A Randomized, Placebo Controlled Clinical Trial of SOM230 (Pasireotide LAR) In Severe Polycystic Liver Disease.

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Medical Affairs

SOM230C

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A Randomized, Placebo Controlled Clinical Trial of SOM230 (Pasireotide LAR) In Severe Polycystic Liver Disease.

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Protoco

List of abbreviations

5-HIAA	Urinary 5-hydroxyindole acetic acid
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
b.i.d.	*bis in diem*/twice a day
BG	Blood Glucose
CPO	Clinical Pharma Organization
CRF	Case Report/Record Form
CRD	Clinical Research and Development
CRO	Contract Research Organization
CS&E	Clinical Safety and Epidemiology
CT	Computer Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DM	Diabetes Mellitus
ECG	Electrocardiogram
GCP	Good Clinical Practices
GEP	Gastroenteropancreatic
GH	Glycosylated Hemoglobin
GI	Gastrointestinal
GOT	Glutamic pxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
HSST	Human somatostatin receptor
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular(ly)
ITT	Intent to Treat
IV	intravenous(ly)
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LAR	Long Acting Release
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
o.d.	*omnia die*/once a day
PK/PD	Pharmacokinetic/Pharmacodynamic
p.o.	*per os*/by mouth/orally
PRL	Prolactin
PT	Prothrombin time
PTT	Partial thromboplastin time
q.d.	*quaque die*/every day
REB	Research Ethics Board
SAE	Serious Adverse Event
SQ	Subcutaneous
$SRIF_a$	Somatotropin release-inhibiting factor analog/somatostatin analogs
SOP	Standard Operating Procedure
SST	Somatostatin
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit Normal

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1 Introduction

1.1 Overview of Autosomal Dominant Polycystic Kidney and Liver Disease:

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease, affecting 1 in 400 to 1000 live births.[1] ADPKD is caused by mutations in the *PKD1* and *PKD2* genes, and progresses to end-stage renal disease at a mean age of 55 years and 69 years, respectively.[1-3] Hepatic cysts are the most common extra-renal manifestation of ADPKD and occur in the majority of these patients.[4] Cysts increase with age and may cause considerable morbidity; including abdominal pain and distension, rupture, hemorrhage, dyspnea, venous or biliary obstruction, and ascites. Some of these individuals are incapacitated due to massive polycystic liver disease (PLD). With increased lifespans due to dialysis and kidney transplantation, more patients with ADPKD develop severely symptomatic PLD. There are also patients with PLD without kidney disease due to mutations in different genes, some who develop severe incapacitating liver disease.[5,6]

1.2 Background

1.2.1 Somatostatin Analogs – the first medical therapy for PLD

Somatostatin (SST) analogs are the first medical therapy that have been demonstrated to be effective in reducing liver volume and improving quality of life in treated individuals with PLD. SST may blunt cyst development by acting at multiple levels: inhibition of secretin released by the pancreas;[7] inhibition of secretin-induced cAMP generation and fluid secretion in cholangiocytes;[8-10] vasopressin-induced cAMP generation and water permeability in collecting ducts by its effects on G_I protein-coupled receptors;[11-14] and suppression of the expression of IGF-1, vascular endothelial growth factor, and other cystogenic growth factors and of downstream signaling from their receptors.

1.2.2 Pre-Clinical Studies with Somatostatin

We have previously tested the effect of cAMP inhibition with the SST analog octreotide in an animal model of PKD, the PCK rat, and observed a reduction in liver and kidney weight, cyst volume, fibrosis & cell proliferation.[15]

1.3 Somatostatin analogs in the treatment of patients with PLD

In clinical trials SST analogs retard progression of PLD with up to one year of treatment.[16-19] Octreotide therapy also maintained the reduction in liver volume over two years in the Octreotide LAR treated group, while it did not increase significantly during Year 2 (Δ% -5.96 ±8.90%; p =0.002) in our small study.[20] Furthermore, using pooled analyses of all individuals who received Octreotide LAR depot® (OctLAR®) for 12 months (n=40, in years one or two), the cumulative reduction in liver volume was -6.08% ±7.58% (p=0.001) compared to a net growth of 0.9±8.35% in the historical placebo treated group.[21]

While OctLAR stimulates distinct SST receptors – SSTr 2, 3 and 5, all five receptor subtypes are expressed in rat and human and mouse cholangiocytes. Pasireotide (SOM230) exhibits high affinity binding to four of the five known human SST (HSST) receptors (SSTr 1-5) and binds with a 30 to 40 fold higher affinity than octreotide to the SST1 and -5 receptor subtypes with a five-fold higher affinity to SST3. Because of the broader SST binding profile of pasireotide, and the

known SST receptor subtype expression in liver tissue, pasireotide has the potential to be more effective than preferential SST2 receptor- binding SST analogs. Therefore we hypothesized that the pharmacological targeting of cAMP by pasiroetide will be even more effective than cctreotide in inhibiting cAMP levels, in decreasing the rate of cell proliferation and reducing hepato-renal cystogenesis.

1.4 Pasireotide (SOM230)

Pasireotide is an injectable SST analog. It is a novel cyclohexapeptide with the following chemical name: (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2-aminosuccinic acid] salt.

Like natural SST and other SST analogs (SRIFa), pasireotide exerts its pharmacological activity via binding to SST receptors. There are five known SST receptors: SST 1, 2, 3, 4 and 5. SST receptors are expressed in different tissues under normal physiological conditions. SST analogs activate these receptors with different potencies[22] and this activation results in a reduced cellular activity and inhibition of hormone secretion. Sst receptors are strongly expressed in many solid tumors, especially in neuroendocrine tumors where hormones are excessively secreted e.g. acromegaly[23] GEP/NET tumors[24] and Cushing's disease.

The SRIFs currently approved for use in the clinic (octreotide and lanreotide) have a high affinity to the SST subtype 2 (SST2) receptor, with moderate or no affinity to the remaining subtypes. Pasireotide is a novel cyclohexapeptide SST analog that exhibits a unique binding profile, binding with high affinity to four of the five known HSST receptors (Table 1). Compared to Sandostatin® (octreotide acetate), pasireotide exhibits a binding affinity, which is 30-40 times higher for HSST1 and HSST5, 5 times higher for HSST3, and 2.5 times lower for HSST2 receptor. A detailed summary of available preclinical data is provided in the Investigators' Brochure.

Additionally, preclinical studies suggest anti-tumor activity of SOM230. SOM230 has been found to significantly reduce cell proliferation of the neuroendocrine tumor cell line NCI-H727, whereas the conventional analog SMS 201-995 did not.[25]

Table 1 Binding profile for octreotide and pasireotide at HSST1-5 (IC50, M)

Compound	SST1	SST2	SST3	SST4	SST5
Octreotide acetate (SMS 201-995)	$2.8x10^{-7}$	$3.8x10^{-10}$	$7.1x10^{-9}$	$>10^{-6}$	$6.3x10^{-9}$
Pasireotide (SDZ 227-230)	$9.3x10^{-9}$	$1.0x10^{-9}$	$1.5x10^{-9}$	$>10^{-6}$	$1.6x10^{-10}$
Ratio of IC_{50}:octreotide acetate / pasireotide SMS/SOM230	30	0.4	5	--	40

1.5 Clinical experience with pasireotide

Pasireotide is available as a short-acting subcutaneous (SQ) formulation and a long acting release (LAR) intramuscular (IM) formulation.

1.5.1 Pasireotide SQ

Single dose of pasireotide SQ up to 1500 µg q.d. and 750 µg b.i.d. multiple SQ doses (7-14 days) up to 1500 µg q.d., 750 µg b.i.d. and 2100 µg b.i.d. (up to 5 days), and continuous (7-day) SQ infusion by insulin pump, have been well-tolerated, with mostly mild, transient side effects reported. The most reported adverse events (AEs) were GI related (mild diarrhea and nausea), requiring no treatment or study discontinuation. The frequency of these AEs appeared to de-

crease with time in multiple-dose studies. AEs were assessed using the NCI-CTC for Adverse Events, version 3.0 (CTCAEv3.0, [http://ctep.cancer.gov/forms/CTCAEv3.pdf]).

Single and multiple doses of pasireotide SQ have generally been well-tolerated by patients with acromegaly, metastatic carcinoid tumor, or Cushing's disease. Pasireotide has been studied in phase II studies at doses of up to 600 µg b.i.d. for acromegalic patients, 900 µg b.i.d. for patients with Cushing's disease, and 1200 µg b.i.d. for patients with carcinoid tumors, with pasireotide treatment periods of 4 years, 4.8 years and 1.6 years, respectively. For all these indications the most frequent AEs are similar to what have been reported in healthy volunteers, predominantly mild diarrhea, nausea, and abdominal pain.

Hyperglycemia was also observed across all indications. The effect on blood glucose was more pronounced in patients with Cushing's disease, a setting in which glucose metabolism is inherently dysregulated. The hyperglycemic effect in healthy volunteers (phase I study) is less pronounced when administered with a breakfast meal and appears to decrease after multiple doses indicating an attenuation of effect over time. The underlying mechanism of hyperglycemia following pasireotide is thought to be due to the decrease in insulin secretory capacity with no effect on insulin sensitivity; however the effect of pasireotide on glucagon level is smaller. In phase II studies, fasting blood glucose increase tended to occur with increasing doses and appeared to be more notable in patients who had a history of hyperglycemia or diabetes mellitus, hypertension and hyperlipidemia prior to receiving pasireotide. Although hyperglycemia was frequently reported, few grade 3 or 4 AEs or SAEs or discontinuation due to AEs related hyperglycemia were reported.

Although no pre-clinical or clinical studies have revealed any specific pasireotide-related cardiac toxicity issues, an effect of pasireotide on QTcF interval at 1950 µg SQ b.i.d. in healthy volunteers was demonstrated. The QTcF change from baseline showed a peak effect at 2-hour post-dose of pasireotide SQ was 17.5 ms versus placebo.

1.5.1.1 Pasireotide LAR

A total of 85 patients were enrolled in the [CSOM230C2110] study and received at least one dose of pasireotide (SQ and/or LAR injection). Of these, 40 patients were diagnosed with acromegaly and 45 with carcinoid tumors. Patients received a single dose of 300 µg Pasireotide SQ followed by a washout period of at least 5 days. Patients subsequently received 3 monthly administration of pasireotide LAR IM.

In patients with acromegaly, the most common AE overall and by treatment group was diarrhea affecting 12/35 patients in total, 3/10, 3/12 and 6/13 in the pasireotide LAR 20 mg, 40 mg and 60 mg group, respectively. Majority of the diarrhea were CTCAE grade 1 and none were serious. Frequent AEs only reported in the 40 mg and 60 mg groups included abdominal distension, cholelithiasis, blood glucose increased, hyperglycemia and hematuria. All events but blood glucose increased in the 40 mg group (2 patients) and hyperglycemia in the 60 mg group (3 patients) were observed for one patient in each of the two groups.

In patients with carcinoid tumors, diarrhea was the most frequent AE affecting 4 patients in each treatment group (4/12 in the 20 mg group, 4/14 in the 40 mg group, and 4/16 in the 60 mg group). Diarrhea side-effects were of CTCAE grade 1 or 2 for all patients, except for one patient in the pasireotide LAR 20 mg group, for which the AE was reported as grade 3. Other frequently reported AEs were fatigue (9/42 patients), asthenia (5/42 patients), diabetes mellitus (6/42 patients), anorexia (5/42 patients), back pain (4/42 patients) and muscle spasms (3/42 patients). CTCAE grade 3 or 4 that were suspected to pasireotide LAR were primary hyperglycemia and

were reported in all dose groups. CTCAE grades 3/4 elevation of blood glucose level was reported in 18/42 (43%) patients. Median time to grades 3/4 elevation of blood glucose occurred on day 1 of cycle 1 (range 1-1131 days), approximately 6 hours (range 2-8 hours) post-dose.

Given the observed suppression of insulin secretion associated with pasireotide administration, the use of insulin secretagogs and/or incretin-based therapies may be particularly suited for the treatment of pasireotide induced glucose dysregulation.

1.5.1.1.1 Clinical pharmacokinetics

Pasireotide SQ and LAR have been studied in healthy volunteers, patients with acromegaly, Cushing's disease and carcinoid syndrome. Following a single IM injection of 40 mg or 60 mg in healthy volunteers [CSOM230C2101], pasireotide LAR demonstrated a controlled release type of concentration-versus-time profile, with an initial spike phase on day 1 followed by a slow-release process for up to 42 days. The Cmax of the extended release phase was observed approximately on day 20 for both dose levels. Pasireotide LAR was also investigated in patients with acromegaly and carcinoid tumors [CSOM230C2110]. Following monthly (q28 days) IM injections of 20, 40, or 60 mg pasireotide LAR, preliminary results showed an approximately linear dose-exposure proportionality and a steady state achieved following 3 injections. The PK exposure to pasireotide at steady state in acromegalic patients was comparable to the simulated PK exposure at steady state in healthy volunteers, whereas, the PK exposure in patients with carcinoid tumors was roughly 2-fold that in acromegalic patients.

1.5.1.2 Phase II studies of pasireotide SQ in neuroendocrine tumors

Preliminary safety data are available from a Phase II study [CSOM230B2202] in 45 patients with symptomatic metastatic carcinoid disease who received pasireotide SQ doses from 300 µg SQ b.i.d. up to 1200 µg b.i.d. for a mean of 20 weeks. Overall pasireotide SQ has been found to be generally well-tolerated by these patients, with the most common adverse events being mild diarrhea, nausea and abdominal pain. Blood glucose increases tended to occur with increasing dose, but were moderate and generally managed easily by adjustment in oral hypoglycemic medications. Weight loss was also observed in 18 patients. Maximum weight loss occurred within 4-6 months on the study drug, with a stabilization of effect after approximately 6 months. There was no apparent relationship between the weight loss and pasireotide dose.

Preliminary efficacy data from this study also support that pasireotide is active in patients refractory/resistant to Sandostatin LAR, as partial or complete symptom control was observed in 12 of 44 patients (27%). Complete response was achieved in two patients at the pasireotide 600 µg SQ b.i.d. dose and one at the 900 µg SQ b.i.d. dose. Nine patients achieved partial response to treatment, three at each of the following doses: 600, 750, and 900 µg SQ b.i.d.

1.5.2 Pasireotide LAR

Most of the experience with pasireotide comes from healthy volunteer and patient studies evaluating the subcutaneous formulation of pasireotide. Pasireotide LAR is being evaluated in two studies, one healthy volunteer study and one study involving patients with acromegaly and carcinoid disease.

1.5.2.1 Pasireotide LAR in healthy volunteers

Preliminary data from the healthy volunteer study found single IM doses of pasireotide LAR, at doses of up to 40 mg and 60 mg, respectively, to be well-tolerated. The most common AEs

were gastrointestinal. Diarrhea was experienced by most of the subjects and was sometimes associated with abdominal pain, flatulence, and/or nausea. The gastrointestinal events were mild or moderate in severity. About 38% of subjects reported mild injection site pain and about 15% reported headaches.

Transient elevations in liver function tests and/or pancreatic enzymes were observed in three subjects, all of which resolved and were not accompanied by any clinical symptoms. Mild increases in fasting blood glucose were observed in some subjects during the pasireotide LAR treatment period. All elevations were asymptomatic, considered not clinically significant, and generally returned to normal within 3-4 weeks after the pasireotide LAR IM injection.

1.5.2.1.1 Serious adverse events

A cumulative search (data lock point 12 Oct 2011) of the Novartis safety database was performed using MedDRA 14.0 on SMQ “Drug related hepatic disorders – comprehensive search.” This search retrieved one serious case of increased liver enzymes which meets Hy’s law criteria in a young female patient with Cushing’s disease who appeared jaundiced and fully recovered upon discontinuation of pasireotide. Nine days after the start of pasireotide the laboratory values were as follows: total bilirubin 94 µmol/l (3.9x ULN), ALP 157 U/L (1.4x ULN), ALT 568 U/L (10.3x ULN), AST 251 U/L (5.6x ULN), and lactate dehydrogenase 300 U/L (1.3x ULN). All liver function tests were within normal limits 45 days after discontinuation of pasireotide. This report was released as an Investigator notification in September 2010, with follow-up Investigator notifications in October 2010 and May 2011 (PHHO2010AU13717).

1.5.2.1.2 Liver safety analysis of studies conducted with pasireotide–phase I-III studies

A review of the unblinded data from the clinical program with the pasireotide LAR formulation did not reveal cases meeting the Hy’s law criteria. Across the clinical development program with pasireotide SQ to date:

654 healthy volunteers have been exposed to pasireotide SQ:

3 (0.5%) met the biochemical criteria of Hy's law (see details above)

16 (2.4%) subjects had an ALT/AST > 3x, < 5x ULN

3 (0.5%) of the subjects had an ALT/AST > 5x ULN

17 (2.6%) subjects had a total bilirubin of 2x ULN (including 7 patients with pre-existing liver disease and elevations of total bilirubin);

156 patients in phase 1 and phase 2 trials have been exposed to pasireotide SQ:

None of the patients met the biochemical criteria of Hy's law

6 (3.8%) patients had an ALT/AST > 3x, < 5x ULN

4 (2.6%) patients had an ALT/AST > 5x ULN

2 (1.3%) patients had a total bilirubin of 2x ULN;

162 patients with Cushing’s disease in phase 3 trials have been exposed to pasireotide SQ:

None of the patients met the biochemical criteria of Hy's law

8 (4.9%) patients had an ALT/AST > 3x, < 5x ULN

1 (0.6%) patients had an ALT/AST > 5x ULN

None of the patients out of 162 with Cushing's disease had a total bilirubin of 2x ULN.

Approximately 200 patients in the compassionate use program have been exposed to pasireotide SQ to date. There was one serious case of a patient with Cushing's disease who met the biochemical criteria for Hy's law. This case (PHHO2010AU13717) is discussed above. (See Investigator Notification for pasireotide [SOM230] October 31, 2011)

Novartis released an Investigator Notification dated 31 Oct 2011 that provided updated information regarding reversible liver chemistry elevations in 3 healthy volunteer subjects meeting the biochemical criteria for Hy's Law in two cases and potentially meeting Hy's Law criteria in one case (missing ALP value and confounding concomitant medication). All three cases were asymptomatic and reversible and the degree of the increase in aminotransferase levels was < 4x ULN. The investigators did not consider the laboratory abnormalities in healthy volunteers as adverse events and consequently did not report them as such.

While Novartis considers the risk-benefit ratio for SOM230 to remain positive, they are implementing the following urgent safety measures by means of this communication to ensure the safety of patients.

For studies with ongoing enrollment using the LAR formulation: Liver function tests (LFTs) must be assessed at screening, baseline, Day 22 after the first injection, Day 29, Day 50, Day 57 and Day 85. After Day 85, monitoring should follow the existing protocol schedule. The Day 22 and Day 50 LFTs must be available and assessed prior to dosing on Day 29 (2nd injection) and Day 57 (3rd LAR injection). For studies with ongoing enrollment using s.c. or LAR formulation: Revised exclusion criteria for LFTs (**Table 1**).

For all ongoing studies: Additional hepatic management (i.e. liver-directed history and physical examination, LFTs, hepatitis screen, abdominal ultrasound, and PK sample) is to be implemented within 72 hours of awareness of abnormal liver function tests. Follow-up LFT monitoring will take place at 3-4 day intervals for all s.c. and LAR studies (**Table 2**).

For all ongoing studies: Additional LFT discontinuation criteria are to be implemented (**Table 7**).

An algorithm of LFT management for all SOM230 s.c. and LAR studies is provided in appendix 4.

1.5.2.2 Pasireotide LAR in PLD patients

Preclinical studies in the PCK rat (a recessive model of polycystic kidney and liver disease) showed that the SST analog octreotide reduces cAMP levels in kidney and bile ducts and slows the progression of hepato-renal cystogenesis.[15] We previously completed a double-blinded, randomized, placebo-controlled clinical trial (NCT00426153) using OctLAR over 1 year in forty-two patients with severe polycystic liver disease (PLD), due to autosomal dominant polycystic liver disease (ADPLD) or autosomal dominant polycystic kidney disease (ADPKD). By magnetic resonance imaging, the mean liver volume decreased from 5907 to 5557 ml (4.95 ±7.00%) in the octreotide group (n = 28) compared with 5374 to 5361 ml (0.92 ±_7.00%) in the placebo group (*n* =14). This difference (mean 4.95 *versus* 0.92%) was significant (*P*= 0.045). The self-reported SF-36 quality of life form demonstrated a significant improvement in perception of body pain and physical function in octreotide-treated patients.[18] Moreover, three separate prospective clinical trials have now shown similar positive effects of SST analogs in ADPLD and ADPKD.[16-19,26] A few other published reports relating to the use of SST analogs further substantiate these observations.[17,26-28] All of these studies were limited by small numbers of enrolled patients with a

short follow-up of 6-12 months. In order to evaluate whether SST analog therapy sustains retardation of liver and kidney growth beyond one year, our protocol design included a second year of open-label active therapy with OctLAR. We completed an open-label extension with OctLAR for 1 additional year, to assess safety & clinical benefits over 2 years (O→O) and examine drug effects in the placebo group who crossed over to OctLAR in year 2 (P→O).[21] The primary endpoint was a change in total liver volume (TLV); secondary endpoints were changes in total kidney volume (TKV), glomerular filtration rate (GFR), quality of life (QOL), safety, vital signs, & lab parameters. Forty-one of 42 patients that received OctLAR (n=28) or placebo (n=14) in year 1 received OctLAR in year 2 (max dose 40 mg). Patients originally randomized to placebo (P→O) showed substantial reduction in TLV after treatment with OctLAR in year 2 (-7.66±9.69%; p= 0.011). The initial reduction of TLV in the OctLAR group (O→O) was maintained for 2 years (-5.96± 8.90%), although it did not change significantly during year 2 (-0.77±6.82%). OctLAR inhibited renal enlargement during year 1 (+0.42±7.61%), but not throughout year 2 in the O→O group (+6.49±7.08%); and in the P→O group in year 2 (-0.41±9.45%). Using pooled analyses of all individuals who received OctLAR for 12 months (n=40; in years 1 & 2), reduction in TLV was -6.08%±7.58% (p=0.001) compared to net growth of 0.9±8.35% in the (P→O) group.

Changes in GFR were similar in both groups. Over 2 years OctLAR significantly reduced the rate of increase in TLV and possibly the rate of increase in TKV. While OctLAR inhibited renal enlargement within the first year of treatment, it appeared to lose effectiveness during year 2. Several reasons may account for the reduction of effect seen in year 2. First, SST receptors may undergo receptor down-regulation / desensitization (probably by endocytosis of the receptor-ligand complexes) after prolonged exposure to OctLAR.[29-31] Second, we did not monitor OctLAR levels in plasma, its metabolism, cAMP concentration, or whether levels of the effectors IGF, GH, or EGF were modulated by therapy. In the pre-clinical animal studies, liver and kidney effects were dose-dependent, therefore higher doses of SST analogs may be required.[15] Third, OctLAR is known to bind to three out of five known SSTs (SST2, SST3 and SST5). At this point, we do not know what SST receptors are present in liver and kidneys of our patients, and how their expression is different from normal hepatic and renal epithelia. Thus, the use of more potent SST analogs (e.g. SOM230, pasireotide) that bind to a broader range of SST receptors might be more efficient (figure 1). This treatment if successful could impact greatly on quality of life and decrease morbidity and mortality related to PLD in these patients. A subset of individuals is incapacitated due to massive PLD and the numbers of patients in this subset are steadily increasing, due to increased lifespan because of dialysis and kidney transplantation. This study will evaluate the effect of SOM230 LAR® on the liver volumes of patients with severe PLD who are not candidates or decline surgical treatments such as liver cyst fenestration, liver resection or liver transplantation and therefore have no further therapeutic options.

1.5.2.2.1 Pre- Clinical Studies with Pasireotide in PLD

Dr. Masyuk (Mayo Clinic) has recently completed comparative studies of octreotide and pasireotide and shown that pasireotide decreased hepatorenal cystic and fibrotic volumes in PCK rats and Pkd2ws25/- mice. She found in all experiments that the effects of pasireotide were significantly greater compared to octreotide – see Tables 2 and 3.[32]

Table 2 Gross anatomy, cystic and fibrotic volumes, in PCK rats

Parameters	Control	OCT	PAS	OCT vs control		PAS vs control		OCT vs PAS	
				p	% change	p	% change	p	% change
Body wt (g):									
Male	430.3±22.9	411.8±8.93	371.6±6.11	NS	-4.3	0.003	-13.6	0.006	-9.8
Female	253.7±6.57	244.0±6.54	232.8±12.86	NS	-3.8	0.05	-8.2	NS	-4.6
Liver wt (g):									
Male	27.20±1.59	23.60±0.83	19.36±1.17	0.02	-13.2	0.003	-27.7	0.001	-16.6
Female	18.63±0.42	16.10±0.71	14.17±0.54	0.05	-13.6	0.009	-23.9	0.05	-12.0
Liver wt (% bw):									
Male	6.32±0.11	5.74±0.18	5.30±0.14	0.01	-9.2	0.002	-16.2	0.02	-7.7
Female	7.35±0.17	6.59±0.18	6.07±0.11	0.03	-10.4	0.003	-17.4	0.04	-7.8
Kidney wt (g):									
Male	6.27±0.16	5.60±0.16	4.82±0.11	0.01	-10.6	0.001	-23.1	0.003	-13.9
Female	4.20±0.17	3.75±0.11	3.33±0.10	0.03	-10.7	0.001	-20.6	0.01	-11.1
Kidney wt (% bw):									
Male	1.47±0.12	1.36±0.09	1.30±0.08	0.01	-6.6	0.001	-11.3	0.05	-5.0
Female	1.66±0.05	1.54±0.08	1.44±0.05	0.008	-7.3	0.04	-12.8	0.006	-5.9
Hepatic cystic volume	12.20±1.67	9.22±1.75	7.11±1.11	0.0001	-24.4	0.0001	-41.7	0.0001	-22.9
Hepatic fibrotic volume	7.55±0.56	6.74±0.34	6.11±0.39	0.05	-10.9	0.002	-19.3	0.05	-9.4
Renal cystic volume	17.23±1.62	13.48±1.33	11.99±1.28	0.0001	-21.7	0.0001	-30.4	0.0001	-11.06
Renal fibrotic volume	2.68±0.11	2.22±0.15	2.07±0.14	0.001	-17.3	0.001	-22.9	0.04	-6.7

In the PCK rat model of PLD, liver weight decreased by 27.7% in males and 23.9% in females and cyst volume decreased by 41.7% compared with controls. Renal cyst volume decreased by 30.4% compared with controls (p 0.0001). In a second animal model Pkd2ws25/- mice (Table 3), liver weight decreased by 26% compared with controls (p=0.05), hepatic cystic areas decreased by 44.1% compared with controls (p=0.0007). Hepatic fibrotic area decreased by 35.6% compared with controls (p=0.0001). Renal cystic area decreased by 35.6% on pasireotide compared to controls (p=0.0001). In primary cultures of normal and rat cholangiocytes, pasireotide was more effective in reducing proliferation of PCK cholangiocytes and growth of normal cholangiocytes (p<0.05, compared with octreotide) and also in reducing cyst growth in primary (3D) cell culture (p<0.05 compared with octreotide) (Figure 1). Therefore these preclinical data provide strong justification for further clinical evaluation of the effects of pasireotide in individuals with polycystic liver and kidney disease.

Table 3 Gross anatomy, cystic and fibrotic volumes, in Pkd2ws25 -/- mice

Parameters	Control	OCT	PAS	OCT vs control		PAS vs control		OCT vs PAS	
				p	% change	p	% change	p	% change
Body wt (g):	31.60±3.57	33.76±2.49	33.92±1.53	NS	6.8	NS	7.3	NS	0.5
Liver wt (g):	3.60±0.47	2.76±0.18	2.65±0.12	0.05	-23.3	0.05	-26.4	NS	-3.9
Liver wt (% bw):	11.57±1.21	8.35±0.73	7.62±0.53	0.02	-27.9	0.01	-34.1	NS	-8.7
Kidney wt (g):	0.65±0.09	0.56±0.04	0.55±0.06	NS	-13.5	NS	-14.2	NS	-0.8
Kidney wt (% bw):	2.08±0.14	1.69±0.11	1.59±0.08	0.03	-18.6	0.008	-23.7	NS	-6.2
Hepatic cystic area	41.55±4.73	29.75±2.53	23.24±1.16	0.03	-28.4	0.0007	-44.1	0.03	-21.9
Hepatic fibrotic area	2.29±0.16	1.77±0.12	1.39±0.09	0.02	-22.5	0.0001	-39.5	0.003	-21.7
Renal cystic area	31.83±2.85	23.69±2.15	20.24±1.99	0.002	-25.6	0.0001	-35.6	0.03	-13.5
Renal fibrotic area	1.49±0.11	1.23±0.04	1.06±0.06	0.0006	-18.0	0.0001	-29.5	0.003	-14.1

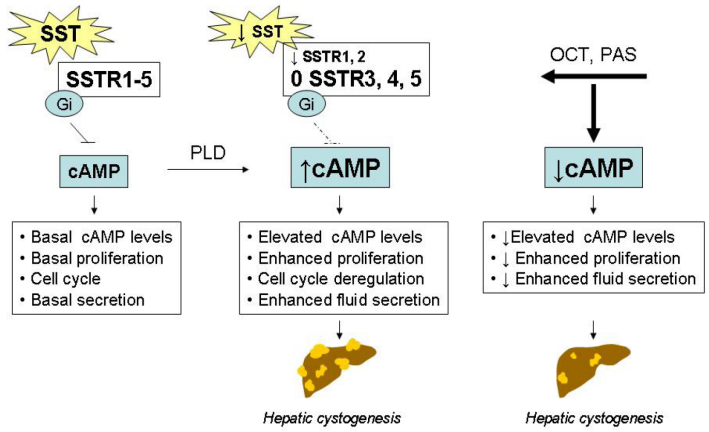

Figure 6 *Role of octreotide (OCT) and Pasireotide (PAS) treatment in hepatic cystogenesis.* Our experimental data suggest that expression of SSTR1, 2 and somatostatin (SST) level are decreased in cystic cholangiocytes that results in cAMP elevation and activation of the cellular processes involved in hepatic cystogenesis. However, the expression of SSTR3, 4 and 5 did not change. Thus, treatment of cystic cholangiocytes with OCT (binds to SSTR2, 3 and 5) or PAS (binds to SSTR1, 2, 3 and 5) should lead to cAMP inhibition and decreased growth of hepatic cysts.

Figure 1: Role of octreotide (OCT) and Pasireotide (PAS) treatment in hepatic cystogenesis. Our experimental data suggest that expression of SSTR1, 2 and somatostatin level are decreased in cystic cholangiocytes that results in cAMP elevation and activation of the cellular processes involved in hepatic cystogenesis. However, the expression of SSTR3, 4 and 5 did not change. Thus, treatment of cystic cholangiocytes with OCT (binds to SSTR2, 3 and 5) or PAS (binds to SSTR1, 2,3 and 5) should lead to cAMP inhibition and decreased growth of hepatic cysts.

2 Study Rationale/Purpose

Pasireotide (SOM230) is a novel multi-receptor-targeted analog that has high affinity for four of the five SST receptor subtypes (SSTr1, SSTr2, SSTr3 and SSTr5);[22 33 33] it has a 40-fold higher affinity and 158-fold higher functional activity for the SST5 receptor than octreotide. Because of its broad receptor binding profile, pasireotide may be more potent in PLD than octreotide. In this randomized double blind placebo controlled trial we will compare SOM230 treatment to placebo for 12 months in patients with PLD. The primary endpoints will be assessed at 12 months and patients receiving placebo then crossed over to SOM230, permitting all participants to receive SOM230 for the subsequent two years. MRI will be used to assess liver volume – the primary endpoint, which will be assessed at baseline, end of years 1 and 3. This study will assess the efficacy and safety of SOM230 in reducing total liver volume and improving quality of life over 12 months (we will not be assessing efficacy at 24 months. The therapy way be effective in PLD but also may prove to be effective for many more patients with PKD which will be evaluated using eGFR and kidney volume using MRI.

2.1 Selection of doses

Patients will be treated with SOM-230 (pasireotide LAR) 60mg IM once every 28 days or placebo year 0-1. All participants will receive pasireotide LAR years 2 and 3. Each cycle is 28 ± 2 days. There will be no dose titration above the 60mg dose but there may be dose reduction to 20mg if patients do not tolerate 60mg or 40mg.

2.2 Placebo dose

The placebo dose will be monitored and adjusted monthly in a similar fashion.

3 Objectives

3.1 Primary objectives

The primary objectives of this study will be to evaluate the absolute and percent changes in liver volume from baseline to month 12 in the treatment arm compared to the placebo arm. We will also evaluate the adverse events throughout the length of the study and as reported at 12 and 36 months of treatment.

3.2 Secondary objectives

Absolute and percent changes in liver volume in the placebo group before (year 1) and after (years 2-3) cross-over to active treatment

Absolute and percent changes in liver volume in the treatment arm during years 2-3 compared to the placebo arm during year 1

Changes in eGFR from baseline (or from month 3) at 12 and 36 months in individuals with ADPKD

Changes in kidney volume from baseline at 12 and 36 months in individuals with ADPKD

Symptoms at baseline,12 and 36 months. Changes in symptoms, measured by SF36-questionnaire QOL-questionnaire

Quality of Life at baseline,12 and 36 months. Changes in quality of life, measured by SF36-questionnaire (SF-36v2™)

Responders at 12 and 36 months.

3.3 Tertiary objective

Longitudinal changes beyond 12 months in above factors, stratified by treatment sequence.

4 Study design

This study will be conducted over 3 years as a randomized, double-blind control, clinical trial through year 1, followed by an open-label extension phase for the subsequent 2 years. Screening and randomization visits will take place at Mayo Clinic and patients will then be followed by Mayo Clinic for three years. We will monitor the patients with blood and urine tests on days 22, 29, 50, 57 and 89 and then at Months 6,9, 12, 15, 18, 24, 27, 30, 33 and 36. Follow up visits will occur at one and three months post last dose of study drug. For patients who received placebo during year one, the labs on days 22,29,50,27 and 85 will be repeated as these are safety labs. All patients will be required to undergo MRI or CT scan imaging at the baseline, 12 month (end

of year 1) and 36 month (end of year 3) visits to fulfill the primary study endpoints. Safety monitoring with ECG, Hemoglobin A1C, liver function and glucose testing will be performed locally at the study sub-sites and monitored centrally by study staff at Mayo Clinic.

Patients will be recruited during visits to the Department of Nephrology and Hypertension

Patients who had participated in previous studies will also be contacted as long as they meet all eligibility criteria. We will also recruit through clinicaltrials.gov (http://clinicaltrials.gov), Mayo Clinic Trials website (http://clinicaltrials.mayo.edu/) and PKD foundation clinical trials (http://www.pkdcure.org/Research/ClinicalTrials/ActiveRecruiting.aspx)listed on the web . Patients who contact the study coordinator will be given information regarding the study and participation. The study coordinator will screen those interested and proceed with the study design for all patients who would like to participate.

4.1 Treatment

Forty-eight patients with severe PLD identified at a single Center, Mayo Clinic, Rochester, MN will be stratified with randomization in a 2:1 allocation to SOM230 or placebo in year 1, in this study. All participants will be offered SOM230 in years 2 and 3. Recruitment of patients is expected to occur relatively rapidly (over the first 6 months) as a result of the Mayo Clinic's large referral base for patients with ADPKD and ADPLD and we have more than 140 patients who wish to be notified if clinical trials with SST analogs for PLD become available.

4.2 Follow-up

Follow up will continue until 3 months after last injection to monitor hemoglobin A1C.

4.3 Treatment extension

No further treatment extension is planned beyond the three years of this protocol.

5 Population

5.1 General criteria

A total of 48 patients (45 + 3 to allow for dropouts) with severe PLD with either autosomal dominant polycystic kidney (ADPKD) or autosomal dominant liver disease (ADPLD) will be enrolled. To enroll a patient, call [redacted]. Study personnel will check patient eligibility and the existence of a signed consent form before treatment is begun.

Limited Travel reimbursement is provided. Costs of tests obtained for the sole purpose of this study will be defrayed from study funds. Costs of tests necessary for patient's usual evaluation and management will be borne by patient and his/her health coverage. Pasireotide-LAR safety data, the absence of other medical treatment modalities for this group of patients, and preliminary experimental and clinical observations justify such a study. Patients must meet all criteria listed below. The investigator or her designee must ensure that all patients who are offered enrollment in the study meet all of the following inclusion and exclusion criteria. This will be a single center study at Mayo Clinic, Rochester, MN.

5.2 Inclusion/exclusion criteria

The investigator or her designee must ensure that all patients who are offered enrollment in the study meet all of the following inclusion and exclusion criteria:

5.2.1 Inclusion criteria

Male or female Age ≥ 18 years.

Diagnosis of PLD associated with ADPKD (meeting the Modified Ravine's criteria)[34] or isolated ADPLD (defined by the criteria described by Reynolds et al)[35].

Severe PLD defined as a liver volume >4000mL or symptomatic disease due to mass effects from hepatic cysts (must be able to undergo MRI or CT scan to determine this).

Not a candidate for or declining surgical intervention.

Capable of providing informed consent.

Life expectancy ≥12 weeks

Patients with a known history of impaired fasting blood glucose (glucose >100 and <126) may be included at the discretion of the PI. These patients should be monitored closely throughout the trial and anti-hyperglycemic treatment adjusted as necessary. Patients that are deemed non eligible due to elevated glucose can be re-screened after adequate medical treatment.

Adequate end organ function as defined by:

Adequate bone marrow function:

- WBC ≥ 2.5 x 10^9/L
- Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
- Platelets ≥ 100 x 10^9/L
- Hb ≥ 9 g/dL

No evidence of significant liver disease:

- Serum bilirubin ≤1.5 x ULN
- INR < 1.3
- ALT and AST ≤ 2 x ULN

Estimated glomerular filtration rate (eGFR) >30 ml/min/m2

Serum amylase and lipase ≤ 1.5 x ULN

Alkaline phosphatase ≤ 2.5 x ULN

Written informed consent obtained prior to any screening procedures

Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures

5.2.2 Exclusion criteria

Patients will be considered ineligible for this study if they meet any of the following criteria:

Patients with a known hypersensitivity to SST analogs or any component of the pasireotide LAR or SQ formulations.

Patients with known malabsorption syndrome, short bowel or chologenic diarrhea not controlled by specific therapeutic means.

Patients with abnormal coagulation (PT or a PTT elevated by 30% above normal limits).

Patients on continuous anticoagulation therapy. Patients who were on anticoagulant therapy must complete a washout period of at least 10 days and have confirmed normal coagulation parameters before study inclusion.

Patients with symptomatic cholelithiasis.

Patients who are not biochemically euthyroid.

Patients with known history of hypothyroidism are eligible if they are on adequate and stable replacement thyroid hormone therapy for at least 3 months.

Serum magnesium ≥ ULN

QT-related exclusion criteria:

QTcF at screening > 470 msec

Patients with a history of syncope or family history of idiopathic sudden death

Patients who have sustained or clinically significant cardiac arrhythmias

Risk factors for Torsades de Pointes such as hypokalemia, hypomagnesemia, cardiac failure, clinically significant/symptomatic bradycardia, or high-grade AV block

Patients with concomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes, or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure

Family history of long QT syndrome

Concomitant medications known to prolong the QT interval.

Potassium < or = to 3.5

Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

Patients who have Uncontrolled diabetes as defined by HbA1c>8%* despite adequate therapy

Patients with the presence of active or suspected acute or chronic uncontrolled infection or with a history of immunodeficiency, including a positive HIV test result (ELISA and Western blot). An HIV test will not be required; however, previous medical history will be reviewed.

Non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with this study treatment.

Liver disease such as cirrhosis, decompensated liver disease, chronic active hepatitis or chronic persistent hepatitis.

Baseline ALT or AST >3x ULN

Patients with life-threatening autoimmune and ischemic disorders.

Uncontrolled hypertension

Patients who have a history of a primary malignancy, with the exception of locally excised non-melanoma skin cancer and carcinoma in situ of uterine cervix. (Patients who have had no evi-

dence of disease from primary cancer for 3 or more years are allowed to participate in the study.)

History of pancreatitis

Patients with a known history of hepatitis B or C

Presence of Hepatitis B surface antigen (HbsAg)

Presence of Hepatitis C antibody (anti-HCV)

Patients with a history of, or current, alcohol misuse/abuse within the past 12 months

Known gallbladder or bile duct disease, acute or chronic pancreatitis

Patients who have any current or prior medical condition that may interfere with the conduct of the study or the evaluation of its results in the opinion of the Investigator or the Sponsor's Medical Monitor

Use of an investigational drug within 1 month prior to dosing

Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study

Females who are pregnant or lactating, or are of childbearing potential (defined as all women physiologically capable of becoming pregnant) and not practicing an effective method of contraception/birth control. Sexually active males must use a condom during intercourse while taking the drug and for 2 months after the last dose of the study drug and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Effective contraception methods include:

Use of oral, injected or implanted hormonal methods of contraception

Placement of an intrauterine device (IUD) or intrauterine system (IUS)

Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

Total abstinence or

Patient sterilization (male or female)

6 Treatment

6.1 Investigational and control drugs

6.1.1 SOM230C / Placebo

Pasireotide LAR (long-acting release) IM depot injection:

Inactive ingredients of pasireotide LAR include: mannitol, carmellose sodium (carboxymethylcellulose sodium), poloxamer 188 and water for injection. Inactive ingredients of pasireotide SQ include: mannitol, tartaric acid, sodium hydroxide and water for injection. For detailed information on pasireotide, please refer to Sections 1.3 and 1.4 of the Pasireotide Investigator Brochure.

Placebo:

The placebo will have an appearance similar to SOM230.

6.1.2 How supplied

Pasireotide LAR IM depot injections will be supplied in open-label packaging by Novartis as a powder in vials containing 20 mg, 40 mg and 60 mg labeled as SOM230 LAR or placebo, with ampoules containing 2mL of vehicle (for reconstitution).

No syringes or needles will be provided with the pasireotide study drug supplies.

The placebo will be supplied (as powder) for mixing with injection solution by Novartis.

6.1.3 Preparation and storage

Prior to reconstitution, vials should be brought to room temperature. Pasireotide LAR should then be prepared as shown in Table 4.

Table 4 Handling and preparation of pasireotide LAR dose

Dose	Volume to be injected
20 mg	1 x 20 mg vial + 2 mL vehicle; whole volume to be injected
40 mg	1 x 40 mg vial + 2 mL vehicle: whole volume to be injected
60 mg	1 x 60 mg vial + 2 mL vehicle; whole volume to be injected

Doses should be prepared and administered immediately after preparation. *For additional details regarding preparation, refer to Appendix 4.*

Novartis will supply pasireotide LAR as long as the patient remains on study, shows continuous benefit from treatment, and there are no safety concerns. Medication labels will comply with the legal requirements of the U.S. and will be printed in English. The storage conditions for pasireotide LAR will be described on the medication label. Bottles must be stored in a safe, secure location.

All study medication will be supplied to Mayo by Novartis. Mayo Research Pharmacy will be responsible for storage of medication. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the investigator must not destroy any drug labels. All unused or damage drug will be sent to ALMAC Clinical Services. The storage condition for the study drug will be described on the medication label.

6.1.4 Administration

Pasireotide LAR/placebo will be administered IM intragluteally, every 4 weeks. The starting dose will be 60 mg. The reconstitution has to be performed just prior to administration of the suspension. A minimal standing time can be tolerated for the reconstituted suspension in the vial. Prior to administration, the reconstituted suspension in the vial should be shaken again before withdrawal in the syringe. The IM injection must be given immediately after withdrawal of the reconstituted suspension from the vial to the syringe.

All dosages prescribed and dispensed to the patient and dose changes during the study must be recorded. The investigational study drugs used in the course of this trial are pasireotide LAR (SOM230C)/ placebo. Novartis will supply pasireotide LAR and placebo free of charge for study participants.

6.2 Treatment arms

There will be stratified randomization for PLD patients with ADPLD and ADPKD (see Table 5):

All participants who receive the placebo during year one will be given the option to continue on study to receive active study drug for years two and three. Thus, all participants will be receiving SOM230 years two and three.

Table 5 Stratified randomization

Disease Group	SOM230	Placebo
ADPLD	8	4
ADPKD	24	12
Total	32	16

The initial assessment will be derived on a clinical basis as some individuals with ADPLD also may have kidney cysts.

6.3 Patient numbering

Randomization numbers will be provided by the study statistician to Research Pharmacy.

The recommended blinding methods are as following: randomization data are kept strictly confidential until the time of treatment un-blinding. This information will not be accessible with the following exceptions: pharmacist, as needed for reconstitution; an independent biostatistician, who will perform the analysis or database lock; the investigator and only immediately relevant study staff after LPLV. The identity of the treatments will be concealed by the use of study treatments that are all identical in packaging, labeling, schedule of administration and appearance after reconstitution. Once the last patient completes LPLV, the database will be cleaned and an interim or final database lock will be placed. Subsequently, the database will be unblinded to the investigator and the sponsor.

6.4 Treatment blinding

Pasireotide LAR/ placebo will be administered IM every 28 ± 2 days in the clinic only by an unblinded study nurse. The current recommended starting doses for pasireotide LAR is 60 mg for NET and 40 mg or 20 mg for acromegaly.

Medication labels for SOM230 LAR and placebo will comply with the US legal requirements. There will be no information about the patient provided on the study drug label.

Study drug, SOM230 /placebo IM depot injections will be supplied by Novartis as a powder in vials containing 20 mg, 40 mg and 60 mg labeled as SOM230 LAR or placebo, with ampoules containing 2mL of vehicle (for reconstitution).

For this blinded study, patients, investigator, site personnel and data analysts will be blinded to the identity of the treatment from the time of randomization until protocol specified schedule of un-blinding. An unblinded pharmacist or a study nurse identified prior to start of the study are to be the only site personnel to reconstitute the study drug.

Un-blinding will only occur in the case of patient emergencies, after LPLV for the investigator only, and after final database lock (at end of year 1, and at end of year 3). Pasireotide LAR is to be stored in a secure locked area while under the responsibility of the investigator. An authorized person at the investigational site must record receipt and dispensation of the study medications. The vials for pasireotide LAR IM depot formulation must be stored at refrigerated temperatures between 2°C and 8°C (36°F-46°F) and protected from light until the time of use. The pasireotide LAR drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. For pasireotide LAR, the reconstitution must be performed just prior to administration of the suspension. Doses should be administered immediately after preparation. For doses higher than 40 mg, contents of 2 or 3 low dosage vials will be combined into one or two injections. Each injection will have maximum volume of 2 ml. A maximum of three vials will be combined per injection and a maximum of 2 injections, at 2 separate injection sites of each patient, will be given to reach the dosing level.

Table 6 Handling and preparation of pasireotide LAR different doses

Dose (mg)	Volume to be injected
20	1 x 20 mg vial +2mL vehicle: whole volume to be injected
40	1 x 40 mg vial + 2mL vehicle: whole volume to be injected
60	**1 x 60 mg vial + 2mL vehicle: whole volume to be injected**

A matching placebo for the pasireotide LAR formulation will be provided by Novartis. Syringes will be concealed by pharmacy to maintain blinding.

6.5 Pasireotide LAR dose adjustment

We will use the oncology dosing (including NETs) as already described above, pasireotide LAR at 60 mg every 28 days being the recommended starting dose for oncological indications If tolerability issues occur, the treatment dose may be reduced to pasireotide LAR at 40 mg with next scheduled injection. Patients requiring a dose reduction can return to the higher dose once the tolerability issue is resolved. However, patients not able to tolerate the minimum pasireotide LAR dose of 20 mg are recommended to be discontinued from study.

All dose changes must be recorded on the Dosage Administration Record CRF. Table 7 outlines the dose reduction steps for pasireotide.

Emergency un-blinding will be done at the discretion of the Principal Investigator [redacted] in cases where she feels it is necessary for the safety of the patient.

6.5.1 Permitted study drug adjustments

Toxicity will be assessed using the NCI-CTC for Adverse Events, version 3.0 (CTCAEv3.0, [http://ctep.cancer.gov/forms/CTCAEv3.pdf]). For patients who are unable to tolerate the protocol-specified SOM230C dosing schedule, dose-adjustment guidelines are given below.

6.6 Pasireotide LAR / placebo dose adjustment

As already described above, pasireotide LAR/placebo at 60 mg every 28 days is the recommended starting dose for oncological indications (including NETs). If tolerability issues occur, the treatment dose may be reduced to pasireotide LAR at 40 mg with next scheduled injection. Patients requiring a dose reduction can return to the higher dose once the tolerability issue is resolved. However, patients not able to tolerate the minimum pasireotide LAR dose of 20 mg are recommended to be discontinued from study.

All dose changes must be recorded on the Dosage Administration Record CRF. Table 7 outlines the dose reduction steps for pasireotide.

Table 7 Guideline for treatment of patients experiencing adverse events

Recommended dose modifications for pasireotide/ placebo	
Worst toxicity CTCAE Grade* (value)	**Recommended dose modification any time during a cycle of therapy**
No toxicity	Maintain dose level
Hematologic	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level • If resolved ≤ 7 days, then maintain dose level • If resolved > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 500/mm^3)	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level • If resolved ≤ 7 days, then maintain dose level • If resolved > 7 days, then ↓ 1 dose level

Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level • If resolved ≤ 7 days, then maintain dose level • If resolved > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then ↓ 1 dose level
Renal	
Serum creatinine	
< 2 x ULN	Maintain dose level
2-3 x ULN	Omit dose until resolved to ≤ Grade 1, then • If resolved ≤ 7 days, then maintain dose level • If resolved > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose and discontinue patient from study treatment
Grade 4 (> 6.0 x ULN)	Omit dose and discontinue patient from study treatment
Hepatic See also section 7.5.4.1	
Bilirubin	
Grade 1 (< 2 x baseline value)	Maintain dose level
Grade 2 (2-3 x baseline value)	Omit dose until resolved to ≤ Grade 1, then • If resolved ≤ 7 days, then maintain dose level • If resolved > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then • If resolved ≤ 7 days, then maintain dose level • If resolved > 7 days, then ↓ 1 dose level
Grade 4 (> 10.0 x ULN)	Omit dose and discontinue patient from study treatment NOTE: If grade 3 or 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator
AST or ALT	
Grade 1 (> ULN - 2.5 x ULN)	Maintain dose level
Grade 2 (> 2.5 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 and ≤ 8x ULN)	For ALT or AST > 5x ULN and ≤ 8x ULN: • Study medication should be temporarily interrupted & liver chemistry monitored every 3-4days until resolution or return to baseline. • If resolution or return to baseline does not occur after 2 weeks, the patient should be discontinued. • If ALT or AST returns to less than 5x ULN, study drug can be resumed and patient can continue study per protocol • If ALT or AST rises above 5x ULN anytime after study drug is resumed, then study drug should be discontinued immediately.
Grade 4 (> 20.0 x ULN)	Omit dose and discontinue patient from study treatment
Pancreatic	
Pancreatitis	
Grade 1	Maintain dose level

Grade 2	Maintain dose level
Grade 3	Omit dose and discontinue patient from study treatment
Grade 4	Omit dose and discontinue patient from study treatment
Amylase and/or lipase	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN)	For asymptomatic: Omit dose until resolved to ≤ Grade 1, then • If resolved ≤ 7 days, then maintain dose level • If resolved > 7 days, then ↓ 1 dose level For symptomatic: Omit dose and discontinue patient from study treatment
Grade 4 (> 5.0 x ULN)	Omit dose and discontinue patient from study treatment A CT scan or other imaging study to assess the pancreas, liver and gallbladder must be performed within 1 week of the first occurrence of any ≥ CTCAE grade 3 of amylase and/or lipase.

Endocrine/metabolic

Fasting plasma glucose (FPS) or 2-hour postprandial capillary glucose (PPG)	
FPG <126 mg/dL or PPG < 140 mg/dL	Maintain dose level
Grade 1 (> ULN – 160 mg/dL)	appendix 2 section 12.2.
Grade 2 (> 160 – 250 mg/dL)	appendix 2 section 12.2.
Grade 3 (> 250 – 500 mg/dL)	appendix 2 section 12.2.
Grade 4 (> 500 mg/dL)	appendix 2 section 12.2.
Cardiac	
Cardiac - prolonged QTc interval	
• QTcF > 480 ms and ≤ 500 ms	If at any time a QTcF > 480 ms and ≤ 500 ms is observed a cardiology consultation must be sought to re-evaluate the abnormal ECG finding.
• QTcF > 500 msec	1. Triplicate ECGs (2-3 minutes apart) need to be taken approximately 1 hour after the initial ECG. 2. If the mean QTcF is > 500 ms, the patient must postpone study treatment until a cardiologist has re-evaluated the ECG. 3. The re-evaluation of ECG needs to be done as soon as practical but within 7 days of the initial abnormal ECG. 4. If the cardiologist confirms a mean QTcF > 500 ms, the patient must be discontinued.
Cardiac general	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Omit dose and discontinue patient from study treatment
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Omit dose and discontinue patient from study treatment

Detailed treatment guidance on QT prolongation, hyperglycemia and diarrhea will be provided as appendices of the protocol

6.7 Concomitant therapy

All medications administered within 4 weeks prior to the administration of study drugs and all concomitant therapy administered during the study, along with the reasons for therapy, will be recorded.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug including all over-the-counter medication. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug CRF.

The patients should also be discouraged from taking over-the-counter medications for diarrhea. The use of prescription medication for diarrhea is also to be avoided while patients are receiving study drug treatment, but exceptions may be made if the medication is to treat an adverse event.

The concomitant medication CRF is to be used as an ongoing log, and must be updated as necessary to reflect all medications taken.

The use of anticoagulant medication should be avoided. Patients currently receiving supplemental pancreatic enzymes may be enrolled, but they should not start such treatment or increase the dose while on study.

The use of concomitant medications that might lead to QT prolongation is prohibited and would require the discontinuation of the patient prior to starting the respective QT prolonging medication. Please check http://www.azcert.org/medical-pros/drug-lists/browse-drug-list.cfm for a list of QT prolonging drugs.

6.8 Study drug discontinuation

Study drug must be discontinued and the subject withdrawn from the trial if the investigator determines that continuing would result in significant safety risk for that subject. The following circumstances require study drug discontinuation:

Pregnancy

The occurrence of an adverse event or of a clinically significant laboratory change or abnormality that, in the judgment of the investigator, warrants discontinuation of treatment.

Subjects who have fasting plasma glucose > 240 mg/dL confirmed by repeat measurement

Any CTC grade 3 or higher abnormalities in hematology or chemistry parameters judged clinically significant by the Investigator

Any confirmed QTcF > 500 ms or confirmed increase of QTcF > 60 ms from baseline

ALT or AST > 3x ULN and Total Bilirubin ≥ 2 x ULN and ALP > 2 x ULN

ALT or AST > 5x ULN and ≤ 8 x ULN persistent for more than 2 weeks

ALT or AST > 8 x ULN

6.9 Premature patient withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. These patients will be asked to complete an Early Termination Visit. Patients may be withdrawn from the study if any of the following occur:

Lack of efficacy

Uncontrolled diabetes mellitus (DM)

Pregnancy

Adverse event(s)

Abnormal laboratory value(s)

Abnormal test procedure result(s)

Protocol violation

Subject withdrew consent

Lost to follow-up

Administrative problems

Death

New therapy for disease being investigated

Disease progression

6.10 Overall Study Stopping Rules

Stopping criteria for hyperglycemia and other side effects, e.g. related to changes in hematology, chemistry, or cardiac test values are **listed in section 6.8**. Pasireotide has already demonstrated acceptable tolerability and efficacy in several completed or ongoing clinical trials (**page 38 Investigator Brochure**) and the LAR formulation is being examined in a phase 3 study for treatment of Acromegaly NCT00600886; Novartis data on file, and for Cushing disease (sc formulation; CSOM230B2305]) recently reported (Colao, Petersenn et al. 2012). In the latter study hyperglycemia-related adverse events occurred in 73% of patients necessitating 6% discontinuing study treatment Plasma glucose levels increased 10% from baseline compared with a 2% increase in placebo ($P<0.02$) after commencing octreotide treatment and no patient developed diabetes in our prior somatostatin analog study using OctLAR.

Gastrointestinal problems are the most commonly reported AEs associated with the use of SOM230, (predominantly mild diarrhea grade 1 or 2, and nausea requiring no treatment or study discontinuation). In our prior somatostatin analog study in PKD, only 1/42 individuals discontinued that study after one year (due to steatorrhea) and none discontinued because they developed diabetes. Based on our prior experience and others' studies of tolerability and side effects associated with OctLAR (and also with lanreotide in PKD and PLD), we do not anticipate there will be patient discontinuation >15%, since both drugs have a similar tolerability profile (**Investigator brochure section 6.2**). Hence, we do not anticipate we will need to stop this study in this patient population due to lack of study power. If there is no efficacy found after the first year analysis is complete then we will terminate the open label extension. We will be monitoring each patient closely (**table 8**) for expected and unexpected drug side effects. If there are any

serious suspected adverse reactions (>1) that were unexpected these would be evaluated by the sponsor-investigator and the risk/benefit of study continuation would be analyzed. Novartis also reserves the right to stop the study (**section 13.1.3**).

• Colao, A., S. Petersenn, et al. (2012). "A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease." New England Journal of Medicine **366**(10): 914-924.

6.11 End of treatment

Treatment duration will be completed per the protocol

7 Visit schedule and assessments

Table 8 lists all of the assessments and indicates the visits at which they are to be performed with an “X”. All data obtained from these assessments must be supported in the patient’s source documentation. In year 2, safety assessments for patient’s crossing over from placebo to SOM 230 will be required. These will be per the same schedule after the first SOM230 injection as was performed in year 1 for all patients enrolled.

Table 8 Visit/Study Procedure Schedule

Test / Procedure	S	R	Days after 1st injection					Months after initial visit										Mos. after end	
			22/2	**29**	50	**57**	85	6	9	12[13]	15	18	21	24	27	30	33	36 / Early Term	1	3
Consent	X																			
History/physical	X							X		X		X		X		X		X		
Height,[1] Weight	X							X		X				X		X		X		
ECG[2]	X	X	X		X		X	X	X	X	X	X	X	X		X		X		
Heme Group[3]	X							X	X	X	X	X	X	X				X		
PT APTT	X							X		X				X				X		
Metabolic panel[4] eGfr[5]	X		X	X	X	X	X	X	X	X	X			X				X		
Hemoglobin A1C[6]	X						X	X	X	X	X	X	X	X	X	X	X	X		X
Thyroid cascade[7]	X							X		X	X	X		X		X		X		
MRI (CT) Scan	X									X								X		
Genotyping	X																			
Cyclosporin level[8]	X				X			X	X	X	X	X		X				X		
Microalbumin	X									X				X				X		
Fasting glucose[9]	X	X	X		X		X	X	X	X	X	X	X	X		X		X	X	
Pregnancy Test[10]	X									X										
QOL SF-36v2TM	X							X		X		X		X		X		X		
SOM230/Placebo[11]		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant meds	X	→	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Gallstone (6 mo)[12]								X				X		X		X				
PK Bloods	X			X			X	X		X										

S= Screening

R = Randomization

1 Height required only at pre-study

2 12 lead ECG & interpretation at screening and ½ hour after first injection. Repeat ECG on 21st day after injection for the first 3 months then every third month. All ECGs are faxed to the Mayo Clinic ECG Core lab.

3 Includes WBC with differential

4 Comprehensive fasting metabolic panel includes: albumin, total bilirubin, calcium, CO_2, (bicarbonate) chloride, creatinine, BUN, potassium, total protein, sodium, AST, ALT, ALP,, and glucose. Liver function tests are assessed at baseline (if baseline LFTs are **done within 7 days of day 1 of treatment** they do not have to be repeated on day 1), day 22 after first injection, day 29, day 50, 57 and 85. After day 85 and the 4th LAR Injection, monitoring should follow the existing protocol schedule. Day 22 & 50 LFTs must be available & assessed prior to dosing on days 29 (2nd injection) and 57 (3rd injection).

5 Only in patients with associated PKD.

6 Hemoglobin A1C is done at baseline and 3 monthly

7 Thyroid function is also acceptable if checked within 30 days of the screening visit

8 Bi-weekly cyclosporin levels will be monitored for the first month in enrolled patients who are on this medication (mail in test)

9 Plasma glucose is required 6 hours after first injection. Monitor FPG or finger stick at baseline and at 21st day of treatment for first 3 months. Monitor FPG or finger stick monthly (or as clinically appropriate), thereafter.

[10] Women of childbearing potential only (urine pregnancy test). If CT scan is needed, a negative pregnancy result will need to be obtained prior to performing the CT. For women of child bearing potential who will be having an MRI – a pregnancy test is not required at month 12.
[11] SOM230/placebo IM injections will be given every 28 days, +/- 2 days.
[12] No gallstone assessment is needed on visits where MRI is performed, as gallstones will be detected on MRI if present.
[13] In year 2, safety assessments for patients crossing over from placebo to SOM 230 will be required. These will be per the same schedule after the first SOM230 injection as was performed in year 1 for all patients enrolled.

At a minimum the following safety evaluations (Table 9) are to be included in all protocols.

Table 9 Core safety evaluation and frequency

Evaluation	Frequency
ECG	Baseline ECG prior to and 30 minutes after the first dose. Repeat ECG on 21st day after injection for the first 3 months Repeat ECG every 3 months thereafter.
Gallstone assessment by CT/MRI is part of the evaluation	Baseline and every 6 months (done by ultrasound, at Mayo outside of baseline 12 and 36 months visits when MRI is performed)
Fasting glucose finger stick	Monitor FPG or finger stick at baseline and at 21st day of treatment for the first 3 months. Monitor FPG or finger stick monthly (or as clinically appropriate), thereafter. Monitor of FPG 4 weeks after the end of the treatment is recommended.
TSH/Free T4	Baseline and at 6 months
HbA1c*	Baseline and every 3 months Monitoring HbA_{1c} 3 months after the end of the treatment is recommended

7.1 Information to be collected on screening failures

Information on all screen failures will be collected and the analysis will be performed for all patients will be included who received at least one dose of the randomized study drug.

7.2 Patient demographics/other baseline characteristics

The ADPKD database at the Mayo Clinic includes 4577 patients. Approximately 500 patients with ADPKD or ADPLD are seen in the PKD Clinic, the Renal Transplant and Hepatobiliary Clinics every year. Mayo Clinic has the largest experience in combined hepatic resection/cyst fenestration for severe PLD. Ten percent of the patients undergoing renal transplantation at the Mayo Clinic in Rochester (~250 patients per year) have ADPKD. Pregnant women, children, prisoners, institutionalized individuals will not be randomized to this study. The proposed consent form is attached to this proposal.

7.3 Treatments

All current medication used to treat diabetes mellitus should be documented

All medications, including over-the-counter medication, taken prior to study drug administration and which continue during the course of the study must be documented

Compliance will be assessed by the investigator and/or study personnel at each visit. Records of study medication used, treatment administered, and intervals between visits will be kept during the study. Drug accountability will be noted. Patients will be asked to return all used medication ampoules at each visit and the end of the study.

7.4 Efficacy

7.4.1 Liver & total kidney volume, hepatic cyst volume, renal cyst volume

7.4.1.1 Primary outcome

The primary outcome is the percent change in liver volume as assessed by MR at baseline, 12 and 36 months follow-up. Patients will also be classified as “responders” if their liver volume decreases, does not change, or increases by <2% over the 12 month study period. The MR techniques for imaging and interpretation of volumetric measurements established in the CRISP study will be employed in the present study, as early results from the CRISP study indicate that this MR protocol will provide an effective means for longitudinal evaluation of liver and kidney volume and of cyst volume and is much more sensitive in detecting cholelithiasis when compared to CT, because CT cannot differentiate between the density of bile in the gallbladder and the more common, non-calcified gallstones. T-2 weighted images on MR can easily demonstrate stark contrast between the bright fluid (bile) in the gallbladder from the dark gallstones which do not have any signal intensity on MRI. The MR Procedure comprises of the following (30 minutes):

1. Since no gadolinium will be used in this study, patients will not have an angiocatheter placed at the time of their MRI. (See exception for patients undergoing CT below.)
2. ECG pads will be placed over the chest. If ECG gating is not available or functioning, it may be replaced with a peripheral pulse gating. Hair may need to be shaved off to place the leads.
3. Subjects will be placed supine on the MR table with their arms to their sides.
4. A phased-array surface coil will be positioned with its center over the liver.
5. Scout scan to locate the scan range of the entire liver.
6. The field-of-view (FOV) should be kept as small as possible (30-35 cm) without producing wrap-around artifacts.
7. Obtain breath-hold coronal Regular T2 scan (SSFSE/HASTE with fat sat) with 9mm fixed slice thickness, usually achievable in a single breath-hold.
8. Obtain breath-hold coronal Regular T2 scan (SSFSE/HASTE with fat sat) of the liver with adjusted slice thickness, 3-9 mm, i.e. the slice thickness best attainable with a single breath-hold (the adjusted slice thickness may not remain the same in a follow-up MR scan if there is a change in the subject's breath-hold capacity or liver size).
9. Repeat the scan over the kidneys with the same slice thickness.

The measurements of liver, kidney and cyst volumes will be performed without knowledge of group assignment using the technology developed for the CRISP study.[36] Liver and kidney vol-

umes will be measured in T1-weighted images with a stereology method and calculated from the set of contiguous images by summing the products of the area measurements and slice thickness. A region-based threshold method will be used to calculate cyst volumes.

In patients who are unable to undergo MRI (e.g. due to claustrophobia) a CT scan of the liver and kidneys will be substituted. CT scans will be performed with or without contrast, depending of renal function. If estimated GFR is greater that 60 iodinated IV contrast will be employed. If renal function is less than 60mls/min, no iodinated contrast will be used. A peripheral IV cannula will be inserted for patients requiring IV contrast and removed immediately after the scan is completed.

7.4.1.2 Secondary efficacy assessments

Absolute and percent changes in liver volume in the placebo group before (year 1) and after (years 2-3) cross-over to active treatment will be assessed base on comparison of baseline volumes as assessed by MRI/CT in each subject. The measurements will be performed in the Biomedical imaging core facility by blinded assessors. Similarly, absolute and percent changes in liver volume will be assessed in the treatment arm during years 2-3 compared to the placebo arm during year 1. Similarly, changes in kidney volume from baseline at 12 and 36 months in individuals with ADPKD will be assessed by MRI.

Changes in eGFR, vital signs, creatinine, liver function tests, APTT, PT, glucose values from baseline (or from month 3) at 12 and 36 months in all individuals and treated as a continuous variable. Data from ADPLD patients will be excluded from the renal outcome sub-analyses.

Measurement of Effect (Subjective Response):

Changes in quality of life at baseline and 12 and 36 months will be measured by SF36-questionnaire QOL-questionnaire (SF-36v2™).

7.4.1.3 Tertiary objectives

We will assess longitudinal changes beyond 12 months in the above factors, stratified by treatment sequence.

7.4.2 Treatment/Follow-up Decisions at Patient Evaluations

Response to treatment will be analyzed by measuring changes in liver volume. The study is intended to provide information after 12 months of treatment. Follow-up decisions will proceed as follows: if the treatment is found to be definitively or possibly effective (reduction in liver volume, no increase or increase < 2% per year), all participants treated with will be offered Pasireotide LAR® Depot treatment for another 24 months. The participants treated with placebo will also be offered at this point treatment with Pasireotide LAR® Depot for 24 months.

7.5 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the regular monitoring of hematology (including glycosylated hemoglobin and coagulation parameters), blood chemistry (including fasting glucose, thyroid function tests), urine for microalbumin, regular monitoring of vital signs, gallbladder by MRI/CT ultrasound, will be recorded from study enrollment until study completion.

Patients with diabetes are to be instructed to check blood glucose levels via a fingerstick several times daily, particularly for the first few days of treatment.

7.5.1 Adverse events

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study drug(s). Please refer to the adverse event section of the protocol for the protocol-specific definitions of study drug and study treatment.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events [CTCAE] version 3.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, or grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment.

Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Electronic Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events CRF. SAEs occurring after signing the Informed Consent are recorded on the Adverse Event CRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4)
2. Its relationship to each study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined as one which:
    - Is fatal or life-threatening
    - Results in persistent or significant disability/incapacity
    - Constitutes a congenital anomaly/birth defect
    - Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
        - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
        - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
        - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see protocol section on Serious Adverse Event reporting.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigator's Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.5.2 Vital signs

Body weight, body temperature, supine blood pressure, and supine pulse rate will be assessed. Height will be noted during the screening/baseline period.

7.5.3 Performance status

SF36 quality of life form and Gastrointestinal Symptom Questionnaire will be used.

7.5.4 Laboratory evaluations

Patients are to fast overnight for 8 hours prior to all biochemistry samples being taken. Blood samples are to be taken in the morning. Water is allowed during this time. Laboratory samples will be analyzed locally at Mayo Clinic. Albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine with calculated eGFR, γ-GT, fasting blood glucose, potassium, total protein, AST, ALT, sodium, urea/BUN. If the total bilirubin concentration is increased above 1.5 times the upper normal limit (UNL), total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

7.5.4.1 Abnormal liver function management:

Perform within 72 hours of awareness of abnormal LFTs:

Perform liver-directed medical history and physical examination (i.e. assess occupational hazards, concomitant medications including OTC meds, intercurrent illness, etc)

Liver chemistry tests: ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is > 2.0x ULN), Alb, PT (INR), ALP, and GGT

Perform hepatitis screen: anti-HAV, IgM (to confirm acute hepatitis A), HbsAg, Anti-HBc, anti-HCV (if positive PCR viral load should be assessed), Anti-HEV, ANA antibodies, anti-smooth muscle anti-bodies, CMV, EBV

Perform abdominal ultrasound (liver and biliary tree)

Liver chemistry tests should be monitored every 3-4 days for LAR studies until resolution or return to baseline status.

For ALT or AST > 5x ULN and ≤ 8x ULN:

- Study medication should be temporarily interrupted and liver chemistry tests monitored **every 3-4 days** until resolution or return to baseline
- If resolution or return to baseline does not occur after 2 weeks, the patient should be discontinued.
- If ALT or AST returns to less than 5x ULN, study drug can be resumed and patient can continue study per protocol
- If ALT or AST rises above 5x ULN anytime after study drug is resumed, then study drug should be discontinued immediately.

Resolution return to baseline does not occur after two weeks the patient should be discontinued

If ALT or AST rises about 5X ULN anytime after study drugs resumed and study drug to be discontinued immediately

Study medication should be discontinued immediately if any of the discontinuation criteria below are met: (see appendix 4)

ALT or AST > 3x ULN and Total Bilirubin ≥ 2x ULN and ALP < 2x ULN

ALT or AST > 5x ULN and ≤ 8x ULN persistent for more than 2 weeks

ALT or AST > 8x ULN

Re-challenge of study medication is prohibited once discontinuation criteria are met.

7.5.4.2 Thyroid function tests

Free T4 and TSH will be assessed prior to enrollment and at 6 months.

7.5.4.3 Urine tests:

Serial spot urine microalbumin measurements will be followed.

7.5.4.4 Hormone assessments

GH, IGF-1 and prolactin (PRL), will not be assessed.

7.5.4.5 Urinalysis

Specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood will be assessed.

7.5.4.6 Pregnancy test

Study drug treatment should be withdrawn in the event of pregnancy. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.5.4.7 Gallbladder Imaging

The gallbladder will be imaged at baseline (by MRI or CT) and repeated 6 monthly until the end of study. Patients with a history of symptomatic cholelithiasis are excluded from participating in the study.

7.5.4.8 Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) and rhythm strip will be performed at baseline and 30 minutes after the first dose one half and 3 monthly for the first year and every 6 months in year 2. Repeat ECG on the 21st day after the injection, then every 3 months thereafter.

If a clinically significant abnormality is detected, the electrocardiogram will be repeated at the discretion of the Investigator until the abnormality has been resolved. *A cardiology consultation must be sought as soon as practical but within 7 days of the initial abnormal ECG and the cardiologist must re-evaluate the ECG (this can be done by the central cardiologist). An echocardiogram may also be required.*

- If a QTcF > 480msec is NOT confirmed, no further action needs to be taken.
- If a QTcF > 480msec is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination, including at least a cardiac auscultation) to assess the patient for cardiovascular risk factors.

7.6 Pharmacokinetics

Blood levels of pasireotide will be done in this protocol.

8 Other Safety Considerations:

The potential risks to patients should be limited to study drug use as no specific change in diet and pharmacologic treatment will be introduced throughout the study, unless deemed clinically appropriate to control blood pressure or limit the signs of renal or liver dysfunction. Antihypertensive treatment will be adjusted in order to maintain a target systolic/diastolic blood pressure <130/80 mm Hg. Blood glucose levels will be carefully monitored during the study and antidiabetic therapy adjusted if indicated. Other medications necessary for medical management or symptomatic treatment, including analgesics, antiemetics, antidiarrheals, and thyroxine, will be administered as clinically indicated. Claustrophobic patients will be provided a standing order of oral lorazepam 1mg 45 minutes before their MRI according to the standard Mayo Radiology Department Protocol.

The NCI common toxicity criteria 3.0 will be used to classify adverse events (both patient and event counts) by organ system (neuro, GI, etc.), individually, by severity and, for each severity, by investigator-assessed relationship to study drug. Fisher's exact test will be used to compare treatment groups (placebo, SOM230) regarding adverse events during year 1. Patients who received at least one dose of the randomized study drug will be included. Adverse events in years 2 and 3 (all subjects on SOM230) will be reported separately. A data safety committee will meet **every six months** (comprising of two physicians; [redacted]). The committee will meet with the study coordinator and PI and review safety labs and monitoring and study conduct.

8.1.1.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions / diseases present before starting the study drug are only considered AEs if they worsen after starting the study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- the severity grade (mild, moderate, severe) or (grade 1-4)
- its relationship to the study drug(s) (suspected/not suspected)
- its duration (start and end dates or if continuing at final exam)
- action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.1.1.1 Serious adverse events

Information about all serious adverse events will be collected and recorded. To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity

- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

8.1.2 Novartis instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Integrated Medical Safety (IMS).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by **FAX** [redacted]), to Novartis Pharmaceuticals IMS Department within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 1 working day.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

8.1.2.1 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

9 Protocol amendments, or changes in study conduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials,
2. minor changes in the packaging or labeling of study drug.

10 Data management

10.1 Data collection

Every patient will have a study folder containing source documents, report forms; original signed consent, and stored in a locked area in the study coordinator's office [redacted] Serial data entry recording the information required by the protocol from initial and subsequent visits will be entered on SDMS spreadsheets, and maintained on a password protected Nephrology secure server. Statistical methods

10.2 Statistical methods

Demographics and laboratory data will be plotted (e.g. box plots) and summarized by treatment group. Frequency distributions will be used to describe categorical values and basic summary statistics (mean, standard deviation, median, and inter-quartile range) used to describe continuous values. All tests will be two-sided with alpha level 0.05. For quantitative endpoints (e.g. change in kidney and liver volumes, renal function, and SF-36 scales) the two-group independent samples t-test will be used to test for an effect of treatment. Should the assumptions of normality and equality of variances be untenable, we will consider a data transformation or use of the Wilcoxon rank sum test. Both point estimates (mean) and 95% confidence intervals will be used to summarize treatment effects. For qualitative endpoints (e.g. presence or absence of response) we will compare treatment groups using the chi-square or Fisher's exact test as appropriate.

Efficacy (Liver & kidney): The primary analysis of treatment efficacy will follow intent-to-treat principles, attempting to include all randomized patients. For the primary endpoint (change in

liver volume) we will not be able to include anyone without a 12 month MRI (kidney volumes will be handled in the same way). For the "response" endpoints, those without a 12 month MRI will be included in the analysis as non-responders. Secondary analysis – Efficacy (QOL): We will have up to 5 longitudinal assessments of QOL for each patient. Repeated measures analysis of variance will be used to compare mean QOL profiles over time between treatment groups. Also, within patient rates of change or slopes in QOL measures will be estimated (using simple linear regression) and compared between groups using the two-sample t-test.

Secondary analysis–Kidney volume will be measured as part of the efficacy analysis: AEs (both patient and event counts) will be tabulated by organ system (neuro, GI, etc.), individually, by severity and, for each severity, by investigator-assessed relationship to study drug. Fisher's exact test will be used to compare treatment groups regarding adverse events. Patients who received at least one dose of the randomized study drug will be included.

Statistical power: The primary endpoint is one year percentage change in liver volume. Prior data in untreated patients suggest a growth rate (SD) of 5(±3) % per year[4,37]. We have planned a 2:1 randomization in order to allow as many patients as possible to receive SOM230. The goal is to detect up to a 7.3% percentage point decrease in the mean cyst growth using SOM230 LAR® Depot. With **15 placebo and 30** SOM230 patients, the study will have 80% power (alpha=.05, two-sided) to detect a 7 percentage point difference. To allow for dropouts (1 placebo and 2 SOM230 patients without endpoint data); the study will randomize 16 placebo and 32 SOM230 patients. For any quantitative endpoint the study is powered to detect a difference in treatment means of at least one standard deviation. Secondary endpoints include comparison of responder rates (based on liver and renal growth) and adverse event rates between the two groups. With 16 and 32 patients, a true placebo response (or adverse event rate) of 8 % (1 of 13) vs. 30, 40, or 50% for SOM230 can be detected with 45%, 70%, and 88% power, respectively.

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12 Appendices

12.1 Appendix 1 Guidance for diarrhea management

General recommendations:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (Metamucil, Procter & Gamble), and stool softeners (docusate sodium; Colace, Roberts)
- Drink 8 to 10 large glasses of clear liquids per day (water, Pedialyte (Ross),Gatorade (Quaker), broth)
- Eat frequent small meals (bananas, rice, applesauce, Ensure, toast)
- Stop high-osmolar food supplements such as Ensure Plus and Jevity Plus (with fiber)

It is recommended that patients be provided loperamide tablets. It is mandatory that patients are instructed on the use of loperamide in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide (initial administration of 4mg, then 2mg every 4 hours -maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided during each office visit and the site should ensure that the patient understood the instruction. At the beginning of treatment, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the site should question the patient regarding the actions taken for these symptoms.

Treatment of diarrhea grade 1 or 2

Diarrhea grade 1 or 2 will be treated with standard loperamide (initial at first administration 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) or after each unformed stool).

12-24 hours later:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12-hours diarrhea-free interval

Diarrhea unresolved

Persisting diarrhea grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of patients condition to rule out dehydration, sepsis, ileus) medical check and selected workup if patient does not need hospitalization (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response to antidiarrheal treatment.

Persisting diarrhea grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours) and addition of opium tincture or dihydrocodeine tartrate tab-

lets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe patient for response.

After 24 hours:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12-hours diarrhea-free interval

Diarrhea unresolved

- If diarrhea still persisting (NCI CTC grades 1 and 2), after 2x 24 hours with high dose loperamide and opiates then admit to hospital and employ measures as for grade 3 and 4 until diarrhea resolved
- If diarrhea still persisting and progressed to NCI grades 3 and 4, employ measures described below.

Treatment of diarrhea grade 3 or 4

Severe diarrhea grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response.

After 24 hours:

- If diarrhea persisting administer SQ Sandostatin/octreotide (100-500 µg tid)
- Continue IV fluids and antibiotics as needed
- If diarrhea grade 3 or 4 still persists patients should receive opium tincture or dihydrocodeine tartrate injections SQ or IM
- If diarrhea grade 3 or 4 is still persisting SQ Sandostatin/octreotide (500-1000 µg tid) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.

Diarrhea workup

Perform appropriate tests (Fine and Schiller 1999).

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood

- Fecal leukocytes (Wright's staining and microscopy) or
- Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed patients), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic examinations

Endoscopic examinations may be considered **only if absolutely necessary**. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

12.2 Appendix 2 Guidance for hyperglycemia management

Hyperglycemia is known to be associated with the treatment with SST analogs. Clinical studies of pasireotide in healthy volunteers and in patients with Cushing's disease, acromegaly or carcinoid syndrome have reported transient, asymptomatic increases in fasting and postprandial glucose levels. Novartis has conducted 2 clinical studies ([SOM230B2216] and [SOM230B2124]) to further understand the mechanism of pasireotide-induced hyperglycemia and to evaluate the clinical utility of anti-diabetes agents in the management of pasireotide-induced hyperglycemia. Preliminary results suggest that pasireotide induces insulin suppression, particularly in the postprandial period, as being the key mechanistic driver of hyperglycemia. Based on the mechanisms of pasireotide-induced hyperglycemia and findings from the [SOM230B2124] study, appropriate management for the pasireotide-induced hyperglycemia includes the use of oral anti-diabetic agents for mild to moderate hyperglycemia, such as incretin enhancers (e.g. GLP-1analogs or DPP4 inhibitors or insulin secretagogues). Metformin is not recommended. Insulin should be used for moderate to severe hyperglycemia. Clinical monitoring and self-monitoring of blood glucose level

Finger -stick measurements:

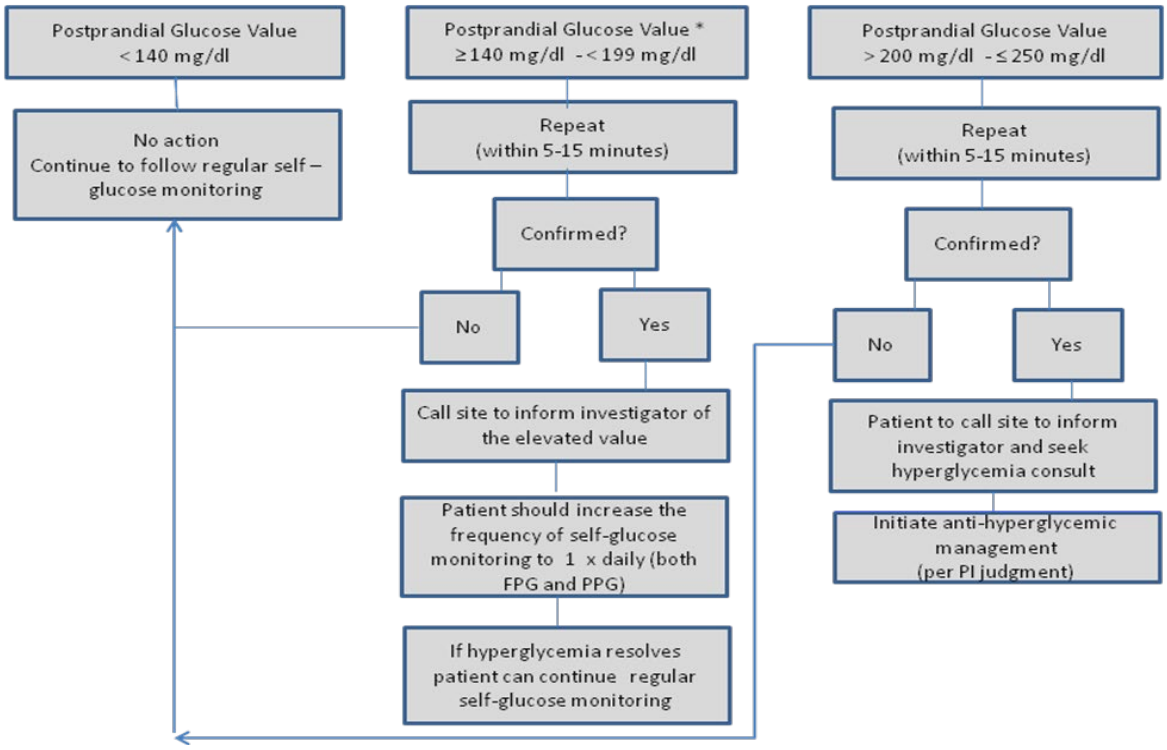
Fasting assessment: Patients will have these checked during follow up assessments.

The glucose values from the will be recorded and sent to Mayo Clinic. At screening all patients should be informed of the signs/symptoms of hyperglycemia and educated on how to complete the patient glucose diary. The glucose values do not need to be entered into the database and should only be kept as source documentation.

The below algorithm has been created as a general guidance tool on the management of pasireotide-induced hyperglycemia during this study. The choice of therapeutic agent is primarily at the discretion of the treating physician. It is encouraged to follow the established guidelines from the ADA/EASD for the management of diabetes and consider a consultation with a diabetes expert as needed anytime during the study.

Postprandial Plasma Glucose Criteria

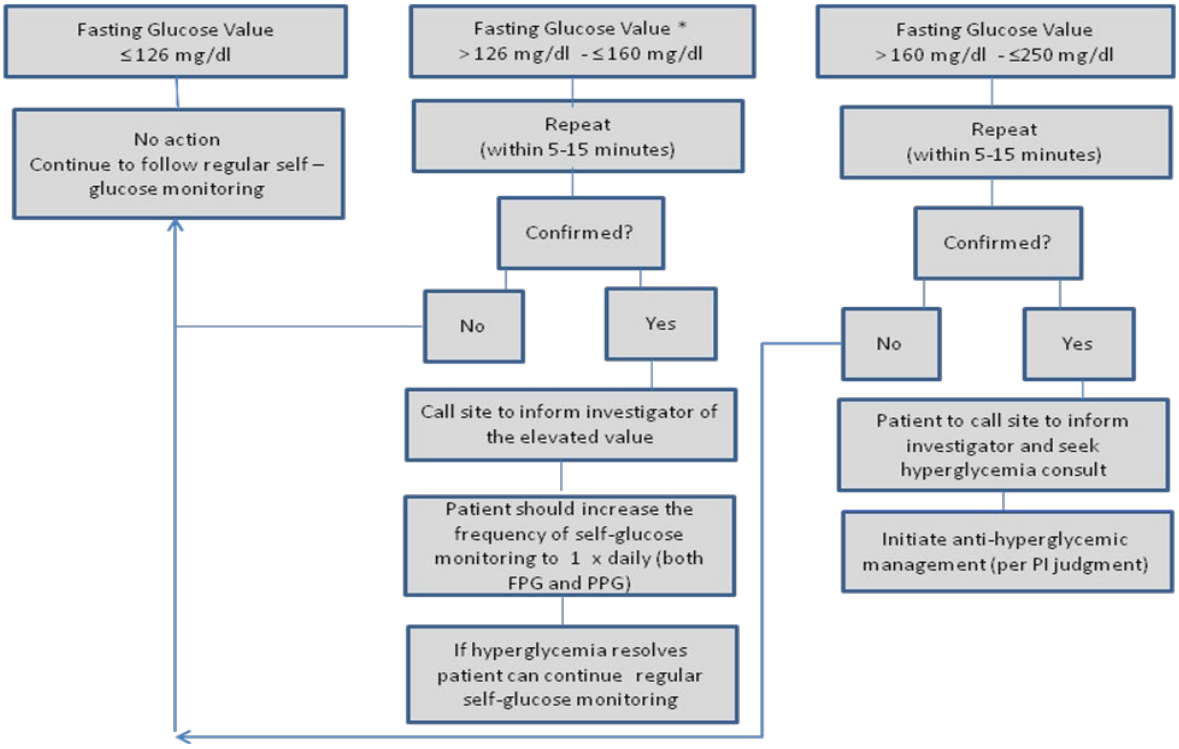
The patient should be instructed on the steps to take in the event a glucose value is elevated. The below criteria is recommended:



* Value confirmed on 2 separate occasions during the observation period.

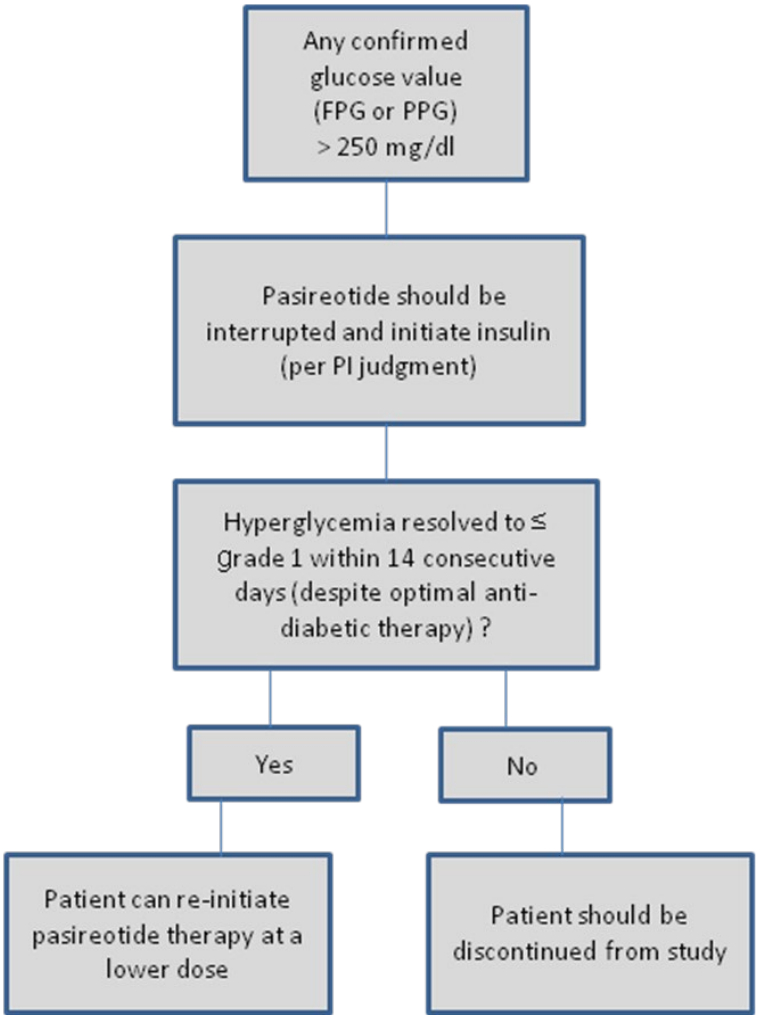
Fasting Plasma Glucose Criteria

The patient should be instructed on the steps to take in the event a glucose value is elevated.



* Value confirmed on 2 separate occasions during the observation period.

Fasting plasma glucose or postprandial plasma glucose > 250 mg/dL (≥ CTCAE grade 3)



12.3 Appendix 3 Guideline for the treatment of QT prolongation

QT-related cardiology consultation/Holter monitoring

If at any visit a QTcF > 500msec is observed, triplicate ECGs, each 2-3 minutes apart, need to be taken approximately 1 hour after the initial ECG. The mean QTcF from the triplicate ECGs will be determined. If the mean QTcF is > 500msec, the patient has to interrupt (SQ treatment)/ postpone (LAR treatment) study treatment until a cardiologist has re-evaluated the ECG (this will be done by the central cardiologist). The re-evaluation needs to be done as soon as practical but within 7 days of the initial abnormal ECG. If the cardiologist confirms a mean QTcF > 500msec, the patient has to discontinue. Otherwise and if the cardiologist confirms that at least one ECG shows a QTcF > 480msec, the cardiac assessments described for a confirmed QTcF > 480msec need to be followed.

If at any visit a 480msec < QTcF/mean QTcF ≤ 500msec is observed, the following steps need to be taken:

A cardiology consultation must be sought as soon as practical but within 7 days of the initial abnormal ECG and the cardiologist must re-evaluate the ECG (this can be done by the central cardiologist if the trial has one).

If a QTcF > 480msec is NOT confirmed, no further action needs to be taken.

If a QTcF > 480msec is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination, including at least a cardiac auscultation) to assess the patient for cardiovascular risk factors.

- If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient needs to be discontinued immediately (discontinuation criteria to be followed).
- If following the examination by the cardiologist, the investigator considers that there is not an acute cardiovascular safety risk and that the patient could continue to receive study medication, a Holter ECG (24hr or 48hr depending on the study) must be recorded soon as practical but within 7 days after the initial abnormal ECG / at the next pasireotide/octreotide LAR injection (for studies using LAR). The Holter-ECG must be started 30min prior to an injection of study medication.

The results of the ECGs, cardiac examination, Holter-ECGs and the recommendation by the cardiologist must be evaluated by the investigator to determine whether the patient should continue in the trial or not (discontinuation criteria to be followed).

QT-related discontinuation criteria

- Confirmed QTcF >480msec and discontinuation recommended by a cardiologist
- Mean QTcF > 500 msec measured by triplicate ECGs
- Significant arrhythmia findings from Holter monitoring such as:
  1. Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic compromise
  2. Sustained ventricular tachycardia (>30 sec) irrespective of symptoms
  3. Recurrent non-sustained VT (≥ 3 beats) during any 24-hour monitoring period
  4. Torsades de Pointes (TdP)
  5. Cardiac arrest
  6. Pause >5 seconds
  7. Second or third degree AV block
- New occurrence of clinically significant/symptomatic bradycardia
- Increased risk of QT prolongation by use of QT prolonging medication
- Hypokalemia (<3.5 mmol/L) or hypomagnesaemia (<0.7 mmol/L) confirmed by repeat testing that is either a new finding or accompanied by vomiting or diarrhea and not corrected by treatment

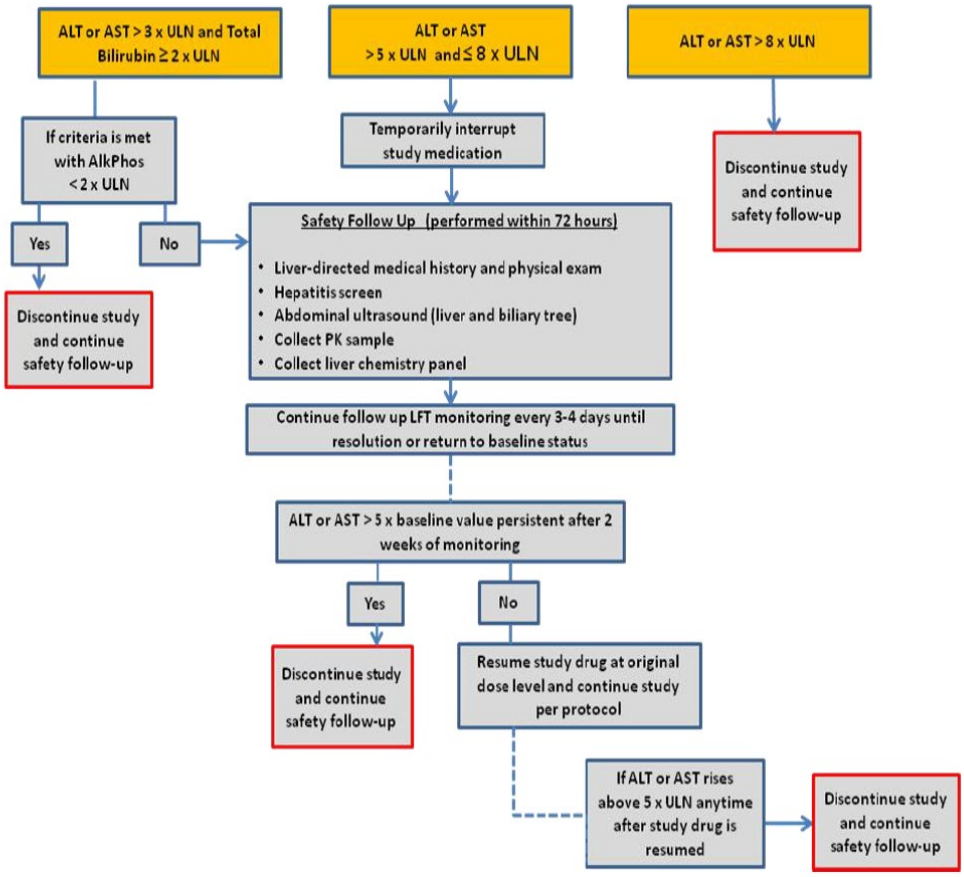
QT prolonging medication

The following drugs are generally recognized to have an association with QT prolongation. This list is not considered to be all inclusive and any questions regarding the QT prolongation potential should be discussed with the Novartis Medical Monitor.

Drugs that are generally accepted by the QTdrugs.org Advisory Board of the Arizona CERT to have a risk of causing torsade de pointes are listed below.

Generic Name	Brand Name	Class
Bepridil	Vascor®	Anti-anginal / heart pain
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal heart rhythm
Procainamide	Procan®	Anti-arrhythmic / abnormal heart rhythm
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm
Clarithromycin	Biaxin®	Antibiotic / bacterial infection
Sparfloxacin	Zagam®	Antibiotic / bacterial infection
Erythromycin	Erythrocin®	Antibiotic;GI stimulant / bacterial infection; increase GI motility
Erythromycin	E.E.S.®	Antibiotic;GI stimulant / bacterial infection; increase GI motility
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia
Astemizole	Hismanal®	Antihistamine / Allergic rhinitis
Terfenadine	Seldane®	Antihistamine / Allergic rhinitis
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia
Chloroquine	Aralen®	Anti-malarial / malaria infection
Halofantrine	Halfan®	Anti-malarial / malaria infection
Domperidone	Motilium®	Anti-nausea / nausea
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia
Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation
Pimozide	Orap®	Anti-psychotic / Tourette's tics
Chlorpromazine	Thorazine®	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea
Cisapride	Propulsid®	GI stimulant / heartburn
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence
Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence
Droperidol	Inapsine®	Sedative;Anti-nausea / anesthesia adjunct, nausea

12.4 Appendix 4 SOM230 LFT Management Algorithm (s.c. and LAR Studies)



Revised SOM230 Abnormal liver function discontinuation criteria:

Hepatic-related discontinuation criteria for all ongoing studies
Study medication should be discontinued immediately if any of the discontinuation criteria below are met: • ALT or AST > 3x ULN and Total Bilirubin ≥ 2x ULN and ALP < 2x ULN • ALT or AST > 5x ULN and ≤ 8x ULN persistent for more than 2 weeks • ALT or AST > 8x ULN Re-challenge of study medication is prohibited once discontinuation criteria are met.

13 Procedures and instructions

13.1.1 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority

shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

13.1.2 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

13.1.3 Discontinuation of study

Novartis reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

13.2 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Novartis standard operating procedures and:

ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

13.2.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board / Independent Ethics Committee / Research Ethics Board (IRB / IEC / REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Any amendments to the protocol, other than administrative ones, must be reviewed by Novartis approved by this committee.

13.2.2 Informed consent

We will explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign

the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

13.2.3 Declaration of Helsinki

We will conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.