediatric study (including full acute, chronic, juvenile,***

developmental and reproductive, and carcinogenicity toxicology studies) and a large clinical safety database (approximately 1000 adults for up to 2 years of treatment at the proposed dose of 25 mg daily and approximately 150 children for up to one year at 0.8 mg/kg/day).

Human Subjects Involvement and Characteristics of the Current Proposal:
Aim 1: This is an open-label study of ibutamoren in otherwise healthy adults with BMI ≥25 kg/m^2 (*BMI≥23 kg/m^2 for subjects whose background is South Asian, Chinese, Middle Eastern, Black African, or African-Caribbean)* with NAFLD. We will enroll 15 individuals ages 21 to 60 (approximately 50% women) for a goal of at least 10 completers. The following exclusion criteria are designed to ***1) exclude subjects at greatest risk for any adverse events*** and ***2) preserve data integrity and avoid confounding effects of medical conditions, medications and/or active weight loss.*** We exclude children in this proposal as GH augmentation in children causes linear growth, and dedicated Phase 2b trials of ibutamoren for pediatric GH deficiency will be initiated shortly.

Subjects must be age 21-60 years old and meet all inclusion/exclusion criteria as outlined above to ensure that subjects are generally healthy. Select notable exclusion criteria are reviewed below in relation to the current study:

- Current or prior history of malignancy
- AST or ALT elevations >300 U/L that is beyond what is expected in NASH
- Cirrhosis (compensated or decompensated), given that this is a more ill population and less appropriate for the current study.
- Known cardiovascular disease or heart failure. Just as with our prior trials of GH administration, this is an exclusion criterion for the proposed trial, as growth hormone (given directly or released through a secretagogue like ibutamoren) could cause edema and worsen congestive heart failure (CHF).
- Diabetes: Subjects may have prediabetes, but the following are exclusionary:
    (1) A clinical history of diabetes mellitus
    (2) Current drug treatment for diabetes mellitus
    (3) Screen A1C ≥ 6.5%
    (4) Screen fasting glucose ≥126mg/dL on two separate, consecutive screening measurements
- Although GH administration itself can cause insulin resistance and reversible glucose elevations in a minority of patients, ibutamoren's action as a GH secretagogue prevents hyperstimulation of the hypothalamic-pituitary axis by maintaining rather than overriding physiological feedback control within the GH/IGF-1 axis, and clinically significant deteriorations in glucose homeostasis with augmentation of GH pulsatility by ibutamoren have not been reported (see section below on *Monitoring Glucose Homeostasis*).
- Women who are pregnant, actively seeking pregnancy or breastfeeding. Pregnancy tests will be performed in women of childbearing potential at each visit and use of contraception will be reviewed for both men and women through one month after study end.
- Subjects may be excluded for other active medical conditions at the discretion of the evaluating study physician to ensure a generally healthy study population.

[redacted]

The following exclusion criteria are to additionally ensure an appropriate study population and data integrity:

- Other known liver disease (beyond NAFLD/NASH)
- Significant alcoholic use, due to the possibility of alcoholic fatty liver disease
- Medications known to cause NAFLD, including chronic oral steroids, tamoxifen or methotrexate
- Weight instability prior to study entry
- Routine MRI exclusion criteria, as this would preclude measurement of primary endpoints
- Presence of pituitary disorders affecting the GH axis, as these individuals may not respond to a GH secretagogue.

[redacted]

Potential Risks of Aim 1:

Administration of Ibutamoren:

[redacted]

Oral ibutamoren has been studied in pediatric GH deficiency,[45] healthy aging populations (60-81 years old),[46] hip fracture recovery,[47, 48] osteoporosis,[49] Alzheimer's disease,[50] adult hemodialysis patients,[51] and obesity.[52, 53] In all of these populations, ibutamoren mesylate showed sustained increases in circulating GH and IGF-1. Specifically, 25 mg oral ibutamoren daily effectively augments IGF-1 levels by approximately 40-84%, within the range of normal.[52, 53] This is the proposed dose in the current study and the dose used in the longest study of ibutamoren administration (2 years).[46] **Importantly, no serious adverse events related to ibutamoren mesylate have been reported to date in the proposed population (adults, ages 21-60 years).**[53]

GH secretagogues such as ibutamoren preserve physiologic GH/IGF-1 axis feedback mechanisms. As an oral growth hormone secretagogue–receptor agonist, ibutamoren mesylate acts on GHSR1a receptors on the anterior pituitary and hypothalamus and restores the amplitude of the physiologic pulsatility of endogenous GH that is specifically lost in obesity. **This mechanism of GH augmentation by ibutamoren has inherent feedback mechanisms, preventing hyperstimulation of the GH/IGF-1 axis and associated safety concerns.** This is

in contrast to daily, subcutaneous GH administration, where a single daily, supraphysiologic pulse of GH is administered with dosing titrated to IGF-1 levels. *Fixed dose ibutamoren mesylate (25 mg orally daily) has been shown to augment IGF-1 levels by 40% in healthy obese men,[52] which is comparable to or slightly below the 50% increase in IGF-1 levels we achieved (targeting upper-normal IGF-1 levels) with daily, subcutaneous GH administration at 6 weeks in a similar population.[29]* Because IGF-1 levels (an integrated measure of GH secretion) will be raised to within the normal range appropriate for age and sex,[46, 52] we expect the risks of ibutamoren mesylate administration to be minimal.

Additionally, IGF-1 levels will be monitored pre-treatment and at 1 month, 3 months and 6 months on treatment. Significant elevations of IGF-1 above the normal range for age (Z score >2.5) will prompt either a 30% dose reduction (18 mg daily) or discontinuation from the study. *This is not expected based on prior data or drug mechanism, given that ibutamoren's action as a GH secretagogue preserves physiologic GH/IGF-1 axis feedback mechanisms*. Moreover, hypopituitarism is associated with an increased mortality risk, which has been attributed to GH deficiency as one of the causes.[62] GH augmentation (by direct, subcutaneous GH injection) improves cardiovascular risk markers in such patients; moreover studies show that GH replacement may reduce the increased mortality conferred by hypopituitarism.[62-64]

Routine cancer screening will be required prior to study entry to ensure a healthy, low-risk study population. Because GH is a growth promoting agent, there is the theoretical risk that GH or a GH secretagogue could promote tumor growth. [redacted] Moreover, subcutaneous GH is not associated with an increase in malignancy even is administered for years.[62-64] To protect against risk in this protocol, all subjects will be required to be up-to-date with age- and sex-specific cancer screening guidelines before inclusion into the study, similar to protocols involving GH administration.

Subjects with known congestive heart failure (CHF) will be excluded to minimize risk. The only group of study subjects in whom possibly related serious adverse events occurred with ibutamoren administration was for that of elderly subjects after hip fracture, where a higher incidence of congestive heart failure (CHF) was found in the ibutamoren (n=4) versus placebo (n=2) groups (n=123 randomized).[47] However, heart failure only occurred in subjects over 80 years old, and 3 of 4 of ibutamoren-treated subjects who developed CHF had a pre-existing diagnosis of heart failure. Heart failure has not been reported in any patient less than 80 years of age on ibutamoren. Mild fluid retention is a known potential side effect of GH itself, offering a potential mechanism for these events in a predisposed, elderly population, most of whom had preexisting heart failure. [redacted]

Ibutamoren has been shown to increase fat-free mass. Ibutamoren is a long-acting ghrelin receptor (GHSR1a) agonist, however, it is critically important to recognize that its effects in vivo are markedly different from ghrelin, largely due to the differences in pharmacokinetic properties.

Ghrelin is highly unstable with a half-life in humans of about 5–10 minutes, whereas the half-life of ibutamoren is 8 hours.[48] In contrast to short-acting ghrelin that has been associated with increased adiposity in mouse models, long-acting ibutamoren is not associated with an increase in abdominal fat. Changes in body composition and energy expenditure were anabolic in obese subjects, with an increase in fat-free mass and no change in visceral or subcutaneous adipose tissue depots over the 8 weeks.[52] Similarly, in 2-year, double-blind, randomized, placebo-controlled clinical trial of healthy older adults (ages 60-81 years), ibutamoren produced a sustained enhancement of GH pulsatility and IGF-1 and resulted in an increase of fat-free mass with no significant differences in abdominal visceral fat or total fat mass.[46] Daily, subcutaneous GH administration is generally weight-neutral, with the following body composition changes consistently observed: decrease in fat mass (including liver fat and abdominal fat, including visceral fat), increase in fat-free mass (including skeletal muscle) and an increase in total body water. In addition to measuring effects of ibutamoren on liver fat, we will measure effects on other fat depots, skeletal muscle, fat-free mass and total body water. Overall, we anticipate that ibutamoren may have beneficial effects on body composition (included as secondary endpoints) in the proposed population, and weight will be monitored at every study visit.

[redacted]

Summary of Drug Interaction Procedures: Subjects will be informed during the consent process that there is a potential for drug interactions with ibutamoren. They will be instructed to contact study staff before starting any prescription and/or over-the-counter medications or supplements. They will also be instructed to tell their doctor and any physician caring for them in the event of hospitalization that they are taking a study medication with a potential for drug interactions. Concomitant medications will be reviewed at every study visit with the subject. Any newly started medications will be brought to the attention of the PI for review. Concomitant medications will also be reviewed regularly with the PI at scheduled safety meetings. Study participants will be given a letter they should share with their primary physician to inform them of study participation and concomitant medication restrictions. Subjects will also be informed to contact the study staff between study visits to discuss any new potential medications. The study team has compiled a list of drugs that qualify under the above interactions and will continue to review all medications as the study proceeds.

Radiation exposure: A portion of this research study involves exposure to radiation from up to two DXA scans. Scans will be performed at the baseline visit and six month visit in Aim 1.

[redacted]

MRI/ MR spectroscopy: MRI and MR spectroscopy will be performed using FDA approved devices and pulse sequences. There are no known foreseeable risks associated with exposure to MRI, provided there are no metallic implants (i.e., vascular clamps or pacemakers). All potential subjects will be screened for the presence of such prior to the exam. A standard MRI questionnaire will be administered to all potential study subjects, and no study subject with a contraindication to MR testing will be admitted to the study. Some subjects report some claustrophobia during MRI scans. If a patient expresses any discomfort during the scan, the procedure will be aborted and not repeated without his/her full consent.

General Considerations: IV placement and blood sampling is performed in the study, and there is a minor risk of infection, bruising, or syncope during a blood draw. There is also potential discomfort of having an IV placed and having blood drawn. Lightheadedness is a possible side effect from overnight fasting. The blood draws will be performed by trained staff who have certificates documenting their ability to draw blood.

[redacted]

[redacted]

B. Protection Against Risk

In addition to the formal safety monitoring plan described, below, the procedures to protect against or minimize potential risks include the following: (1) the assignment of unique study subject numbers to patients, (2) the use of these primary identifiers throughout the study, (3) storage of information in locked file cabinets, and (4) access limited to study personnel for these file cabinets and data. The blood draws will be performed by trained staff who are certified to draw blood. We are performing a physical examination and routine laboratory tests prior to allowing anyone to enter the protocol to ensure that subjects are medically stable. Close monitoring of patients throughout the study will ensure that adverse effects from our

interventions. All study subjects will be instructed on how to contact study clinicians in the case of an emergency.

8. Benefits

There is no expected benefit to participation in this study. If a subject receives ibutamoren in this protocol, it is possible that their amount of liver fat may decrease during the study. However, those effects are not promised or guaranteed. If benefits occur, there is no way to know how long they will last. If a medical condition is discovered, one will be referred to your physician. It is possible that information learned from this study may help improve therapy for people who are obese. [redacted]

9. Statistical Analysis

A. Statistical power and Analysis

Aim 1A Statistical Power: The primary endpoint of Aim 1A is change in liver fat by 1H-MRS. With N=20 completers (10 open-label ibutamoren and 10 historical placebo-group controls studied with identical procedures from Protocol [redacted] we will have 80% power to detect a 2% absolute difference in change in liver fat between GH and placebo utilizing an estimated SD of the change in liver fat of 1.6% based on a study of a diet-based intervention for NAFLD.[65] Notably, this calculation already allows for a generous dropout rate of 17% (2 dropouts from 12 enrolled). Additionally, Stanley *et al.*[66] reported a 2.9% change between a subcutaneous GH secretagogue and placebo, which is likely an underestimation of our expected effect given that study involved subjects unselected for NAFLD.

Aim 1B Statistical Power: The primary endpoint is the cT_1 Score by [redacted] We will have 80% power for a cohort of N=20 subjects with a two-tailed significance level of 0.05 to detect a difference of 76 ms in cT_1 between the ibutamoren and placebo groups assuming a SD of 57.4 ms as reported in a NAFLD treatment-study by Harrison *et al*.**[67]** Allowing for dropouts (n=18), the detectable difference in cT1 is 80 ms. [redacted]

Aim 1A and 1B Data Analysis Plan: A pooled random slopes model analysis of treatment effect across sexes with weights equaling the frequency of sexes in the sample. A secondary analysis will test for the treatment-sex interaction. For all analyses, an intent-to-treat analysis will be performed. We will apply guidelines developed by the National Research Council regarding missing data.[66] Our primary analysis assumes that data is missing at random. We will conduct two sensitivity analyses: (1) assumes that the missing data is a function of the unobserved random effect[82] and (2) tests the model's assumptions under other missingness mechanisms.[83]

[redacted]

[redacted]

[redacted]

10. Monitoring and Quality Assurance

A number of procedures will be instituted to protect against potential risk involved in this prospective protocol, as follows:

Monitoring for Side Effects: The side effects of ibutamoren are similar to those expected with GH administration.[46, 52] We will monitor for all potential known GH-related side effects, which based on prior studies are generally minor and reversable. These include mild swelling, mild joint discomfort, muscle aches, median and ulnar nerve paresthesias or headaches. Ibutamoren has generally been well tolerated in pediatric patients and adults in the age groups proposed in this study (ages 21-60 years). Additionally, our prior NIH-funded study titled "*Growth Hormone, Cardiovascular Risk and Visceral Adiposity*" (NCT00131378), we administered low-dose, subcutaneous daily GH to obese men and women of the same age range as proposed in this protocol with a similar expected increase in IGF-1 levels. There was no significant difference in side effects between the GH group and placebo in this study with the exception of a higher incidence of reversable median/ulnar neuropathy in men versus placebo.[29, 30] Moreover, in patients with hypopituitarism, it has been clearly shown that physiologic dosing of GH, i.e. dosing which results in IGF-1 levels in the normal range, do not result in development of complications suggestive of acromegaly, even when administered for years. ***Therefore, we should expect minimal if any side effects related to GH augmentation itself.*** [redacted]

To protect against risk in the proposed study, patients will be carefully monitored for any GH-related side effects, with assessment at every study visit, including a 2-week on drug phone call and the 1-month, 3-month and 6-month study visits. Additionally, study subjects will have access to an on-call study physician or nurse practitioner at all times (24 hours/day, 7

days/week), and are encouraged to contact the study team at any time with any changes in their baseline health status or symptoms. If any study subjects experience significant side effects that do not resolve on oral ibutamoren mesylate, we will perform a dose reduction by 30% to 18 mg or discontinue the subject from the study, depending on the clinical scenario.

Monitoring Glucose Homeostasis: ***Although GH administration itself can cause insulin resistance and reversible diabetes mellitus in a minority of patients, clinically significant deteriorations in glucose homeostasis with augmentation of GH pulsatility by ibutamoren has not been reported.*** There are two opposing effects of GH on insulin resistance – direct negative effects and indirect positive effects mediated through changes in body composition. Moreover, while GH itself may have a subtle, direct effects on increasing insulin resistance, restoration of IGF-1 provides a counterregulatory effect of improving insulin sensitivity. In some studies of ibutamoren, very mild elevations in mean glucose levels within the normal range were observed that were statistically but not clinically significant. In one study of older adults, one subject in the ibutamoren group and one subject in the placebo group developed diabetes. Additionally, no subject was discontinued due to elevations in glucose the from the 2-month study of 25 mg oral daily ibutamoren mesylate in abdominally obese males (ages 18-50 years) that best approximates the proposed population.[52] Studies of tesamorelin, a subcutaneously administered GH secretagogue similar to ibutamoren, also showed no difference in glycemia or insulin resistance compared to placebo over 6-12 months, including in a study of 60 abdominally obese subjects similar to the proposed population.[66, 75] [redacted]

To protect against risk in the proposed study, frequent assessments of glucose intolerance will be made according to the Data Safety and Monitoring plan. [redacted]

If any subject is discontinued from the study due to worsening glucose homeostasis, he/she will also have follow-up labs measured off of treatment. Based on prior studies, we would expect blood glucose to return to the subject's pre-treatment level after drug discontinuation.[29, 30]

The chair of the proposed Data Safety Monitoring Board , will be instrumental to the continuation of the monitoring of the study.

Monitoring Liver Function Testing: Patients with NAFLD/NASH often have mild, baseline elevations in liver transaminases (AST/ALT) as well as fluctuations in these tests over time. Liver function tests will be monitored at baseline, with subjects excluded for AST or ALT greater than 300 U/L to exclude subjects with liver disease other than NAFLD. We will also exclude patients with known liver disease other than NAFLD and history of compensated or decompensated cirrhosis. Mild, asymptomatic, self-limited and reversable elevations in LFTs have been observed in a small number of subjects on ibutamoren mesylate. However, these elevations all resolved either on drug or after drug discontinuation, and notably also occurred in equal frequency in the placebo group of multiple studies. ***There have been no liver-related SAEs reported in studies of ibutamoren mesylate.[53]*** We expect any potential elevation in transaminases to improve over time, either by regression to the mean with the inherent variability in this population or due to improvement in NAFLD/NASH with ibutamoren. Published studies in adults do not suggest a concern for elevations in transaminases with GH augmentation by other methods, including direct GH administration[29, 30] or GHRH-mimetics.[66, 75]

Assessments of liver function tests will be made frequently throughout the study, including at screen, baseline, 1 month, 2 months, 3 months, 4.5 months and 6 months. This frequent

reassessment also provides two pre-treatment measurements (screen and baseline), allowing exclusion of any subject with significant rises in liver function tests prior to drug administration.

Pregnancy and Breastfeeding: There was no fetal harm shown in preclinical toxicology studies of ibutamoren. However, there is no existing clinical experience in pregnant or nursing women. Therefore, precautions against administration to pregnant or breastfeeding women will be instituted. All premenopausal female patients will have pregnancy tests on admission to the study prior to receiving study medication or radiation. Premenopausal women will also have serial pregnancy tests – one at every study visit.

Subject Requirements and Counseling for the Prevention of Pregnancy: Females participating in this study must be of non-childbearing potential or must be using highly effective contraception for the full duration of the study and for 1 month after the last drug intake:

- Non-childbearing potential is defined by cessation of menses for at least 12 months due to ovarian failure or surgical sterilization such as bilateral oophorectomy, or hysterectomy
- Highly effective contraception includes:
    - Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation, including oral, intravaginal or transdermal preparations
    - Progestogen-only hormonal contraception associated with inhibition of ovulation, including oral, injectable or implantable preparations
    - Intrauterine device (IUD)
    - Intrauterine hormone release system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Sexual abstinence
- If female subjects are unable to use the above combination methods, they may choose to use the physical barrier method (used consistently and correctly) such as a diaphragm/cervical cap or male condom. Pregnancy tests will be monitored for all women of childbearing age at every visit. Women of childbearing age will also be instructed to call the study team immediately if they have a missed period and/or believe that they might be pregnant.

- Males enrolled in the trial who are sexually active will be instructed to use highly effective contraception for the full duration of the study and for 1 month after the last drug intake.

A. Independent Monitoring of Source Data
A number of procedures will be instituted to protect against potential risk involved in this protocol. All women of reproductive age will have pregnancy tests on admission prior to receiving radiation or study medication. Such subjects will also have serial pregnancy tests – one at every study visit – and study participation will be discontinued if a subject becomes pregnant.
Side effects of ibutamoren include effects of GH augmentation such as mild swelling or arthralgias, which occur in a minority of patients and resolve after the first few days of therapy in the vast majority of patients. In those study subjects in whom such side effects do not resolve,

we will reduce the dose. Because of the potential importance of insulin resistance to cardiovascular risk, we will investigate with validated techniques the effects of GH on insulin resistance in our population. Because glucose tolerance may deteriorate with GH augmentation, especially acutely, we will not allow patients with uncontrolled DM to participate and we will discontinue study participation if a subject meets strict discontinuation criteria as outlined in the "***Monitoring Glucose Homeostasis***" section on page 25.

A physician will be available at all times during the study by pager to answer any questions a patient might have. The physician will arrange to immediately see every patient with a concern. All efforts will be made to protect the confidentiality rights of the study subjects who will be referred to by code numbers only. Confidentiality of the patients will always be of paramount importance to study investigators. No data on patients will be shared with persons other than those directly involved in the study, except at the documented request of the patient. Samples that are sent to laboratories outside of MGH will be labeled with a non-identifying numeric code.

B. Safety Monitoring
A Data Safety Monitoring Board (DSMB) will be established consisting of: 1) a biostatistician, [redacted] endocrinologist and 3) [redacted] hepatologist in [redacted] The Data Safety Monitoring Board will meet every six months after study activation to oversee the interventional study (AIM 1) only. The DSMB will review safety data, including adverse events, at each meeting and will be available in the interim to consider any urgent matters. Any serious or unexpected adverse events, or any other unanticipated problems involving risks to subjects or others, will be formally reported to the Mass General Brigham Institutional Review Board (IRB).

Data Safety Monitoring Board Meetings:
DSMB meetings will take place every 6 months. In addition, the Chairman of the Board may call ad hoc meetings. The Board will be provided with reports of serious adverse events as they occur and the chair of the committee has the responsibility of calling an ad hoc meeting if the type or frequency of the serious adverse events is of concern. The Board may request additional information from the Investigator in the course of its review. The Investigator shall not be present for part of the Board's meeting.

Safety Monitoring:
1. Review of all adverse events (expected, unexpected and serious)
   -Severity, frequency and reporting protocol adherence
2. Review safety assessments described below
4. Recruitment, enrollment (adherence to eligibility criteria)
5. Dropout rates
6. Protocol changes

The major outcome choice following the data review by the Board is: 1) continuing the trial unchanged, or 2) modify the protocol and/or consent form, or 3) terminate the trial.

The chairperson will be responsible for overseeing the meetings, developing the agenda and summarizing the meeting. The chairperson is the contact person for the DSMB.

The DSMB responsibilities will include:

1. Review of the research protocol, informed consent documents and plans for safety and data monitoring of the study. This review is to determine the risks and benefits to research subjects, protection and safety of the subjects and to offer suggestions for improving the study design.
2. Review interim data to detect adverse effects to determine if the trial should continue as originally designed, should be changed or should be stopped based on the data.
3. Evaluate the progress of the trial including recruitment goals, accrual and retention of participants and other factors that may affect the study outcome.
4. Protect confidentiality of the study participants, trial data and results of the monitoring.

Safety assessments for subjects in Aim 1:

1. IGF-I levels:
    a. Measurements at screen, baseline, 1 month, 3 month and 6 month
    b. Dose decrease (to 18 mg daily) for IGF-I levels above the upper limit of normal
2. Glucose: Fasting glucose at screen, 1, 3 and 6 month visits.
3. HbA1c: screening, 3 and 6 months
4. Pregnancy testing at all visits for premenopausal women
5. Liver function tests at screen, baseline and at the 1-month, 2-month (if 1-month transaminases are above the normal range and elevated compared to baseline), 3-month, 4.5-month, 6-month visits, with action taken per the section below titled *Liver-related Adverse Event Assessment and Drug Induced Liver Injury Monitoring*.

Safety assessments for subjects in Aim 2:

1. INR
2. Platelets

The physician investigator will review all laboratory results and those that are clinically significant.

Drug-drug Interaction Management Plan:

A letter will be sent to the subject's primary care physician to inform them of the subject's study participation and the possibility of concomitant medication restrictions.

Individual subjects on the active study drug who will have acute medical conditions that require the use of a new non-study drug will have to be assessed by a study provider to ensure that there is no drug interaction with ibutamoren. A study provider will contact the subject and investigate the non-study medication:

Subject discontinuation criteria:
Subjects will be discontinued from Aim 1 of the study if they develop

1. Glucose homeostasis criteria: Please refer to the ***"Monitoring Glucose Homeostasis"*** section on page 25. This protocol prevents unnecessary discontinuations for spuriously elevated single fasting glucose results.
2. Positive pregnancy test
3. Severe / intolerable side effects of ibutamoren
4. Development of malignancy
5. Initiation of the following medications: OCPs, pioglitazone, or strong CYP3A4 inhibitors
6. Liver-related discontinuation criteria as outlined per the section below titled *Liver-related Adverse Event Assessment and Drug Induced Liver Injury Monitoring*.

Liver-related Adverse Event Assessment and Drug Induced Liver Injury (DILI) Monitoring:
Liver-related adverse events (AEs) will be graded on the Common Terminology Criteria for Adverse Events (CTCAE), Version 5. Abbreviations that follow include alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (TB).

Drug stop, drug induced liver injury (DILI) monitoring and subject discontinuation rules: For individual subjects, drug will be stopped if the subject develops any of the following:

(1) Study drug will be stopped with the potential for restart for the following criteria outlined below (CTCAE Grade 2 and additional DILI Monitoring Guideline Criteria) regardless of relationship to ibutamoren mesylate.

- Liver-related CTCAE Grade 2 AE based on ALP, ALT, AST or TB
  - Alkaline phosphatase: Between 2.5 and 5x ULN if normal baseline or between 2.5 and 5x baseline if baseline was abnormal.
  - ALT or AST: Between 3 and 5x ULN if normal baseline or between 3 and 5x baseline if baseline was abnormal.
  - TB: Between 1.5 and 3x ULN if normal baseline or between 1.5 and 3x baseline if baseline was abnormal (i.e. in Gilbert's).
- Additional DILI Monitoring Guideline Criteria[76]
  - ALT ≥300 U/L, regardless of baseline
  - ALT ≥2x baseline if abnormal with liver-related symptoms, including severe fatigue, nausea, vomiting and/or RUQ pain

Repeat liver function testing (including ALT, AST, ALP and TB) will be repeated in 2-5 days and subject will be referred to patient's clinician to evaluate for other etiologies of abnormal liver function tests per DILI Consensus Guideline recommendations. Study

drug can only be restarted if alternative etiology identified and liver enzymes return to baseline (e.g. after episode of viral illness). It is expected that resolution and drug restart will occur within 14 days of drug discontinuation.

(2) Study drug will be stopped without the potential for restart for any liver-related CTCAE AE grade 3 or higher based on ALP, ALT, AST, TB or clinical symptoms criteria, regardless of relation to ibutamoren mesylate. These include:

- Alkaline phosphatase, ALT or AST: Greater than 5x ULN if normal baseline or greater than 5x baseline if baseline was abnormal.
- TB: Between 3 x ULN if normal baseline or greater than 3x baseline if baseline was abnormal.
- Clinical evidence of hepatic failure, including asterixis, mild encephalopathy, drug-induced liver injury, limiting self-care ADL, evidence of portal vein flow abnormalities associated with varices and/or ascites.

Subjects will be discontinued from the study at this time without possibility of drug restart.

Study discontinuation rules: Study discontinuation will be considered if any of the following occur, including (1) three subjects develop the same Grade 3 CTCAE attributed to ibutamoren mesylate; (2) two subjects develop any Grade 4 CTCAE attributed to ibutamoren mesylate; or (3) any one patient develops a Grade 5 CTCAE.

If any of these patient or study discontinuation criteria are met, the clinical data will be reviewed by the data safety monitoring board (DSMB) for safety. An agreement will be reached regarding any additional safety monitoring or protocol changes. Minutes recorded during any such DSMB meeting will be recorded and sent to the FDA for review.

C. Adverse Events Reporting

All adverse events will be reported to the IRB in a timely manner according to the guidelines provided by Partner's Human Subjects Research Committee.
All treatment emergent serious adverse events will be documented and reported immediately to the IRB at General Brigham, as well as to the DSMB. An event that is serious must be recorded on the case record and requires expeditious handling to comply with regulatory requirements. In the event that a patient becomes ill or injured as a direct result of participation in the research study, necessary medical care will be made available. All adverse effects will be reported as per Mass General Brigham requirements. Potentially serious adverse events (SAEs) will be followed to resolution or stabilization and reported as SAEs if they become serious. Necessary dates related to the subject's SAE will be provided [redacted] ensure proper report, record, and documentation of the subject's SAE.
A serious adverse event is one that meets any one of the following criteria:

a) Fatal or life-threatening
b) Requires inpatient hospitalization
c) Results in persistent or significant disability or incapacity
d) Congenital anomaly
e) Important medical event that may jeopardize the patient or require intervention to prevent serious outcome
f) Cancer
g) Overdose
h) Results in development of drug dependency or drug use

[redacted]

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