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COMPARISON OF COMBINATION LOW-DOSE SRL +DAILY PEGVISOMANT THERAPY AND LOW DOSE SRL + WEEKLY PEGVISOMANT THERAPY AND HIGH DOSE SRL + WEEKLY PEGVISOMANT THERAPY

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Hypothesis and Specific Aims

Therapeutic modalities employed for the treatment of acromegaly include surgery, medical therapy, and radiotherapy. Strict biochemical control with attainment of normal growth hormone (GH) and insulin-like growth factor (IGF-1) levels is important to normalize mortality (Holdaway 2008). Surgery is curative in approximately 50-75% of patients with acromegaly, depending on the tumor size and invasiveness and the experience of the surgeon (Nomikos 2005). Seventy percent of acromegaly patients harbor GH-secreting pituitary macroadenomas at the time of presentation, and thus medical therapy frequently exhibits enhanced efficacy compared to surgery. Medical therapy options include somatostatin receptor ligands (SRLs), GH receptor antagonist (pegvisomant), combination therapy with SRLs and pegvisomant, and combination SRL and dopamine agonist therapy.

Somatostatin receptor ligands (SRLs), octreotide (Sandostatin) LAR and lanreotide (Somatuline Autogel), normalize GH and IGF-1 levels in about 50% of patients with acromegaly (Freda 2005). Pegvisomant (Somavert) monotherapy is effective in attainment of normal IGF-1 levels in up to 97% of patients (Vander Lely 2001a, Stewart 2003). Recent ACROSTUDY results show lower efficacy. Potential risks of long-term pegvisomant monotherapy include continued growth of residual pituitary tumor remnant, if present, as well as the requirement for high doses of pegvisomant to achieve adequate blockade of the effects of high GH levels. Both of these potential risks may be ameliorated by combined therapy with concomitant SRL.

Co-treatment with SRLs and pegvisomant (combination therapy) is a novel therapeutic approach, especially in those patients not completely resistant to SRLs (Gola 2006). Furthermore, combination therapy could reduce the potential risks of long-term pegvisomant monotherapy.

Pegvisomant (either as monotherapy or in combination with an SRL), effectively normalizes serum IGF-1 levels in more than 70% of cases. Importantly, during combined therapy, a reduced cumulative dose of pegvisomant is as effective as pegvisomant monotherapy (Feenstra 2005, Van der Lely 2001a, Neggers 2007, Neggers 2009, Higham 2009). Most patients studied on combination therapy have received SRL combined with pegvisomant given once or twice weekly depending on dose (Feenstra 2005, Neggers 2009, Neggers 2007, Neggers 2008 Van der Lely AJ 2001 a); however, combination SRL with daily pegvisomant has also been used (Biering EJE 2006, Jorgenson 2005, Trainer 2009, De Marini 2007). The SRL dosage protocol in all published combination studies (Feenstra 2005, Neggers 2007, Neggers 2008, Neggers 2009, Jorgenson 2005, De Marinis 2007, Trainer 2009) except one (Madsen 2011) continued the high-dose SRL with the addition of weekly or daily pegvisomant. Only one study combined low-dose SRL therapy with daily pegvisomant (Madsen 2011), reporting persistent IGF-1 control, despite a 50% dose reduction from the initial SRL monotherapy phase, with the addition of daily pegvisomant.

In this study we will evaluate whether **combination low dose SRL and weekly or daily pegvisomant** will attain equivalent control of serum IGF-1 levels at a lower cost compared to combination high dose SRL and weekly pegvisomant. Lower doses of therapy will greatly reduce cost of acromegaly therapy.

To this end, this study will first randomize acromegaly patients to one of three different combination treatment arms:

1) High dose SRL + weekly pegvisomant
2) Low dose SRL + daily pegvisomant
3) Low dose SRL + weekly pegvisomant

The following parameters will be evaluated at the end of each combination treatment arm:

a) Combined dose of SRL and pegvisomant required to control serum IGF-1 levels
b) Cost of therapy required to control IGF-1 levels
c) Percentage of patients controlled on combination therapy

The following parameters will be evaluated at baseline and at the end of each treatment arm:

a) Proportion of subjects with normal IGF-1 levels
b) Glucose homeostasis: HbA1C levels, fasting blood glucose and insulin levels
c) Change from baseline in health status (EQ-SD), health related quality of life (ACROQOL), and subject reported acromegaly symptoms (PASQ).

After 6 months of combination therapy, patients with normalized IGF-1 will then enter a pegvisomant monotherapy phase for 6 months. During this phase, the SRL therapy will be discontinued. If the IGF-1 is above the upper limit of normal after 6 months of combination therapy, the subject will continue on combination therapy for an additional two months. If IGF-1 control is not achieved after the two additional months of combination therapy has been completed, the subject will be withdrawn.

For subjects continuing to the monotherapy phase, pegvisomant will be started at the same dose and schedule that they achieved normalization in combination therapy. Thus, in the monotherapy phase, two-thirds of the patients will receive weekly pegvisomant, and one third will receive daily pegvisomant. Four months after the SRL therapy has been discontinued, one can assume that the drug has been washed out, and that the efficacy of pegvisomant monotherapy alone on IGF-1 levels can be evaluated.

The following parameters will be evaluated after 24 weeks on monotherapy:

a) Proportion of subjects with normal IGF-1 levels at 24 weeks on monotherapy
b) Cost of therapy required to control IGF-1 levels at 24 weeks on monotherapy
c) Glucose homeostasis: HbA1c levels, fasting blood glucose
d) Change from baseline in health status (EQ-SD), health related quality of life (ACROQOL), and subject-reported acromegaly symptoms (PASQ).

Safety parameters will be assessed as follows:

a) Liver function and liver enzyme tests and glucose at baseline and monthly for the study duration
b) Pituitary MRI with/without contrast prior to randomization, and at the end of treatment (either at 24 weeks or 48 weeks, depending on whether or not patient continues on to pegvisomant monotherapy)

Background and Significance

B.01. Clinical Features of Acromegaly

Acromegaly is an insidious, debilitating disorder, characterized by soft tissue swelling, skeletal overgrowth, increased morbidity, and reduced life expectancy. Acromegaly is caused by elevated serum GH levels, secreted by a benign GH secreting pituitary adenoma in greater than 95% of cases, with subsequent increased hepatic IGF-1 synthesis. 70% of GH secreting adenomas are macroadenomas (>10 mm) at diagnosis (Melmed 2006), often extending beyond the sella turcica.

Clinical features of acromegaly, caused by the excess GH and IGF-1, include skeletal and soft tissue overgrowth, cardiovascular, cerebrovascular, respiratory, and metabolic comorbidities. GH opposes the effects of insulin on carbohydrate metabolism (Clemmons 2004) and impaired glucose tolerance and diabetes mellitus occur frequently, in up to 50% of patients (Ezzat 1994).

B.02. Treatment of Acromegaly

Acromegaly therapy aims to normalize serum IGF-1 levels and control tumor volume, with reduction in signs and symptoms of acromegaly, improved quality of life, and increased life expectancy, without incurring hypopituitarism or damage to local structures. Treatment modalities include surgery, medical therapy, and radiotherapy.

Microadenomas (<10mm) and intrasellar macroadenomas (>10mm) are amenable to surgical cure, as they are potentially resectable by transsphenoidal surgery performed by an experienced pituitary surgeon. However, as the majority of GH-secreting adenomas present as macroadenomas, surgical cure rates are less than 40% (Bates 2008). Furthermore, complications of surgery include tumor persistence and recurrence, hypopituitarism, and local complications. Medical therapy is used as adjuvant therapy after surgery to control GH excess when the tumor is not resectable, because it is invasive, or extends into the cavernous sinuses. Primary medical therapy may be considered in these cases. Radiation therapy can be used as adjuvant therapy after failed surgical cure; however, medical therapy may still be required for several years until the effects of radiation are manifest.

B.03. Efficacy of Medical Therapy for Acromegaly

Medical therapy comprises two major drug classes:

1) Somatostatin receptor ligands (SRLs) – long acting, parenteral slow-release formulations of octreotide and lanreotide.
2) GH receptor antagonist – pegvisomant.

B.03.a. Somatostatin Receptor Ligands (Standard Care Injectable, Usually Once Monthly)

SRLs normalize IGF-1 and GH levels in 40-50% of patients with acromegaly (Freda 2005). 80% of patients treated with SRLs report improved symptoms including headache and soft tissue swelling (Melmed 2006). The tumor mass shrinks in approximately 50% of patients treated with SRLs, but GH tumors re-expand when treatment is discontinued (Melmed 2006). Efficacy of SRL therapy is determined by the pretreatment GH levels, somatostatin receptor expression on the tumor, drug dose, and treatment compliance by the patients.

The overall effect of SRL therapy on glucose homeostasis is complex and unpredictable, as SRLs have positive effects on insulin sensitivity through control of the GH/IGF-1 axis, but negatively affect insulin secretion from the pancreas (Koop1994). SRLs are well tolerated, but side effects are reported in the

gastrointestinal system, with nausea, bloating, and diarrhea. SRLs may induce cholestasis, but most patients are asymptomatic.

B.03.b. Pegvisomant (Standard Care Injectable, Usually Once Weekly or Daily)

Pegvisomant, a pegylated GH analogue, with eight amino acid substitutions in GH binding site 1 and a glycine substitute for alanine at position 120, has enhanced affinity for the GH receptor, but lacks functional GH receptor signaling activity (Kopchick 2002). Pegvisomant has greater efficacy than SRLs in lowering serum IGF-1 levels. Pegvisomant monotherapy or in combination with an SRL normalizes IGF-1 levels in more than 90% of patients, with improved peripheral soft tissue swelling (Trainer 2000, Van der Lely 2001, Lancet). However, pegvisomant has not been demonstrated to cause pituitary tumor shrinkage. Early concerns that pegvisomant may, in fact, cause tumor growth have not been confirmed (Buchfelder 2009).

Pegvisomant may have a further beneficial effect on the increased insulin resistance, impaired glucose tolerance, and diabetes mellitus reported in 38% of patients with acromegaly (Clemmons 2004, Kasayama 2000). Pegvisomant does not directly alter insulin secretion, but blocks the effects of excess GH on insulin action, resulting in decreased circulating insulin levels and improved peripheral insulin sensitivity (Drake 2003). Side effects of pegvisomant therapy include headache and hepatocellular injury.

B.03.c. Combined Therapy with SRL and Pegvisomant (Combination Therapy)

Combined administration of pegvisomant with an SRL provides an additional therapeutic approach to reduce the elevated serum IGF-1 levels in patients with acromegaly who have not attained normal IGF-1 levels with SRL or pegvisomant monotherapy. Combination therapy facilitates the use of lower doses of pegvisomant, a very costly therapy (Trainer 2000, Van der Lely2001a, Feenstra 2005, Jorgenson 2005). Combination therapy protocols administer pegvisomant either weekly (Feenstra 2005, Neggers 2007, Neggers 2008, Neggers 2009) or daily (Jorgenson 2005, Biering 2006, De Marinis 2007). Most of the patients in these studies received pegvisomant weekly.

Combination therapy has been shown to be as effective as pegvisomant monotherapy in attaining normal serum IGF-1 levels, and thus using a reduced cumulative dose of pegvisomant (Feenstra 2005, Neggers 2007, Neggers 2009, Van der Lely 2001 Lancet, Higham 2009), facilitating a lowered cost of therapy (Feenstra 2005). The weekly mean pegvisomant dose in long-term combination therapy studies is 77mg/wk (Neggers 2007, Neggers 2009), whereas a weekly mean pegvisomant dose of 130 mg/wk is the effective dose reported in pegvisomant monotherapy studies (Van der Lely 2001 Lancet). Furthermore, studies of combination therapy demonstrate improved glucose homeostasis compared with SRL monotherapy (Jorgenson 2005), and improved tumor size control, compared to pegvisomant monotherapy (Neggers2007, Van der Lely 2001 JCEM), as well as improved QOL despite absence of a significant decrease in serum IGF-1 levels after addition of weekly pegvisomant to SRL therapy (Neggers 2008).

The decreased pegvisomant dose requirement during combined therapy could be partly attributable to an approximately 20% increase in serum pegvisomant levels (Jorgenson 2005, Van der Lely 2001b) demonstrated during combined therapy and by the suppressed GH levels caused by SRL therapy as well as direct and indirect hepatic IGF-1 synthesis by SRLs (Neggers 2007, Neggers 2008, Leung 2000, Murray 2004). Combination therapy with SRLs and pegvisomant aims to reduce the dosage and frequency of pegvisomant administration. The rationale for combined therapy is based on the fact that SRLs decrease pathological GH secretion by the pituitary adenoma in patients with acromegaly. When there is less

endogenous GH to compete for the GH receptor, less of the GH receptor antagonist pegvisomant is needed. Furthermore, in vitro data suggest that inhibition of insulin secretion by SRL in the portal vein results in a reduction of GH receptors on the hepatocyte cell surface (Leung 2000). Subsequently, when there are fewer hepatic GH receptors and less endogenous GH, less pegvisomant is required. In addition, SRLs can also directly inhibit hepatic IGF-1 production (Murray 2004). Therefore, SRL action results in lowered hepatic GH sensitivity during SRL therapy, whereas acromegaly symptoms may still persist in other parts of the body.

Significance

This proposed pharmacoeconomic protocol will evaluate the efficacy of three novel dosage regimens comprising different combinations of SRL and pegvisomant for the treatment of acromegaly and compare the cost of each regimen.

Patients will be randomized to one of three treatment arms, and cost of therapy, efficacy, and QOL will be evaluated to determine the lowest combined SRL and pegvisomant dose that is equally effective in controlling IGF-1 levels. Dose titration of pegvisomant will be planned to provide adequate opportunity to attain control of IGF-1 at study end. The combination of a lower SRL dose and a lower pegvisomant dose which is as efficacious as prior higher SRL and pegvisomant doses would facilitate more cost-effective acromegaly therapy.

Both SRL and pegvisomant monotherapy are titrated to an approved maximum therapeutic dose during standard of care. Published reports suggest that combination therapy with maximum doses of SRLs and weekly or daily pegvisomant are equally efficacious in controlling serum IGF-1 levels as pegvisomant monotherapy. The weekly or daily pegvisomant doses used in the published combination protocols are much lower than pegvisomant doses that achieve control using pegvisomant monotherapy, and thus medication costs are substantially lower.

The current proposal is innovative because it evaluates low-dose SRL in combination with weekly or daily pegvisomant dosing, compared to high-dose SRL combined with weekly pegvisomant dosing. This study will thus help determine the lowest dose of combined SRL and pegvisomant acromegaly therapy that is equally efficacious in controlling IGF-1, and will thus determine the most cost-effective therapeutic regimen.

The aim of adding a pegvisomant monotherapy phase is to enable comparison of pegvisomant monotherapy to combination therapy. There is very little published data comparing pegvisomant monotherapy with combination therapy, or with SRL monotherapy. Although this study design is limited by the fact that it is not placebo controlled, here is an opportunity to attain a comparative dataset, as each patient acts as their own control, receiving SRL monotherapy, combination therapy, and then pegvisomant monotherapy sequentially.

There is also very little published data evaluating efficacy/safety of less-than-daily pegvisomant monotherapy compared to daily pegvisomant monotherapy. Adding this new treatment phase will provide some comparative insights into these two different pegvisomant dosing regimens.

Research Design and Methods

Overview: Figure 1 shows an overview of the research plan. We propose enrolling up to 85 patients with acromegaly at the CSMC Pituitary Center. Newly diagnosed patients with acromegaly, non-cured, post-surgical patients who have not received or are currently receiving medical therapy, patients on SRL

monotherapy, pegvisomant monotherapy, SRL and dopamine agonist therapy after 3 months washout of dopamine agonist, or patients on combination therapy with maximum dose SRL and weekly pegvisomant, are eligible for enrollment, irrespective of whether their IGF-1 levels are controlled or uncontrolled. Subjects will be stratified according to pre-treatment response to SRL and will then be randomized (using a pre-generated randomization schedule developed by the CSMC biostatistician, see Appendix A – Stratification for Randomization Worksheet), to one of the following three combination treatment arms for 24 weeks:

a) High-dose SRL + weekly pegvisomant
b) Low-dose SRL + daily pegvisomant
c) Low-dose SRL + weekly pegvisomant

The rationale for stratifying patients according to pre-treatment response to SRL is based on the premise that baseline IGF-1 levels predict the pegvisomant dose that is necessary to control IGF-1 levels in patients with acromegaly (Neggers 2007), and success rates for cure can be stratified by pre-treatment GH/IGF-1 levels in patients receiving octreotide LAR as primary medical therapy (Bevan 2002).
The dose of SRL will remain stable during the 24 week study period; however, the dose of pegvisomant will be uptitrated, as described below, until the patient's serum IGF-1 level is in the age-adjusted normal range.

Combined dose of therapy (at the end of each treatment arm, reached after dose titration to a normal IGF-1) and cost of therapy (based on the dose at the end of each treatment arm) will be assessed at 24 weeks and again at 24 weeks of monotherapy. QOL and pituitary MRI (only for patients who will not continue to pegvisomant monotherapy) will be performed at baseline and after 24 weeks of treatment on each treatment arm. IGF-1 levels and liver function tests and enzymes will be performed monthly. The pegvisomant dose will be titrated (increased or decreased) if the serum IGF-1 level is not in the age-adjusted normal range at each monthly visit.

The study will begin when the combination of octreotide LAR or lanreotide and pegvisomant is first administered. This may occur 1-2 months after the initial screening visit due to logistical issues with subject's insurance coverage for the standard of care medication, octreotide LAR or lanreotide.

In cases where it is not practical to consent subjects in person, investigators may obtain electronic informed consent using REDCap or DocuSign after a telephone consent discussion in accordance with institutional policies for obtaining electronic and remote informed consent. The subject's e-signature will be captured via touch screen or via a typed name in the e-signature field, and the electronically signed form will be stored with the subject's record per institutional policies. Alternatively, the investigator may email, mail, or fax a consent form to the subject and have a telephone consent discussion once received. The subject will sign the form after the telephone consent discussion, return it to the study team by email, mail, or fax, and the investigator who obtained consent will sign it once received. The signed form will then be stored with the subject's record.

Study visits will occur every 4 weeks from the start of the study. In cases where it is not practical to conduct study visits in person due to distance or other factors, video visits may be done for Visit 0 (Baseline) and Visit 6 (24 weeks). These video visits will be done using CS-Link or other HIPAA-compliant platforms in accordance with institutional policies for telehealth. In such cases, the standard of care physical exam at Visit 0 will be done by the subject's local treating physician, and the research pituitary MRI at Visit 6 for those not proceeding on to pegvisomant monotherapy will be done at a local institution and results reviewed by the study investigator. In addition, the study team will facilitate

monthly blood draws as needed at their local Quest laboratory facility. Visits may occur ± 7 days from 4 weeks since the previous visit and still be acceptable. If a subject's medication dose needs to be altered to achieve IGF-1 normalization, the study visit will occur 4 weeks from the start of the new dose, instead of 4 weeks from the last study visit.

After the 24-week combination, if the subject's IGF-1 is not normalized, then the subject may continue combination therapy for up to 2 months. If the subject's IGF-1 remains uncontrolled, they will be withdrawn from the study. Subjects with a controlled IGF-1 will then start pegvisomant monotherapy at the same dose that they attained normalization in combination therapy. IGF-1 levels, liver function test, and blood glucose will be performed monthly. An MRI will be performed at the conclusion of the 48-week treatment period. The dose of pegvisomant will be titrated monthly, as described below, until the patient's serum IGF-1 level is in the age-adjusted normal range.

D.01. Patient Inclusion Criteria. All subjects must fulfill the following:

- Subject has provided written informed consent prior to any study related procedure
- Subject is between 18 and 85 years old
- Subject has a confirmed and documented diagnosis of acromegaly
- Female subject at risk of becoming pregnant agrees to use an effective method of contraception including implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, or vasectomized partner.
    - N/A – male subject
    - N/A – female subject who has been post-menopausal for at least 3 years
    - N/A – female subject who has documented infertility
- Subject has normal liver function tests before randomization to treatment

D.02. Patient Exclusion Criteria. Exclusion criteria for this study are as follows:

- The patient harbors a macroadenoma with visual field defects due to chiasmatic compression
- The patient has clinically significant hepatic abnormalities and/or aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 ULN at the baseline visit
- The patient had pituitary surgery <3 months prior to study entry
- The patient had radiotherapy <12 months prior to study entry
- The patient has abnormal CBC and chemistry panel at the baseline visit, any other medical conditions(s) or laboratory findings that, in the opinion of the investigator, might jeopardize the patient's safety
- The patient has a known hypersensitivity to any of the test materials or related compounds
- The patient has a history of or known current problems with alcohol or drug abuse
- The patient has any mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study, and/or evidence of an uncooperative attitude
- The subject has hypopituitarism and is NOT on hormone replacement therapy
- The subject has received dopamine agonist therapy within 3 months of beginning combination therapy
- To enter pegvisomant monotherapy, patient must have achieved normalization of IGF-1 on combination therapy

D.03. Dose of Combination Therapy in High-Dose SRL / Low-Dose SRL Treatment Arms

Acromegaly patients at the CSMC Pituitary Center will be stratified per IGF-1 levels and randomized to one of three treatment regimens for 24 weeks (see Figure 1). Pegvisomant dose will be titrated monthly, as outlined below, until normal age-adjusted IGF-1 levels are attained.

1) High dose SRL+ weekly pegvisomant: patients randomized to this arm will receive LAR 30mg/LAN120mg IM q 28 days for 24 wks + pegvisomant SQ weekly, starting at 40mg SQ q weekly, with a 10mg/wk dose increase (decrease) every month if the IGF-1 level is above (below) the age-adjusted normal, until a maximum dose of 160mg/week (Neggers 2007) is administered. If the once-weekly dose exceeds 80mg/wk, the dosage will be divided into two equal parts and injected at two sites twice weekly SQ.
2) Low dose SRL + daily pegvisomant: patients randomized to this arm will receive LAR 10mg/LAN 60mg IM q 28days for 24 wks + pegvisomant SQ daily, starting at 15mg SQ q daily. IGF-1 levels will be evaluated monthly, and if the IGF-1 is above (below) the age-adjusted normal, the daily pegvisomant dose will be increased (decreased) by 5 mg/day until a maximum dose of 60mg/day (Yin 2007) is administered.
3) Low dose SRL + weekly pegvisomant: patients randomized to this arm will receive LAR 10mg/LAN60mg IM q 28 days for 24 weeks + pegvisomant SQ weekly, starting at 40mg SQ q weekly, with a 10mg /weekly dose increase (decrease) every month if the IGF-1 level is above (below) the age-adjusted normal, until a maximum dose of 160mg/week is administered. If the once weekly dose exceeds 80mg/week, the dosage will be divided into two equal parts and injected at two sites twice weekly SQ.
4) Pegvisomant monotherapy: after completing combination therapy, those who achieved normalization of their IGF-1 values will be placed on pegvisomant monotherapy starting at the same dose that they achieved normalization in combination therapy. Pegvisomant will be titrated as needed by increments of 5mg if on daily pegvisomant or 10mg if on weekly pegvisomant to a maximum of 80mg/day and 160mg/week, respectively, in order to achieve normalization of IGF-1. If the once weekly dose exceeds 80mg/wk, the dosage will be divided into two equal parts and injected at two sites twice weekly SQ.

D.04. Calculation of Combined Therapy Dose

The SRL dose will be the same for all subjects randomized to a treatment arm. Pegvisomant dosages will be calculated for each patient as mg pegvisomant required to control serum IGF-1 levels after dose titration in each treatment arm and then on monotherapy. Mean ± SD pegvisomant dose for the subjects in each of the three treatment arms will be calculated for the 24-week combination therapy period, then again for the 24-week monotherapy period.

D.05 Cost of Therapy Calculation

Cost of therapy will be calculated using the SRL dose (mg) utilized in each treatment arm multiplied by the average wholesale price (AWP). Similarly, cost of pegvisomant therapy will be calculated using the mean final dose of pegvisomant required at the end of the 24-week combination treatment period for each arm, then again for the 24-week monotherapy period, multiplied by the AWP of pegvisomant.

AWP for SRL

Medication	Monthly Dose	Price per Dose
Lanreotide (Somatuline Depot)	60 mg	$ 2052.00
	90 mg	$ 2481.00
	120 mg	$ 3668.00
Octreotide (Sandostatin LAR Depot)	10 mg	$ 1866.29
	20 mg	$ 2335.79
	30 mg	$ 3453.07

AWP for Pegvisomant

$9.45 per mg pegvisomant

D.06 Study Drug Distribution & Administration

Pegvisomant will be supplied by the sponsor, Pfizer, for participants in this research study. Pegvisomant will be ordered from the sponsor by the research coordinator, using a drug request form and the study medication will be shipped directly to Sonexus Health. Study medication will be shipped to all subjects via Sonexus Health. All drug orders will be sent to Sonexus who in turn will dispense, pack the pegvisomant in coolers, and ship the refrigerated drug overnight to the subject's residence.

Subjects will have monthly IGF-1, fasting glucose, and liver function panels drawn. Before dispensing a 35-day supply of the study medication, the investigator will review the subject's IGF-1, fasting glucose, and liver function panel results. If the subject's IGF-1 is within normal range, then the subject can remain on the same dose. However, if the subject's IGF-1 is out of normal range then the dose of pegvisomant will be up-titrated, or down-titrated. Investigator will also review liver function panel to monitor potential alterations in liver function.

D.07 Quality of Life Questionnaires

For evaluation of self-reported quality of health, patients will be asked to fill out the Euro Quality of Life–5 Dimensions questionnaire (EQ-5D) which comprises five general health-related questions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a visual analog scale (VAS) for overall health status.

In addition, a Patient-Assisted Acromegaly Symptom Questionnaire (PASQ) with six symptom-related questions scoring 0-8 and overall score (0-10) will be used to evaluate disease-specific health issues. Patients will also complete ACROQoL, a 22-item, self-reported acromegaly specific measure of health-related quality of life, rated on a scale from 1 (worst) to 5 (best).

D.08 Monitoring for Safety and Potential Drug Side-Effects (See Table 1)

- Review of medical history during baseline visit
- Physical examinations will occur at Visit 0, 6, and 12
- Serum pregnancy test at baseline visit
- Full pituitary blood panel will occur at Visit 0, 6, and 12
- Evaluate signs of local tumor growth monthly:
    - Increased headache
    - Diplopia
    - Deterioration in visual fields

- IGF-1 levels measured at baseline and every month will determine titration of the pegvisomant dose
- Pituitary MRI at baseline or within 12 months prior to study entry
- Clinical laboratory safety tests at baseline, 24-week, and 48-week visit as specified in the protocol procedure table (CBC, biochemistry)
- Liver function tests and enzymes at baseline and monthly for the entire study duration. ALT and/or AST >3x ULN will be considered clinically significant, and both study drugs will be discontinued
- Glucose homeostasis: HbA1c, fasting blood glucose, and insulin will be measured at baseline, 12, 24, 36 and 48 weeks; fasting blood glucose will be measured every month
- Concomitant medication information will be obtained at baseline and at each visit
- Questionnaires evaluating adverse effects will be performed at each visit

D.09 Follow-Up Period

At the study end, subjects will no longer be able to receive pegvisomant free of charge. With their clinic physician, they will decide on the best course of future treatment. Patients may continue their pegvisomant monotherapy or restart (or continue if applicable) combined therapy if they choose, (however, they would have to pay for the pegvisomant themselves) or they may revert to their original treatment course prior to study enrollment.

D.10 Statistical Analysis

The primary endpoint for the study is the dose/cost of therapy for each treatment arm. Secondary end points include IGF-1 levels, HbA1c levels, fasting blood glucose/insulin levels, LFTs, and QOL scores. Changes from baseline to 24 weeks will be analyzed using ANOVA. 17 patients per group, using a 2-sided test, will have 80% power to detect an effect size of 1 (group mean difference = SD).

Two group t-test of equal means (equal n's)

	1	2
Test significance level	0.050	0.050
1 or 2 sided test?	2	1
Effect size	1.000	1.000
Power (%)	80	80
n per group	17	14

Subjects who achieve IGF-1 normalization after completing treatment on each combination therapy arm will continue on to the next phase of the study using only weekly or daily pegvisomant, depending on what was assigned in their combination treatment arm. Subjects in each combination therapy arm will be compared with their corresponding monotherapy arm with regard to cost and efficacy using the same outcome measures that are being compared in the combination therapy phase, and three independent paired t-tests will be conducted. With n=17 pairs, 2-sided paired t-tests at alpha = 0.05 will have 80% power to detect an effect size of 1.0 with a correlation of 0.05.

Paired t-test for mean difference:
Test significance level = 0.05
2-sided test
Effect size = 1.0
Power = 80%
Correlation = 0.05
Number of pairs = 17

Among the total 51 patients treated, there will be 34 patients on weekly pegvisomant and 17 patients on daily pegvisomant at the end of the monotherapy phase. A two-sample t-test will be conducted to examine differences in mean cost and efficacy between the weekly and daily cohorts. With $n_{weekly} = 34$ and $n_{daily}=17$, 2 sided two-sample t-tests at alpha = 0.05 will have 91% power to detect an effect size of 1.0.

Two sample t-test for difference in means:
Test significance level = 0.05
2 sided test
Effect size = 1.0
Power = 91%
Number of people per group: 34 (weekly), 17 (daily)

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Appendix A. Randomization of Patients

Each patient will be classified as a good, medium, or poor responder, based on the dose of SRL that is required to normalize their IGF-1 prior to enrollment.

10 mg LAR / 60 mg LAN = good responder (G)
20 mg LAR / 90 mg LAN = medium responder (M)
30 mg LAR / 120 mg LAN = poor responder (P)

There are 3 treatment arms:

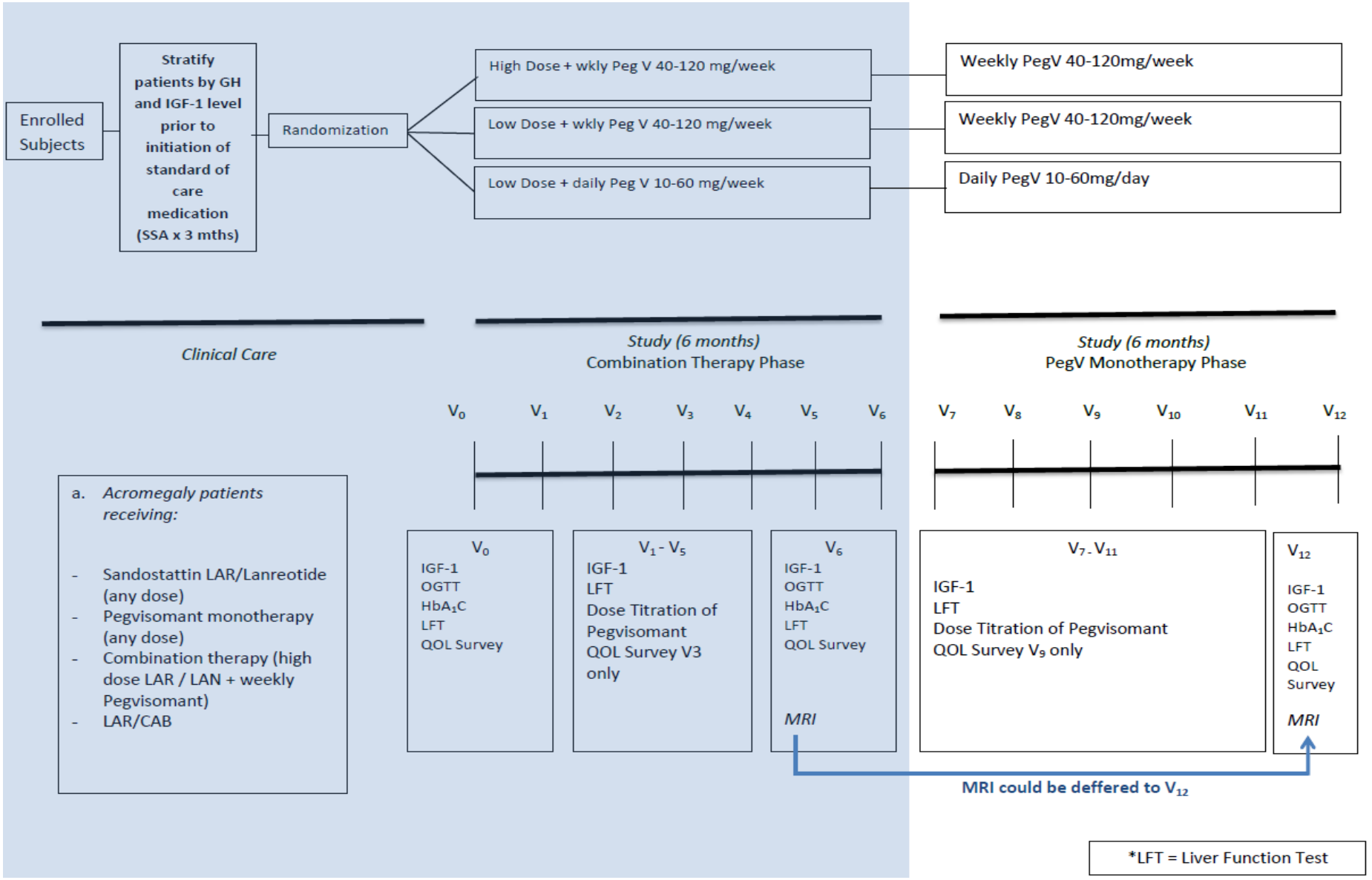
A) High dose (30 mg LAR / 120 mg LAN) + weekly pegvisomant (40-160 mg/wk)
B) Low dose (10 mg LAR / 60 mg LAN) + weekly pegvisomant (40-160 mg/wk)
C) Low dose (10 mg LAR / 60 mg LAN) + daily pegvisomant (15-60 mg/day)

Using a computerized random numbers generator, the table below was generated for the randomized assignment of 38 good, 38 medium, and 38 poor responders.

Good	Medium	Poor
A	B	A
C	A	B
B	C	C
B	B	B
A	A	A
B	C	C
B	B	A
C	C	C
A	A	B
C	A	C
C	A	B
A	C	B
B	A	C
C	A	B
C	B	A
A	C	B
A	B	C
B	C	A
B	C	C
A	B	A
C	A	C
B	C	B
B	B	A
A	A	A
C	C	C
B	B	B
C	C	B
A	A	C
B	A	C
A	B	A
C	A	B

B	C	C
B	B	B
A	A	A
C	C	C
B	B	A
C	C	C
A	A	B
B	A	C
C	A	B
A	C	B
B	A	C
C	A	B
C	B	A
A	C	B

Figure 1. Schema of Research Design



PROTOCOL PROCEDURES TABLE:

Procedures	Visit #0	Visit #1	Visit #2	Visit #3	Visit #4	Visit #5	Visit #6	Visit #7	Visit #8	Visit #9	Visit #10	Visit #11	Visit #12
Week	Baseline	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks	28 Weeks	32 Weeks	36 Weeks	40 Weeks	44 Weeks	48 Weeks
Standard of Care Procedures: Procedures that are part of regular care and would be done even if you did not take part in this research study													
Complete medical/family & menstrual history	X												
Physical exam (including height, weight, vitals)	If clinically indicated												
Laboratory blood tests (CBC, chemistry, hemoglobin A1C)	X_2												
(fasting blood sugar, liver function panel)	If clinically indicated												
Pituitary panel (pituitary hormones)	X_1												
(IGF-1)	X_2												
Pituitary MRI with and without contrast	X_1												
SRL therapy	X	X	X	X	X	X	X_4						
Research Related Procedures: Procedures, drugs, devices, evaluations or other services done only because of your participation in this research.													
Pregnancy test - serum (if pre-menopausal)	X												
Pegvisomant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Pituitary MRI with and without contrast	X						X_3						X
Physical exam (including height, weight, vitals)							X						X
Laboratory blood tests (CBC, chemistry							X						X
Blood test: hemoglobin A1C and insulin				X			X			X			X
(fasting blood sugar, liver function panel)	X	X	X	X	X	X	X	X	X	X	X	X	X
Pituitary panel							X						X
(IGF-1)	X	X	X	X	X	X	X	X	X	X	X	X	X

Acromegaly Signs and Symptoms Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X
Acromegaly Quality of Life Questionnaire (ACROQoL)	X			X			X			X			X
EQ-5D-5L Health Questionnaire	X			X			X			X			X
Pegvisomant dispense	X[6]	X_5	X_5	X_5	X_5	X_5	X_5	X_5	X_5	X_5	X_5	X_5	X_5
Adverse Event		X	X	X	X	X	X	X	X	X	X	X	X

1. If last test performed was more than a year ago or is clinically indicated
2. If last test performed was more than 6 months ago or is clinically indicated
3. Only if patient will not be proceeding on to pegvisomant monotherapy.
4. If the subject's IGF-1 is not normalized then the subject may continue on combination therapy for up to 2 months. If the IGF-1 remains uncontrolled, they will be withdrawn from the study.
5. Before dispensing a 35 day supply of the study medication, the investigator will review the subject's IGF-1 lab results from the previous study visit. If the subject's IGF-1 is within normal range, then the subject can remain on the same dosage. However, if the subject's IGF-1 is out of normal range, then the dose of pegvisomant will be up-titrated. The study medication will be packed in coolers and shipped overnight to the subject's residence.
6. The study will begin when the combination of octreotide LAR or lanreotide and pegvisomant is first administered. This may occur 1-2 months after the initial screening visit due to logistical issues with subject's insurance coverage for the standard of care medication, octreotide LAR or lanreotide.