AN OBSERVATIONAL, MULTICENTRE, OPEN LABEL, NON INTERVENTIONAL PROGRAMME TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF SOMATULINE® AUTOGEL® IN THE TREATMENT OF ACROMEGALY WHEN ADMINISTERED BY PATIENTS OR THEIR PARTNERS ("HOME INJECTION GROUP") OR ADMINISTERED BY HEALTHCARE PROFESSIONALS.

STUDY PROTOCOL
STUDY number A-9B-52030-219
Somatuline Autogel

Protocol Version 1.0: 31st July 2008

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PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the [protocol number] "An observational, multicentre, open label, non interventional programme to assess the long-term safety and efficacy of Somatuline® Autogel® in the treatment of acromegaly when administered by patients or their partners ("Home Injection Group") or administered by Healthcare Professionals."

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (ICH-GCP)[1], local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: SIGNATURE:

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SYNOPSIS

Study Title:	An Observational, Multicentre, Open label, Post-Marketing Surveillance Programme to assess the long-term safety and efficacy of Somatuline® Autogel® in the treatment of acromegaly when administered by patients or their partners ("Home Injection Group") or administered by Healthcare Professionals.
Study Objectives:	**Primary Objective:** To assess the safety and local tolerability of the long-term use of Somatuline Autogel when administered by patients or their partners ("Home Injection Group") and the safety and local tolerability in patients receiving their injection from a healthcare professional (HCP) ("Reference Group"). **Secondary Objectives:** To assess the efficacy of the long-term use of Somatuline Autogel in both groups. To evaluate the training requirements for patients / partners to perform home injection of Somatuline Autogel. To evaluate the acceptability of home injections to patients, partners and healthcare professionals.
Phase of Trial:	Observational Post Marketing Surveillance (PMS) study.
Study Design:	This is an observational (non-interventional), post-marketing surveillance programme. Enrolled patients will have a diagnosis of acromegaly and will have been established on a stable dose of Somatuline Autogel for at least 4 months before entering the programme. The dose and interval between injections will have been determined by the treating clinician in accordance with usual clinical practice. Patients enrolled in this PMS programme may receive their injections from a HCP, or by home injection. Patients receiving home injections will enter the "Home Injection Group". Patients receiving their injections from a Healthcare Professional (HCP) will form a "Reference Group". Whether patients do or do not commence home injection of Somatuline Autogel, this decision will be taken prior to and independently from the decision to enrol the patient in this PMS programme. The number of patients enrolled into each group is not mandated. Patients will be asked to provide written informed consent to have their data included in the PMS programme database and any subsequent analyses. Patients who do not consent to have their data included in the PMS database would continue to receive their injections (from a HCP or by home injection) in accordance with usual clinical practice. Patients choosing to begin home injections of Somatuline Autogel

	will require prior training on the injection technique. If the patient's partner will be administering the injections he/she will also need to attend this training. It is recommended that initially the injection technique is explained and demonstrated by a HCP using existing training materials, with the subsequent injection being administered by the patient / partner under the guidance of a HCP. This step can be repeated for further injections until the patient / partner and HCP are confident that the injection can be administered correctly. Data from these training session(s) will be collected in the PMS database. If available, retrospective data will be recorded for patients already performing home injections. Materials to provide support with self injection are provided by Ipsen as part of usual information delivered to HCP and this can be used as required. Patients should be provided with an injection record card specifying their scheduled injection dates. The card will include space for the patient to confirm the details of the injections administered, and any comments that they may have. Patients will be treated in accordance with usual medical practice during their participation in this programme. No additional assessments or tests will be required. Relevant data collected as part of routine medical care will be captured on an electronic Case Report Form (eCRF). This data will be transmitted to the sponsor for analysis. Data transmitted will be anonymous and will be identified by a patient number and the patient's initials. The data to be recorded in the eCRF will include: • Confirmation that informed consent has been collected. • Demographic details (date of birth, sex, ethnic origin, employment status, distance and appointment time from a patient's home to their usual place of Somatuline Autogel administration). • Relevant medical history. • Details of acromegaly including diagnostic tests performed and diagnosis. • Previous and current medications / therapies / surgery for acromegaly (including dose of Somatuline Autogel, date of initiation of Somatuline Autogel, and details of any previous dose adjustments). • Details of any concomitant medications / therapies / surgical procedures. • Details of any other medications / therapies / surgery administered for acromegaly during the patient's participation in the PMS programme. • Usual geographic location for administration of Somatuline Autogel injections. • Details of injection training given including the number of

	sessions required, the type of training session (HCP demonstration / supervised injection), the duration of the session, the outcome of the session (patient / partner qualified or not-qualified to perform home injections). • Details of who will administer the injections. • Somatuline Autogel injection details (including; scheduled and actual dates of administration, dose administered, site of administration, local tolerability issues, and other issues with injections). • Related Adverse Events. • Growth Hormone (GH). • Insulin-like Growth Factor-1 (IGF-1). • Tumour size (if known). • Relevant routine assessment results (for example; glucose tolerance tests, vital signs (heart rate (HR), blood pressure (BP), weight, height), visual field assessments). • Imaging results, including liver, gall or bladder ultrasound. • Reasons for discontinuation from the PMS programme. As this is an observational PMS programme no recruitment targets have been mandated. It is anticipated that approximately 30 patients will be enrolled within the 2 year recruitment period, and will remain in the PMS programme for at least 2 years.
Study Population:	Approximately 30 patients who are established on treatment with Somatuline Autogel for acromegaly. The precise patient numbers is not specified. All eligible patients at participating centres can enrol in this PMS programme if both they and the clinical staff are willing to do so. Patients **MUST** satisfy all of the following entry criteria in order to be enrolled in this PMS programme. **Inclusion Criteria:** For all patients: • The patient must give written (personally signed and dated) informed consent for their data to be included in the database for this PMS programme and any subsequent analysis. • The patient must have been receiving treatment with Somatuline Autogel at a stable dose for at least 4 months. • The patient must have a diagnosis of acromegaly. • The patient must be at least 18 years of age. For patients receiving or intending to receive Somatuline Autogel by home injection: • The patient must be able to store Somatuline Autogel safely in a refrigerator in their own home and either collect it from their GP/Pharmacy on a monthly basis, or receive the medication by a home delivery service.

	Exclusion Criteria: For all patients: • The patient is pregnant or breast-feeding, unless continued treatment with Somatuline Autogel is clearly needed (as determined by the treating clinician).
Study Treatment:	**Study product:** Somatuline Autogel
	Somatuline Autogel (lanreotide as acetate) is supplied as a white to off-white, translucent and viscous supersaturated solution in a pre-filled syringe, ready for use. Somatuline Autogel should be injected via the deep sub-cutaneous route in the superior external quadrant of the buttock or via deep sub-cutaneous route in the upper outer thigh. The injection may be given by a HCP or by an appropriately trained friend or relative of the patient. Patients who are well motivated and have received appropriate training may self administer the product. Regardless of the site of injection, the skin should be stretched. The needle should be inserted rapidly to its full length, perpendicularly to the skin. Injections should be administered alternating the left and right side. Somatuline Autogel is available in three doses; 60, 90 or 120 mg. Injections are generally administered every 28 days, though the 120mg may be given at up to 56 day intervals for well controlled patients. The dose and frequency of administration will be determined by the treating clinician in accordance with usual medical practice.
	Comparative Compound:
	No comparative compound will be administered; however the programme will have a comparative group. Patients enrolled in the comparative group will also receive Somatuline Autogel 60, 90, or 120 mg, but all of their injections will be administered by their usual healthcare professional.
Study Endpoints and Evaluations:	**Endpoints:** As this is an observational PMS programme, the nature and timing of patient's assessments will not be standardised. Cut-off points will therefore be applied to the data for each patient at 6 month intervals, relative to the date of the patient's enrolment in the PMS programme. Safety, tolerability and efficacy data collected during each 6 month period will be grouped and considered as one assessment time point.
	Safety Evaluations: The following data will be evaluated in order to assess the long-term safety of Somatuline Autogel when administered by home injection, in comparison to administration by a HCP:

	• Incidence of adverse events (AEs) considered to be related to Somatuline Autogel in both groups. • Incidence of serious adverse events (SAEs) considered to be related to Somatuline Autogel in both groups. • Concomitant medications / therapies / surgical procedures. • Other assessment results where available including; liver and gall bladder ultrasound, vital signs (heart rate (HR), blood pressure (BP), weight, height), in both groups. The incidence of safety issues (related AEs) during each 6 month reporting period, (as well as cumulative listings) will be described for the two groups, split by dose and injection frequency as needed.
	Tolerability Evaluations: The incidence of local tolerability issues identified through patient reported comments in the home injection group compared with the reference group will be evaluated.
	Efficacy Evaluations: The long-term efficacy of Somatuline Autogel when administered by home injection will be compared to the efficacy following administration by a HCP. The following efficacy parameters will be analysed where sufficient data is available: • GH Plasma levels. • IGF-1 Plasma levels • Tumour size
	Training Evaluations: For patients switching to home injection during this observational programme the site will be asked to document the amount and type of training required for the home injection of Somatuline Autogel. For patients who are already home injecting, retrospective data will be collected where available. The following parameters will be evaluated. • Number of training sessions required. • Nature of training sessions required (e.g. HCP demonstration of injection technique, patient / partner supervised injection). • Supportive material or documentation used. • Length of training sessions. • Outcome of training session (patient / partner qualified or not qualified to perform home injections).
	Acceptability Evaluations: The acceptability of home injection of Somatuline Autogel will be compared to HCP injection by evaluating the following: • The proportion of patients / partners who successfully qualify to perform home injections (of those who receive at least one training session). • The proportion of patients who discontinue home injection after successfully qualifying to perform them.

	• Treatment compliance (missed injections and deviations between scheduled and actual injection dates). • Any other issues with administration of injections.
Statistical Methods:	As this is an observational programme no formal statistical analysis will be performed, and therefore no sample size calculation has been conducted. All data will be summarised descriptively by administration group and/or by dose and injection interval as appropriate.

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADRAC	Adverse Drug Reaction Advisory Committee
AE	Adverse Event/Experience
CA	Competent Authority
Clinic	The geographic location where the patient would, in normal clinical practice, receive their Somatuline Autogel injections.
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETV	Early Termination Visit
GCP	Good Clinical Practice
GH	Growth Hormone
GHRH	Growth Hormone Releasing Hormone
GMP	Good Manufacturing Practices
HbA1c	Glycosylated Haemoglobin
HCP	Health Care Professional
i.m.	Intramuscular
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor-1
ITT	Intention to Treat (study population)
OGTT	Oral Glucose Tolerance Test
Partner	Any person who the patient trusts and deems responsible enough to administer their injections, including parents, spouse, son/daughter, any other relative, friend or neighbour.
PP	Per Protocol (study population)
PMS	Post Marketing Surveillance
s.c	Subcutaneous
SAE	Serious Adverse Event/Experience
TGA	Therapeutic Goods Association

2 INTRODUCTION

2.1 Disease Review

Acromegaly is a chronic disease caused by excessive secretion of growth hormone (GH). Increased plasma levels of GH cause the symptoms and pathology of the disease, either directly through actions on target tissues, or indirectly by stimulating excess secretion of Insulin-like Growth Factor-1 (IGF-1). The disease develops insidiously causing a gradual progression of symptoms; most patients are diagnosed in their fourth decade of life [2]. More than 90% of cases result from a benign primary pituitary adenoma.

The conventional first-line treatment of acromegaly is surgical excision (adenomectomy) sometimes followed by pituitary radiotherapy. Despite these therapies, acromegaly remains active in over 50% of patients, as defined by increased levels of GH and insulin-like growth factor-1 (IGF-1), and persistence of clinical symptoms [3, 4].

The introduction of somatostatin analogues was a major therapeutic advancement in the management of acromegaly. Slow-release, long-acting formulations, administered by fortnightly or monthly injections, have been found to control plasma GH levels, normalise serum levels of insulin-like growth factor-1 (IGF-1), and reduce clinical symptoms in over 50% of patients [5].

2.2 Compound Review

2.2.1 Lanreotide

Lanreotide Autogel® is a long-acting viscous aqueous formulation of lanreotide, which is supplied in ready-to-use pre-filled syringes intended for deep subcutaneous injection. Lanreotide Autogel provides consistent drug release and is effective in controlling the biochemical markers and symptoms of acromegaly when injected every 28 days [6, 7, 8, 9, 10].

2.2.2 Somatuline (lanreotide) Autogel

Somatuline Autogel is a simple aqueous gel formulation consisting of lanreotide and water for injection, without any additional excipients. Unlike microparticle formulations, Somatuline Autogel does not require reconstitution, but is supplied as a pre-filled syringe, with an injection volume of approximately 0.2 0.4 ml, given by deep subcutaneous injection.

Following a single injection, Somatuline Autogel produces a sustained release profile of lanreotide into the plasma, with almost log-linear (first order) kinetics. This kinetic pattern means that there are few fluctuations in the release pattern over the dosing period. The outcome of dose adjustment thus becomes more predictable. The sustained release of lanreotide provides prolonged physiological control of hormone levels.

Somatuline Autogel is licensed in Australia for the treatment of acromegaly and neuroendocrine tumours. It is administered by deep subcutaneous injection.

2.3 Rationale for Post Marketing Surveillance (PMS) Programme

Somatuline Autogel does not require reconstitution as it comes ready-mixed in a pre-filled syringe, allowing suitably willing and motivated patients the option of home injection.

A phase IV study was conducted to assess the safety and efficacy of home injections compared with a control group (receiving injections from a healthcare professional (HCP)) over a period of 6 months. The study demonstrated that patients or partners were able to

administer Somatuline Autogel injections with no impact on efficacy or safety, and injection site tolerability remained good [11].

This observational post-marketing surveillance (PMS) programme aims to assess the long term safety, tolerability and efficacy of home injections with injections administered by a healthcare professional, over a period of 2-4 years and to evaluate the acceptability of home injections to patients, partners and HCPs.

3 PMS PROGRAMME OBJECTIVES

3.1 Primary Objective

To assess the safety and local tolerability of the long-term use of Somatuline Autogel when administered by patients or their partners ("Home Injection Group") and the safety and local tolerability in patients receiving their injection from a healthcare professional (HCP) ("Reference Group").

3.2 Secondary Objectives:

To assess the efficacy of the long-term use of Somatuline Autogel in both groups.

To evaluate the training requirements for patients / partners to perform home injection of Somatuline Autogel.

To evaluate the acceptability of home injections to patients, partners and healthcare professionals.

4 PMS PROGRAMME DESIGN

4.1 Overview

This is an observational (non-interventional), multicentre PMS programme, designed to assess the long-term safety, tolerability and efficacy of Somatuline Autogel, in the treatment of acromegaly, when administered by the patient or their partner ("Home Injection") or administered by a Healthcare Professional ("Reference Group").

Enrolled patients will have a diagnosis of acromegaly and will have been established on a stable dose of Somatuline Autogel for at least 4 months before entering the programme. The dose and interval between injections will have been determined by the treating clinician in accordance with usual clinical practice.

If patients wish to commence home injection of Somatuline Autogel, this decision will be taken prior to and independently from the decision to enrol the patient in this PMS programme.

Patients enrolled in this PMS programme may either receive their injections from a healthcare professional (HCP), or by home injection. Patients receiving home injections will enter the "Home Injection Group". Patients receiving their injections from a HCP will form a "Reference Group".

The number of patients enrolled into each group is not mandated.

Patients will be asked to provide written informed consent to have their data included in the PMS programme database and for any subsequent data analyses. Written informed consent must be given before any patient data is included in the PMS programme database.

Patients who do not consent to have their data included in the PMS database would continue to receive their injections (from a HCP or by home injection) in accordance with usual clinical practice.

Patients choosing to begin home injections of Somatuline Autogel will require prior training on the injection technique. If the patient's partner will be administering the injections he/she will also need to attend this training. It is recommended that initially the injection technique is explained and demonstrated by a HCP using pre existing training materials, with the subsequent injection being administered by the patient / partner under the guidance of a HCP. This step can be repeated for further injections until the patient / partner and HCP are confident that the injection can be administered correctly. Data from these training session(s) will be collected in the PMS database. If available, retrospective data will be recorded for patients already performing home injections.

It is recommended that patients are provided with reference materials on the injection technique to take home with them. Materials to provide support with self injection are provided by Ipsen as part of the usual information delivered to HCP and can be used as required.

Depending on the local arrangements for the patient's care, it may be necessary to obtain the agreement of the patient's GP before initiating home injections. In all cases the patient's GP should be informed that the patient is receiving home injections.

Patients will be treated in accordance with usual medical practice during their participation in this programme. No additional assessments or tests will be required. Relevant data collected as part of routine medical care will be captured on an electronic Case Report Form (eCRF). This data will be transmitted to the sponsor for analysis. Data transmitted will be anonymous and will be identified by a patient number and the patient's initials only.

4.1.1 Population Characteristics

As this is an observational programme, precise patient recruitment numbers cannot be set. It is hoped that approximately 30 patients (of either sex), who are 18 years of age or above, and who are established on treatment with Somatuline Autogel for acromegaly will be enrolled within the 2 year recruitment period, and will remain in the PMS programme for at least 2 years.

4.1.2 Design

An observational, non-interventional, multicentre, open-label, post-marketing surveillance programme. It is intended that the programme will run for approximately 4 years, which includes a two year enrolment period.

Eligible patients will be asked to provide written consent for their medical data to be included in the PMS programme database. Patients who are already receiving, or wish to receive home injections will be enrolled in the "Home Injection Group". Patients who are receiving and will continue to receive their injections from a HCP will be enrolled in the "Reference Group". During the duration of this observational programme patients may switch from home injection to HCP injection or from HCP injection to home injection. This will be captured in the PMS database.

As this is an observational PMS programme, visit timings and assessments are not specified. Relevant medical data collected as part of routine medical care will be captured for analysis in order to meet the objectives set out in this protocol. Data will be captured in the eCRF from the date of patient consent and this will be considered visit 1, enrolment visit.

Patients enrolled in the programme may be observed for a maximum of four years; the duration for each patient will depend on when they enter the programme, patients who enrol at the start of the recruitment period will be observed for up to four years, patients who enrol towards the end of the recruitment period will be observed for approximately two years.

4.1.3 Stopping Rules and Discontinuation Criteria

No specific stopping rules or discontinuation criteria have been defined as this PMS programme is non-interventional.

Any decision taken as part of routine medical practice that affects whether or not the patient continues to receive Somatuline Autogel and/or starts or stops home injections after their enrolment in the PMS programme will be recorded.

The treating clinician will be asked to record the reason for the decision. If it is due to safety, tolerability or efficacy concerns, details should be supplied.

Patient data can continue to be recorded in the PMS database.

Early Study Termination:

The Sponsor may terminate this programme at any time. Reasons for termination may include but are not limited to, the following:

- The incidence or severity of related adverse events (AE) in this or other studies point to a potential health hazard for trial patients.
- Insufficient patient enrolment.
- Any information becoming available during the programme that substantially changes the expected benefit risk profile of the programme treatments.

4.2 Endpoints and Evaluations

As this is an observational PMS programme, the nature and timing of patient assessments will not be standardised. Safety, tolerability and efficacy data collected at each visit, will be grouped and considered as one assessment time point. All assessments from Day 1 to Day 270 will be allocated to Month 6 assessment time point, all assessments from Day 271 to Day 450 will be allocated to Month 12 assessment time point, all assessments from Day 451 to Day 630 will be allocated to month 18 assessment time point, all assessments from Day 631 to Day 810 will be allocated to month 24 assessment time point etc:

Sub group analysis will be preformed on the Home Injection Group between self-injection and partner injections.

The parameters listed below will be evaluated in order to meet the objectives stated in this protocol. It is anticipated that these assessments will be performed as they usually form part of routine medical practice.

4.2.1 Safety Evaluations

The following data will be evaluated in order to assess the long-term safety of Somatuline Autogel when administered by home injection, in comparison to administration by a HCP:

- Incidence of adverse events (AEs) considered to be related to Somatuline Autogel in both groups.
- Incidence of serious adverse events (SAEs) considered to be related to Somatuline Autogel in both groups.
- Concomitant medications / therapies / surgical procedures.

- Other assessment results where available including; liver and gall bladder ultrasound, vital signs (heart rate (HR), blood pressure (BP), weight, height), in both groups.

The incidence of safety issues (related AEs) during each 6 month reporting period, (as well as cumulative listings) will be described for the two groups, split by dose and injection frequency as needed.

4.2.2 Tolerability Evaluations

The incidence of local injection site tolerability issues identified through patient reported comments in the Home Injection Group compared with the Reference Group will be evaluated.

4.2.3 Efficacy Evaluations

The long-term efficacy of Somatuline Autogel when administered by home injection will be compared to the efficacy following administration by a HCP. The following efficacy parameters will be analysed where sufficient data is available:

- GH
- IGF-1
- Tumour size.

4.2.4 Training Evaluations:

For patients switching to home injection during this observational programme the site will be asked to document the amount and type of training required for the home injection of Somatuline Autogel. For patients who are already home injecting, retrospective data will be collected where available. The following parameters will be evaluated:

- Number of training sessions required.
- Nature of training sessions required (e.g. HCP demonstration of injection technique, patient / partner supervised injection).
- Length of training sessions.
- Outcome of training session (patient / partner qualified or not qualified to perform home injections).
- Supportive material or documentation used.

4.2.5 Acceptability Evaluations:

The acceptability of home injection of Somatuline Autogel will be compared to HCP injection by evaluating the following:

- The proportion of patients / partners who successfully qualify to perform home injections (of those who receive at least one training session).
- The proportion of patients who discontinue home injection after successfully qualifying to perform them.
- Treatment compliance (missed injections and deviations between scheduled and actual injection dates).
- Any other issues with administration of injections.
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4.3 Justification of Design

Approval has been received from the TGA for the licence variation that allows patients who are controlled on Somatuline Autogel to self-inject or to be injected by their carer. Both the patient and carer must be motivated and competent to perform the injection following

appropriate training. In the case of self-injection, the injection should be given in the upper outer thigh. The decision for administration of Somatuline Autogel by the trained patient/carer should be taken by a health professional. A monitoring system should be in place for such patients to ensure the maintenance of their disease control in the long term.

A phase IV study has already been completed which showed that home-injection of Somatuline Autogel is possible and can be performed for 6 months without safety or efficacy concerns. However, the number of patients enrolled in this study was fairly small (15 in the home-injection group), and the treatment period was relatively short, given the usual long-term nature of somatostatin analogue therapy in patients with acromegaly.

It was decided that a PMS programme should be performed, rather than a clinical trial, as home injection is within the scope of the product licence for Somatuline Autogel, and it will ensure that it is tested within the constraints of usual clinical practice. It is hoped that the minimal burden of enrolment of patients into the PMS programme will enable more patients to be included than would be the case if another Phase IV study was conducted.

By its nature, this PMS programme has an observational design. Criteria for patient enrolment have been kept to a minimum to capture the broadest possible patient population. Patients are eligible for inclusion once they have been on a stable dose and injection frequency of Somatuline Autogel for at least four months. The dose and frequency of injections of Somatuline Autogel will be decided by the treating clinician in accordance with normal clinical practice. The site and route of injection will be in accordance with the Product Information, i.e. the product will be administered by deep subcutaneous injection, into either the superior external quadrant of the buttock (HCP or partner injections) or upper, outer thigh (self-injections). This programme will capture and analyse patient data collected during routine clinic appointments and as part of their usual assessments.

As this programme is observational, patients will be considered for inclusion independently from, and after the decision to prescribe Somatuline Autogel has been taken.

Patients enrolled in this PMS programme may either receive their injections from a healthcare professional (HCP), or by home injection. Patients receiving home injections will enter the "Home Injection Group". Patients receiving their injections from a Healthcare Professional (HCP) will form a "Reference Group".

Patients will select which treatment group they enter as it is a matter of patient choice whether or not they wish to receive home injections.

The programme aims to generate additional data that will be useful for patients and clinicians who are considering the option of home injections of Somatuline Autogel.

4.3.1 Study Duration

The overall duration of the PMS programme will be approximately 4 years. This includes a 2 year enrolment period. The programme will be considered to have started when the first centre has received ethics committee approval. The PMS programme will be closed approximately 2 years after the date of enrolment of the last patient. The "end of study" will be defined as the date 2 years after the enrolment of the last patient. All data included in the PMS programme database between the start of the programme and the end of study date will be included in the analyses.

For each individual patient, programme participation will last up to four years, depending on the timing of their enrolment. Participation in the programme will end for all patients 2 years after the date on which the last patient was enrolled in the programme.

5 COMPLIANCE WITH GOOD CLINICAL PRACTICE AND ETHICAL CONSIDERATIONS

This study will be conducted in compliance with independent ethics committee (IEC), informed consent regulations and local regulatory requirements.

Before initiating the trial, the investigator/institution should have written and dated approval/favourable opinion from the IEC for the trial protocol/amendment(s), written informed consent form, any consent form updates and any written information to be provided to patients. The IEC approval must identify the protocol version as well as the documents reviewed.

This programme falls outside of the scope of ICH-GCP guidelines. Although not all elements of GCP apply to this clinical trial, where applicable GCP guidelines will be followed, and the programme will be conducted in accordance with the spirit of the guidelines.

5.1 Informed Consent

As this is an observational programme, any decision to prescribe Somatuline Autogel and/or to receive home injections must be taken prior to, and independently from the decision to enrol the patient in this PMS programme. This decision should be made in accordance with routine clinical practice at the hospital concerned. The clinical justification for prescribing any treatment should be recorded at the outset by the prescribing clinician.

Prior to enrolment of a patient in this PMS programme, the investigator, or a person designated by the investigator, will explain the nature and purpose of the PMS programme to the patient. As all assessments and procedures will be conducted in accordance with routine medical practice, participation in the programme does not convey any additional risks or burdens for the patient. However, the patient will be provided with information on the benefits and risks of their medical treatment. The patient will be required to provide written informed consent to confirm that they allow their medical data to be entered into the PMS programme database, and analysed as part of the PMS programme. This must be obtained prior to patient enrolment and prior to any data being entered on the programme database. Sufficient time should be allowed to discuss any questions raised by the patient. The patient should be allowed as much time as they need to consider their decision.

The Sponsor should provide a sample informed consent form. The final version- controlled form must be agreed to by the Sponsor, and the IEC if applicable, and must contain all elements included in the sample form, in a language readily understood by the patient. Each patient's original consent form will be personally signed and dated by the patient or the patient's legally acceptable representative, and also by the person who conducted the informed consent discussion. The original signed informed consent form will be retained by the investigator, with all enrolled patients receiving a copy of their signed informed consent from the investigator.

The investigator should, with the consent of the patient, inform the patient's primary physician about their participation in this programme. Outside of the scope of this protocol, and if required by local clinical practice, the investigator will involve the patient's primary care physician in any decision to begin home injections of Somatuline Autogel, and ensure that arrangements are made for the ongoing supply of medication to the patient.

6 STUDY POPULATION

6.1 Number of Patients

As this is an observational programme no recruitment targets have been mandated. It is hoped that approximately 30 patients in total will be enrolled within the 2 year recruitment period, and will remain in the PMS programme for at least 2 years.

6.2 Inclusion Criteria

All patients must fulfil the following:

1) The patient must give written (personally signed and dated) informed consent for their data to be included in the database for this PMS programme and any subsequent data analysis.
2) The patient must have been receiving treatment with Somatuline Autogel at a stable dose and frequency for at least 4 months.
3) The patient must have a diagnosis of acromegaly.
4) The patient must be at least 18 years of age.

For patients receiving or intending to start to receive Somatuline Autogel by home injection:

5) The patient must be able to store the Somatuline Autogel safely in a refrigerator in their own home and either collect it from their GP / Pharmacy on a regular basis, or receive the medication by a home delivery service.

6.3 Exclusion Criteria

Patients will not be included in the programme if:

- The patient is pregnant or breast-feeding, unless continued treatment with Somatuline Autogel is clearly needed (as determined by the treating clinician).

6.4 Patient Withdrawal Criteria

As this is an observational programme no specific withdrawal criteria are specified. No further data will be collected if consent is withdrawn.

Patients wishing to discontinue home injection may revert to receiving their injections from a HCP. The reason for discontinuing should be captured in the eCRF. Data will continue to be collected unless the patient withdraws consent.

Patients who stop treatment with Somatuline Autogel to have their control of their acromegaly assessed, may continue in the programme. If Somatuline Autogel is subsequently re-started, the date of recommencement should be documented in the eCRF.

6.5 Discontinuation/Withdrawal Procedures

If the patient is withdrawn from the programme, the primary reason should be recorded in the eCRF. Withdrawal due to AEs should be distinguished from withdrawal due to insufficient response.

Patients who withdraw from the programme will continue to receive treatment in accordance with routine clinical practice.

7 METHODOLOGY

7.1 Assessment Schedule

No assessment schedule has been defined. Patients will be treated in accordance with routine medical practice during their participation in this programme. No additional assessments or tests will be required. Relevant data collected as part of routine medical care will be captured on an eCRF. This data will be transmitted to the sponsor for analysis. Data transmitted to the sponsor will be anonymous and will be identified only by the patient's initials and a patient number.

Two visit types will be available within the eCRF:

- Enrolment visit
- Follow-up visit

The table below shows the data that can be recorded in the eCRF at each of these visits. For each visit type, a number of items constitute the "minimum information" that should be recorded. These items are denoted by a tick. Data that can additionally be recorded in the eCRF if collected at that visit are denoted by a tick in brackets. At the enrolment visit, the results of the most recent assessments can be recorded. For further details of the details to be captured refer to Section 7.2.1.

Table 1 Data to be collected in the eCRF

Assessment / Procedure	Enrolment Visit	Follow-up Visit
Written informed consent	✓	
Visit Date	✓	✓
Eligibility Check	✓	
Demographic Details	✓	
Relevant Medical History	✓	
Date of diagnosis of acromegaly	✓	
Acromegaly diagnostic tests performed	(✓)	
Prior medications / therapies / surgeries for acromegaly	✓	
Details of Current Somatuline Autogel treatment	✓	✓
Other Prior and Concomitant medications / therapies / surgical procedures	(✓)	(✓)
Concomitant medications / therapies /surgery for acromegaly	✓	✓
Usual geographic location of Somatuline Autogel injections	✓	
Details of injection training[i]	✓	
Details of who administers the injections	✓	
Somatuline Autogel Injection Record	✓	✓
Injection Site Tolerability Issues	(✓)	✓
Related Adverse Events		✓
Growth Hormone Plasma levels[ii]	✓	(✓)
Insulin-like Growth Factor-1 Plasma levels[iii]	✓	(✓)
Tumour size	(✓)	(✓)
Haematology (Clinically significant results only)	(✓)	(✓)
Biochemistry(Clinically significant results only)	(✓)	(✓)
Urinalysis(Clinically significant results only)	(✓)	(✓)
Glucose Tolerance Test	(✓)	(✓)
Vital Signs (HR, BP, Height[iv] Weight)	✓	(✓)
Physical Examination Findings (Clinically significant results only)	(✓)	(✓)
Liver and Gall-bladder Ultrasound Findings	(✓)	(✓)
ECG Findings(Clinically significant results only)	(✓)	(✓)
Other Comments / Observations	(✓)	(✓)
Visit status		✓

i Home injection patients only.
ii Most recent results from patient's notes
iii Most recent results from patient's notes.
iv Height only at enrolment visit.

7.2 Data Collection

After written informed consent has been obtained, the following data will be collected in the eCRF for the PMS programme. Items in bold and underlined are minimum information. All other data items can be recorded if available/applicable.

7.2.1 Enrolment Visit

At the enrolment visit the following information where available should be recorded in the eCRF.

- **Date of written informed consent**. One copy of the original signed consent form should be filed in the patient's medical records. A second copy should be given to the patient along with the patient information sheet.
- **Visit date**.
- **Eligibility check** (inclusion/exclusion criteria).
- Demographics (**sex, date of birth**, ethnic origin, employment status, **journey time from patient's home to hospital clinic and from their home to usual place for Somatuline Autogel administration (if different)**.
- Relevant medical history including ongoing medical conditions.
- Details of acromegaly (**date of diagnosis**, diagnostic tests performed).
- Prior and concomitant medications / therapies / surgery for acromegaly (including **current dose of Somatuline Autogel, date of initiation of current dose of Somatuline Autogel,** and details of any previous dose adjustments).
- Other prior and concomitant medications / therapies / surgery.
- Usual geographic location of Somatuline Autogel injections.
- For home injection patients only: Details of injection training given (including; dates of training sessions, nature of training sessions (HCP demonstration / supervised injection), outcome of training session (qualified / not qualified), duration of training session).
- Date of last Somatuline Autogel administration.
- Most recent results for **GH** and **IGF-1** plasma levels.
- Most recent tumour size measurements (if measured previously).
- Most recent biochemistry, haematology and urinalysis results.
- Most recent Glucose Tolerance Test results.
- Most recent vital signs (**heart rate, blood pressure**, height, weight).
- Most recent liver and gall-bladder ultrasound results (if done previously).
- Physical examination findings.
- Electrocardiogram (ECG) findings (if done previously).

7.2.2 Follow-up Visit

At each subsequent visit the following information should be entered into the eCRF if the assessments / procedures have been performed:

- **Visit date.**
- **Details of any concomitant medications / therapies / surgery.**
- **Details of any related Adverse Events.**

- Somatuline Autogel injection details (including; scheduled and actual injection dates, **dose administered**, site of administration (side and location), injector details (patient / partner / HCP), local tolerability issues, any other issues with injections).
- GH and IGF-1 plasma levels.
- Tumour size measurements.
- Glucose Tolerance Test results.
- Vital signs (heart rate, blood pressure, height, weight).
- Liver and gall-bladder ultrasound results.
- If patient starts or stops their Somatuline Autogel Treatment, or changes between home injection and HCP injection the reason will be recorded. If the patient withdraws from the PMS programme and no data will be collected the reason will be recorded.

8 STUDY TREATMENT

8.1 Study Treatment Administered

Patients included in the programme will be currently receiving Somatuline Autogel for acromegaly. The decision to prescribe Somatuline Autogel will be made prior to and independently from the decision to enrol the patient in this PMS programme. If patients wish to begin home injections of Somatuline Autogel, this decision should also be taken prior to, and independently from the decision to enrol the patient in this PMS programme.

Somatuline Autogel (lanreotide as acetate) is supplied as a white to off-white, translucent and viscous supersaturated solution in a pre-filled syringe, ready for use.

Somatuline Autogel should be injected via the deep subcutaneous route in the superior external quadrant of the buttock or via the deep subcutaneous route in the upper outer thigh.

Somatuline Autogel is available in three doses; 60, 90 or 120 mg. Injections are generally administered every 28 days, with the exception of the 120mg which may be given every 42-56 days in well controlled patients. The dose and frequency of administration will be determined on an individual patient basis by the treating clinician in accordance with usual medical practice and may be titrated during the period of this observation programme.

The injection may be given by a HCP or by an appropriately trained friend or relative of the patient. Patients who are well motivated and have received appropriate training may self administer the product.

Regardless of the site of injection, the skin should not be folded. The needle should be inserted rapidly to its full length, perpendicularly to the skin. Injections should be administered alternating the left and right side.

8.2 Patient Identification and Allocation to Study Treatment

All patients will be automatically allocated a unique patient number when an enrolment visit is created in the eCRF. In order to maintain confidentiality, this number, in conjunction with the patient's initials will be used to identify the patient's study data.

All patients enrolled must be identifiable throughout the programme. The investigator will maintain a list of patient numbers and names to enable records to be found at a later date if required.

All patients treated will be treated with Somatuline Autogel, at a dose and injection frequency determined by their treating clinician in accordance with usual clinical practice.

8.2.1 Randomisation

As this is an open-label, PMS programme, no randomisation procedures apply.

8.3 Study Treatment Supply, Packaging and Labelling

Somatuline Autogel will be purchased and prescribed and administered to all patients participating in this PMS programme in accordance with usual medical practice. Somatuline Autogel packs will be labelled in accordance with the approved TGA labelling for the product.

Patients receiving home injections will be supplied with packs of Somatuline Autogel for administration in accordance with the injection schedule set by their treating clinician. The Somatuline Autogel packs will be stored in a refrigerator in the patient's home. Arrangements for supply of these packs will be made by the patients treating clinician/GP in

accordance with local practice. Supplies could be provided either by a home delivery service, or collected from patient's GP/Pharmacy. Patients will also be provided with a sharps bin for the disposal of used devices. Arrangements for the disposal and replacement of sharps bins will be made by the hospital clinic or the patient's GP.

Patients will be provided with an injection record card on which to record scheduled and actual dates of injections, where the injection was administered (home/hospital clinic/GP) and any tolerability or other issues associated with the injection. Patients will be asked to bring their completed injection record cards with them to the hospital at each of their clinic appointments so that compliance can be checked.

Patients who choose not to self administer the injection will continue to receive their prescribed medication as normal. The dose and dates of the injection will be recorded in the patient's eCRF.

8.4 Concomitant Medication/Therapy

The following medication should be used cautiously whilst receiving Somatuline autogel:

- Cyclosporin: Concomitant administration of lanreotide injection with cyclosporin may decrease blood levels of cyclosporin.

9 ADVERSE EVENT REPORTING

9.1 Definition of an Adverse Event (AE)

An Adverse Event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram).

As this is a PMS programme, only those events that are considered to be related to Somatuline Autogel need to be reported. These events will be reported via completion of the eCRF. This includes events occurring from the time of the patient giving informed consent until the end of the programme.

9.2 Categorisation of Related Adverse Events

9.2.1 Intensity Classification

Related AEs will be classified as mild, moderate or severe according to the following criteria:

Mild:	Symptoms do not alter the patient's normal functioning.
Moderate:	Symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the patient.
Severe:	Symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

9.2.2 Causality Classification

Only AEs which are related to the study treatment (Somatuline Autogel) need to be recorded in the eCRF. The relationship of an AE to the study treatment (Somatuline Autogel) is classified according to the following:

Related: Reports including good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal relationship with the IMP in the sense that it is plausible, conceivable or likely.

Not related: Reports sequence and/or attributable to concurrent disease or other drugs to rule out a causal relationship with the IMP.

9.2.3 Assessment of expectedness

The expectedness of an AE shall be determined by the Sponsor according to the Australian Product Information (PI) as Somatuline Autogel is an authorised medicinal product which is being used according to the terms and conditions of the marketing authorisation.

The reference document for assessing expectedness of AEs in this study will be: the Australian PI, for lanreotide Autogel 60, 90 and 120 mg, dated 30th July 2007.

9.2.4 Laboratory Test Abnormalities:

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in the Somatuline Autogel schedule of administration (change in dosage, delay in administration, discontinuation) and are related to Somatuline Autogel.
- They are considered as clinically significant by the investigator and related to Somatuline Autogel.

9.2.5 Abnormal Physical Examination Findings

Clinically significant changes in physical examination findings (abnormalities), which in the judgement of the investigator are related to Somatuline Autogel will be recorded as AEs.

9.2.6 Other Investigation Abnormal Findings

Abnormal objective test findings as judged by the investigator as clinically significant and related to Somatuline Autogel (e.g. electrocardiogram changes) should be recorded as AEs.

9.3 Recording and Follow-up of Adverse Events

At each visit the patient should be asked a non-leading question such as: “Do you feel different in any way since the last visit?”

For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. study treatment or other illness). As this is a PMS programme, only those events that are considered to be related to Somatuline Autogel need to be reported. These events will be reported via completion of the eCRF

Follow-up of the related AEs will be conducted in accordance with usual clinical practice.

Related AEs already recorded and designated as ‘continuing’ should be reviewed at each subsequent assessment.

It is recommended that follow-up should continue until the event or its sequelae resolve or stabilise at a level acceptable to the investigator.

The investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative.

9.3.1 Definitions

All SAEs (as defined below) with a suspected relationship to Somatuline Autogel must be reported immediately (within 24 hours of the investigator's knowledge of the event) to the pharmacovigilance contact specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the Spontaneous Adverse Event Report Form.

An SAE is any AE occurring at any dose that:

1. Results in death;
2. Is life threatening, that is any event that places the patient at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death;
3. Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further);
4. Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;
5. Results in congenital anomaly/birth defect in the offspring of a patient who received the study treatment;
6. Is an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

Regardless of the above criteria, any additional AE that the Sponsor or an investigator considers serious and is related to Somatuline Autogel should be immediately reported to the Sponsor and included in the corporate SAEs database system.

- **Hospitalisation** is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalisation in clinical trials, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus does not need immediate reporting to the Sponsor.
- Pre-planned or elective treatments/surgical procedures should be noted in the patient's screening documentation. Hospitalisation for a pre-planned or elective treatment / surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness and related as described above.

9.3.2 Reporting Requirements

Details of **related adverse events and serious adverse events** should be recorded in the eCRF. .

- Whenever possible, use recognised medical terms when recording. Do not use colloquialisms and/or abbreviations.
- If known, record the diagnosis (i.e. disease or syndrome) rather than component signs and symptoms (e.g. record congestive heart failure rather than dyspnoea, rales, and cyanosis). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g. if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).
- AEs occurring secondary to other events (e.g. sequelae) should be identified by the primary cause. A "primary" AE, if clearly identifiable, generally represents the most accurate clinical term to record on the AE form. If a primary serious AE (SAE) is recorded in the eCRF, events occurring secondary to the primary event should be described in the narrative description of the case. For example:

Orthostatic hypotension	→	Fainting and fall to floor	→	Head trauma	→	Neck pain

The primary AE is orthostatic hypotension.

Death is an outcome of an event. The **event** that resulted in the death should be recorded and reported on the spontaneous AE form if the event is related to treatment with Somatuline Autogel.

For hospitalisation for surgical or diagnostic procedures, the **illness** leading to the surgical or diagnostic procedure should be recorded as the AE and not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.

The following data are captured in the AE form. Some data are pre-filled automatically if the relevant information is in the eCRF.

- Visit date.
- Age at visit.
- Weight.
- Sex.
- Somatuline Autogel treatment details (indication, start date, dose and treatment regime, expiry date and lot number of product used, details of treatment cessation).
- AE details (description, date of onset, intensity, time between last dose of suspected medication and onset of AE, seriousness criteria, outcome at last observation).
- Actions taken with suspect medication.
- Details of relevant diagnostic tests / laboratory data.
- Concomitant medications.
- Details of other factors that could account for the AE.
- Reporter information.

Any SAE must be reported to the Sponsor immediately (within 24 hours), independent of the circumstances, if it occurs or comes to the attention of the investigator at any time during the programme period, and is considered to be related to Somatuline Autogel.

Any SAE with a suspected causal relationship to the Somatuline Autogel occurring at any other time after completion of the programme must be promptly reported.

9.3.3 Mandatory Information for Reporting an SAE

The following information is the minimum that must be provided to the Sponsor pharmacovigilance contact within 24 hours for each SAE:

- Trial number
- Centre number
- Patient number
- AE
- Investigator's name and contact details

The additional information included in the spontaneous adverse event form must be provided to the Sponsor or representative as soon as it is available. Upon receipt of the initial report, the Sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

9.3.4 Reporting Exemptions

As this is a PMS programme, AEs and SAEs which are not considered to be related to Somatuline Autogel **do not** need to be reported to the Sponsor. Unrelated AEs and SAEs will be excluded from any data analysis performed by the Sponsor.

9.4 Pregnancy

Pregnancy is not a criterion of seriousness. However, any pregnancy occurring during treatment with Somatuline Autogel should be reported to the pharmacovigilance contact specified at the beginning of this protocol in the same timelines as an SAE (within 24 hours of becoming aware of it), using the standard pregnancy outcome form and entered on the AE form in the eCRF. The investigator / monitoring physician will be instructed by the Sponsor in the tracking of the pregnancy outcome (a specific form to obtain the information required will be sent to the monitoring physician).

Investigators must instruct all female patients to inform them immediately should they become pregnant during the study. In the event of a pregnancy the investigator will decide whether treatment with Somatuline Autogel should be continued.

9.5 Deaths

All AEs related to Somatuline Autogel and resulting in death must be reported as an SAE within 24 hours of the investigator's knowledge of the event.

The convention for recording death is as follows:

- AE term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction).
- Outcome: fatal.
-

9.6 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to Somatuline Autogel.

If Somatuline Autogel is discontinued due to a SAE it must be reported immediately to the Sponsor's designated representative.

In all cases the investigator must ensure the patient receives appropriate medical follow-up.

9.7 Reporting to ADRAC/IECs/Other investigators

The Sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the Programme to ADRAC, IECs and other investigators involved in the PMS Programme. Reporting will be done in accordance with the applicable regulatory requirements.

10 STATISTICAL CONSIDERATIONS

10.1 Patient Classification and Definitions

- **Enrolled patient:** Patient fully informed about the programme who has given written informed consent to participate.
- **Treated patient :** Enrolled patient for whom the details of at least one treatment with Somatuline Autogel (after signature of informed consent) are recorded in the eCRF.
- **Treatment Completed patient:** Treated patient who has details of at least one treatment with Somatuline Autogel and at least one post-treatment follow-up visit.
- **Drop-out:** Treated patient who discontinued from the PMS Programme data collection prior to closure of the data collection phase of the Programme.

10.2 Analyses Populations Definitions

- **Screened population**: All patients enrolled.
- **ITT / Safety population**: All patients who received at least one dose of Somatuline Autogel after giving written informed consent, and have the details of this treatment recorded in the eCRF.

10.2.1 Populations Analysed

Analyses will be performed on the Safety/ITT population.

10.2.2 Patient Allocation and Reasons for Exclusion from the Analyses

The rules for the allocation of patients to the safety/ITT population will be defined and documented during a data review meeting held prior to database lock.

10.3 Sample Size Determination

As this is an observational programme, no formal statistical analysis will be performed, and therefore no sample size calculation has been conducted.

It is planned to recruit 30 patients at 5 centres in Australia.

10.3.1 Significance Testing and Estimations

As this is a descriptive study, no statistical testing will be carried out.

10.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external Contract Research Organisation (CRO), managed by the Sponsor's Clinical Study Coordinator.

A Reporting and Analysis plan (RAP) describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 8 or higher).

10.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and baseline data medical history, concomitant disease (pre-treatment AEs and on-going medical history, prior medications and therapies, baseline symptoms etc) will be presented by treatment group and overall for the ITT and PP/safety population(s).

10.4.2 Patient Disposition and Withdrawals

The numbers and percentages of patients enrolled and included in the ITT / safety population will be tabulated by centre. The reasons for patient exclusions from the population will also be tabulated. The numbers of patients who were treated, discontinued and completed the programme will be tabulated by treatment group and overall. In addition the number of patients who start/stop Somatuline and patients who start/stop home injection will be tabulated. Primary reasons for discontinuation of programme treatment will be tabulated.

10.4.3 Safety and Efficacy Evaluation

The primary evaluations are:

1) the incidence of related adverse events
2) the use of concomitant medications in the Home Injection Group versus the Reference Group.

The secondary evaluations are:

1) Incidence of tolerability issues through patient reported comments in the Home Injection Group versus the Reference Group.
2) The absolute change in GH/IGF-1 plasma levels over time.
3) Proportion of patients or their partners who can competently perform unsupervised Somatuline Autogel injections on completion of the programme.
4) Number (%) patients discontinuing home injections, and the number (%) of patients choosing to receive home injections.
5) The incidence of safety issues (Related AEs, clinically abnormal lab data) during the 1st, 2nd, 3rd, 4th, etc 6 month period (as well as in a cumulated manner) will be described for the two groups and by dose as needed.

All safety data will be included in the patient data listings. Analyses and summary tables will be based upon the safety population.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA preferred term and system organ class. AE listings will be presented by patient, system organ class and preferred term.

Incidence of all reported treatment emergent AEs (TEAE) and SAEs will be tabulated by treatment group, dose / injection frequency (if relevant) and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and TEAEs associated with withdrawal of programme medication.

A TEAE is defined as any AE that occurs during the active phase of the study if:

- it was present prior to signature of informed consent, but the intensity increased during the patient's participation in the study programme, or
- it was present prior to signature of informed consent, the intensity is the same but the drug relationship became related during the patient's participation in the study programme.

Treatment emergent AEs will be flagged (*) in the AEs listings.

Concomitant medication will be coded by using WHO Drug Dictionary (version x) and will be summarised by treatment group and overall with the number and percentage of patients receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, SD and range as appropriate) by treatment group and overall will be presented for vital signs, blood pressure, heart rate, at each assessment with change from enrolment. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented.

10.5 Subgroup Analyses

Safety data will be presented by dose / injection frequency if considered relevant.

10.6 Interim Analyses and Data Monitoring

As this is an obersevational study, Data monitoring on an annual basis is not mandated and will take place as requested.

10.7 Final Analysis

N/A

11 MONITORING PROCEDURES

The investigator is responsible for the validity of all data collected at the site. Electronic checks and alerts will be programmed into the eCRF to help ensure the accuracy and consistency of data recorded in the eCRF. As this is an observational PMS programme, no monitoring or source data verification by the Sponsor is required.

12 STUDY MANAGEMENT

12.1 Inspections and Auditing Procedures

Authorised personnel from external CAs and Sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the Sponsor.

12.2 Data Recording of Programme Data

In compliance with GCP, the medical records/medical notes, etc., should be clearly marked and permit easy identification of a patient's participation in the specified clinical trial.

The investigator should record relevant data relating to clinical assessments and procedures, Somatuline Autogel administration, laboratory data and safety data on the eCRFs provided for the programme.

The investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF.

12.3 Source Data Verification

The source documents must, as a minimum, contain the following; a statement that the patient is included in this PMS programme, the date that informed consent was obtained prior to participation in the programme, the identity of the programme, diagnosis and eligibility criteria, visit dates (with patient status), Somatuline Autogel administration, and any AEs and associated concomitant medication.

Other relevant data including results of clinical assessments and procedures and laboratory data should also be recorded in the Source Data in accordance with usual clinical practice. Data recorded in the eCRF should also be documented in the patient's medical records.

As this is an observational programme, no source data verification will be performed by the Sponsor.

Definition for source data and source documents are given below:

- **Source Data:** All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). [ICH GCP Section 1.51]
- **Source Documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patient's' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). [ICH GCP Section 1.52]

The patient must have consented to their medical records being viewed by Sponsor-authorised personnel, and by local, and possibly foreign, CAs. This information is included in the informed consent.

12.4 Data Quality

eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

As this is a PMS study, no assessments are mandated at each visit. There will therefore be the option to indicate which assessments / procedures were not done. Reasons will not need to be given on the relevant eCRF for any missing data provided that the data is specified as not done / not available.

Reasons will need to be given for deviations from the mandatory sections of this protocol.

Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the data management group for clarification / correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

12.5 Data Management

Electronic Data Capture (EDC) will be utilized for collecting patient data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only Sponsor authorized users will have access to the eCRF as appropriate to their programme responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO, directed by the Sponsor's Clinical Study Coordinator (CSC). All data management procedures will be completed in accordance with Ipsen's and/or the contracted CRO SOPs.

The Sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical trial, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will be raised within the EDC system.

The Sponsor will ensure that SAE data collected in the eCRF are consistent with information provided to the Sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history and concomitant medication terms will be performed by the contracted CRO and reviewed and approved by the Sponsor. Concomitant medications will be coded using WHODRUG and AEs / medical history terms will be coded using MedDRA.

12.6 Record Archiving and Retention

Routine system backup and archiving will be performed based on the CRO's and Sponsor's standard procedures.

Study records will be retained in accordance with applicable regulations.

13 ADMINISTRATION PROCEDURES

13.1 Regulatory Approval

As this study is post marketing and non interventional Regulatory approval is not required.

13.2 Publication Policy

The Sponsor encourages acknowledgement of all individuals / organisations involved in the funding or conduct of this programme, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this programme may be published or communicated to scientific meetings by the investigators involved in the programme. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the programme investigators or a Steering Committee. The Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the Sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and

authors (or authors' institution) after receipt of the proposed publication by the Sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the Sponsor's request for delay to the proposed publication should the Sponsor reasonably deem premature to publish the results obtained at the then stage of the programme.

13.3 Clinical Study Report

A final clinical study report will be prepared according to the ICH guideline on structure and contents of clinical programme reports. A final clinical study report will be prepared where any patient has signed informed consent, regardless of whether the trial is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

13.4 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the programme, outlining overall Sponsor and investigator responsibilities in relation to the programme. Financial remuneration will cover the cost of data collection only. As this study is observational, no fees will be paid for hospital overheads, pharmacy or laboratory tests.

13.5 Insurance, Indemnity and Compensation

The Sponsor will provide Product Liability insurance for all patients included in the clinical programme.

14 PROTOCOL AMENDMENTS

In the event that an amendment to this protocol is required it will be classified into one of the following three categories:

- ***Non-Substantial Amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs or CA for information purposes.
- ***Substantial Amendments*** are those considered 'substantial' to the conduct of the clinical trial where they are likely to have a significant impact on:
- the safety or physical or mental integrity of the patients;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of the IMP used in the trial.

Substantial amendments must be notified to the IECs and CA. Prior to implementation, documented approval must be received from the IECs. In the case of the CA in the EU member states, approval or 'favourable opinion' can be assumed if the CA has raised no grounds for non-acceptance during an allocated time period (to be confirmed with the Sponsor's Regulatory Affairs (RA) representative) following acknowledgment of receipt of a valid application to make a substantial amendment.

- ***Urgent Amendments*** are those that require urgent safety measures to protect the trial patients from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IECs and CA notification, forthwith.

15 REFERENCES

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8. Ashwell SG, Bevan JS, Edwards OM, Harris MM, Holmes C, Middleton MA, James RA 2004 The efficacy and safety of lanreotide Autogel in patients with acromegaly previously treated with octreotide LAR. Eur J Endocrinol 150:473 80
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