Public Assessment Report

National Procedure

Somatuline Autogel 60mg, solution for injection
PL 34926/0005

Somatuline Autogel 90mg, solution for injection
PL 34926/0006

Somatuline Autogel 120mg, solution for injection
PL 34926/0007

Lanreotide

Ipsen Limited
LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Somatuline Autogel 60, 90 & 120mg Solution for Injection (PL 34926/0005-7). Somatuline Autogel 60, 90 & 120mg Solution for Injection will be termed Somatuline Autogel Solutions for Injection throughout this PAR for ease of reading. It explains how Somatuline Autogel Solutions for Injection were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Somatuline Autogel Solutions for Injection, patients should read the Package Leaflet or contact their doctor or pharmacist.

What are Somatuline Autogel Solutions for Injection and what are they used for?
Somatuline Autogel Solutions for Injection are medicines, used for the:

- treatment of acromegaly (a condition where the body produces too much growth hormone)
- relief of symptoms, such as flushing and diarrhoea, that sometimes occur in patients with neuroendocrine tumours
- treatment and control of the growth of some advanced tumours of the intestine and pancreas, called gastroenteropancreatic neuroendocrine tumours (GEP-NETs), when these tumours cannot be removed by surgery.

How do Somatuline Autogel Solutions for Injection work?
Somatuline Autogel Solutions for Injection contain the active substance lanreotide, which belongs to a group of medicines called “antigrowth hormones”. It is similar to another substance, a hormone called “somatostatin”.

Somatuline Autogel Solutions for Injection are a viscous solution for injection, in a pre-filled syringe ready for use and fitted with an automatic safety system. It is a white to pale yellow, semi-solid formulation. Each pre-filled syringe is packed into a laminated pouch and cardboard box. The box contains a 0.5ml syringe with an automatic safety system and one needle (1.2mm x 20mm).

How are Somatuline Autogel Solutions for Injection used?
The recommended dose is one injection of 60, 90 or 120mg every 28 days for the treatment of acromegaly and relief of symptoms associated with neuroendocrine tumours. The dose may be adapted by a medical practitioner, who may recommend a change in frequency to one 120mg injection every 42-56 days if your condition is well-controlled by the treatment.

The recommended dose for the treatment of GEP-NETs is 120mg every 28 days.

Please read Section 3 of the Package Leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

This medicine can only be obtained with a prescription.

How have Somatuline Autogel Solutions for Injection been studied?
Because Somatuline Autogel Solutions for Injection are “line-extensions” of existing medicines Somatuline LA 30mg Powder for Suspension for Injection, studies in patients have been performed to show that these medicines can be considered the same as Somatuline LA 30mg Powder for Suspension for Injection when given at the same dose.
A pivotal multicentre phase III study (CLARINET) was conducted in 204 patients with Somatuline Autogel 120 mg and demonstrated its efficacy in the treatment of GEP-NETs.

**What are the possible side effects of Somatuline Autogel Solutions for Injection?**

Because Somatuline Autogel Solutions for Injection are “line extensions” of an existing medicine Somatuline LA 30mg Powder for Suspension for Injection, their benefits and possible side-effects are taken as being the same.

For further information, please see Section 4 the Package Leaflet.

**Why are Somatuline Autogel Solutions for Injection approved?**

It was concluded that Somatuline Autogel Solutions for Injection have been shown to have comparable quality and efficacy to Somatuline LA 30mg Powder for Suspension for Injection in the treatment of acromegaly and the relief of NET symptoms. Therefore, the view was that, as for Somatuline LA 30mg Powder for Suspension for Injection, the benefits outweigh the identified risks and it was recommended that Somatuline Autogel Solutions for Injection can be approved for use.

In addition, a pivotal multicentre phase III study (CLARINET) demonstrated the efficacy of Somatuline Autogel 120 mg in the treatment of GEP-NETs. The benefit/risk balance was considered positive in patients with GEP-NETs.

**What measures are being taken to ensure the safe and effective use of Somatuline Autogel Solutions for Injection?**

A risk management plan (RMP) has been developed to ensure that Somatuline Autogel Solutions for Injection are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Somatuline Autogel Solutions for Injection, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Somatuline Autogel Solutions for Injection**

The UK first granted marketing authorisations on 16 October 2001.

The full PAR for Somatuline Autogel Solutions for Injection follows this summary.

For more information about treatment with Somatuline Autogel Solutions for Injection, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in June 2015.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Introduction</td>
<td>5</td>
</tr>
<tr>
<td>II Quality aspects</td>
<td>7</td>
</tr>
<tr>
<td>III Non-clinical aspects</td>
<td>8</td>
</tr>
<tr>
<td>IV Clinical aspects</td>
<td>9</td>
</tr>
<tr>
<td>V User consultation</td>
<td>13</td>
</tr>
<tr>
<td>VI Overall conclusion, benefit/risk assessment and recommendation</td>
<td>13</td>
</tr>
</tbody>
</table>

Table of content of the PAR update Page 17
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Ipsen Limited marketing authorisations for Somatuline Autogel 60, 90 & 120mg Solution for Injection (PL 06958/0013-15) on 16 October 2001.

These products are prescription-only medicines indicated for the treatment of individuals with acromegaly when the circulating levels of Growth Hormone (GH) and/or Insulin-like Growth Factor-1 (IGF-1) remain abnormal after surgery and/or radiotherapy, or in patients who otherwise require medical treatment. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalise these values. These products are also indicated for the treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours.

These products contain the active substance lanreotide. Lanreotide is a chemically synthesised analogue of somatostatin, which is a growth hormone inhibitor.

These applications were made as national applications, under Article 8(3) of Directive 2001/83/EC, as amended, for line-extensions to the existing product Somatuline LA 30mg, Powder for Suspension for Injection, which was initially licensed to Ipsen Biotech on 26 January 1998 (PL 10829/0006).

Non-clinical kinetic and local tolerance studies were conducted, which were supportive of the clinical use of these products.

Suitable pharmacokinetic, pharmacodynamic and efficacy studies have been submitted to show non-inferiority of these products when given in equivalent doses to Somatuline LA 30mg, with respect to GH and IGF-1 levels in acromegalic patients. The safety profiles were also comparable.

All clinical studies were conducted in-line with current Good Clinical Practice.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the MHRA has accepted copies of current GMP Certificates of satisfactory inspection summary reports, as certification that acceptable standards of GMP are in place at those non-Community sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

A change of authorisation holder was granted on 16 September 2011 (PL 34926/0005-7).

On 27 February 2015, a variation was granted to add the following indication to these marketing authorisations:

*The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or*
unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease.

Based on the review of the data provided, it was considered that the marketing authorisation holder’s request for an additional 1-year period of data exclusivity, in accordance with Article 10(5) of Directive 2001/83/EC, as amended by Directive 2004/27/EC, for the above therapeutic indication could be approved for these products. The variation implementation date is used as start date of the additional year of data exclusivity. For this procedure, the start date of the additional year of data exclusivity is 29 March 2015.

II QUALITY ASPECTS
II.1 Introduction
These applications are submitted according to Article 8(3) of Directive 2001/83/EC, as amended. These are line-extensions to the existing product Somatuline LA 30mg, Powder for Suspension for Injection, which was initially licensed to Ipsen Biotech on 26 January 1998 (PL 10829/0006).

Somatuline Autogel is a white to pale yellow, semi-solid formulation in a prefilled syringe (clear polypropylene) fitted with an automatic safety system, a needle (stainless steel), a plastic needle sheath (LDPE) and a plunger stopper (bromobutyl rubber).

Each syringe contains a supersaturated solution of lanreotide acetate, which ensures an actual injection dose of 60, 90 or 120mg of lanreotide. The excipients in each injection are water for injections and glacial acetic acid.

Each pre-filled syringe is packed in a laminated pouch (polyethylene terephthalate / aluminium / polyethylene laminate) and a cardboard box.

II.2 DRUG SUBSTANCE
rINN: Lanreotide
Chemical Name: \([\text{cyclo S-S}] \cdot 3\cdot(2\text{-naphthyl})\cdot D\text{-alanyl-L-cysteinyL-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyL-L-threoninamide}, \text{acetate}\)

Structure:

![Structure of Lanreotide](image)

\[x \text{ (CH}_3\text{COOH)}\]

where \(x = 1.0\) to 2.0

Molecular Formula: \(\text{C}_{54}\text{H}_{69}\text{N}_{11}\text{O}_{10}\text{S}_2\)
Molecular Weight: 1096.33

Appearance: A white to off-white powder

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT
Pharmaceutical development
The objective of the pharmaceutical development was to produce safe, efficacious solutions for injection, provided as supersaturated gel formulations in prefilled syringes, containing 60, 90 or 120mg of lanreotide.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of human origin are used in the final products.

None of the excipients are sourced from genetically modified organisms.

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based
on the results, a shelf-life of 2 years with the storage conditions “Store in the original package” and “Store in a refrigerator (2-8 degrees) have been set, which are appropriate.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

Pharmacokinetics

Two studies have been undertaken in the dog with intra-muscular (im) administration. Lanreotide acetate iv was used as a comparator in one study. The bioavailability of lanreotide was 91-93% and 95% of the peptide was released over 90-150 days. The studies were characterised by initially rapid, followed by a regular, smooth and sustained release of lanreotide from the depot injection. In one study there was a moderate initial “burst” effect, whilst this was absent in the other study.

Local Tolerance

A series of studies have been conducted mainly in the rabbit, but also in the minipig and monkey. Local tolerance following single or repeated im administration in the rabbit was assessed in two studies over 99-150 days. Clinical effects were generally minimal, localised mild induration being observed in the repeated-dose study. Histopathological examination revealed the presence of amorphous particulate material (presumably precipitated lanreotide) and a variety of inflammatory reactions of a type associated with foreign body-type responses, eg initial acute polymorph response evolving into giant cell infiltration and fibrosis with some necrosis, but only of adjacent muscle cells.

Single- and repeated-dose subcutaneous (sc) administration of the product, again being followed over periods of 99-150 days, produced a similar but less marked foreign body inflammatory response.

Administration by the sc route to the rabbit, minipig and monkey produced an acute inflammatory response in all species, which was of lowest intensity in the rabbit.

Conclusions

The kinetic profile of the drug was confirmed in the dog to be appropriate for a sustained-release product. Local inflammatory responses of a slight-to-mild type following sc administration were seen in three species and are not unexpected for this kind of preparation where the drug has the potential to be present in particulate form in the tissues for several months.

The non-clinical kinetic and local tolerance characteristics of these products are supportive of their clinical use. The grant of product licences is recommended from a non-clinical perspective.

IV Clinical aspects

IV.1 Introduction

With the exception of the below studies, no new clinical data have been submitted for these applications. The Applicant’s clinical overview on the clinical pharmacology, efficacy and safety of the product has been written by an appropriately qualified person and is adequate.
IV. 2 Pharmacokinetics

Pharmacokinetics in healthy subjects
- Study E54 52030 093: an open, non-comparative PK study of a single im 40 mg injection of Somatuline Autogel in 13 men (one drop out). The profile of the curves of serum lanreotide levels were the same in all subjects with a coefficient of variation (C.V.) at different time points ranging from 15 to 55%.

- Study E92 52030 007: involved 24 subjects (12 men, 12 women) and compared the pharmacokinetic parameters of an IRF formulation of lanreotide with that of a single injection of 40 or 60 mg of Somatuline Autogel (0.246 mg/mg), all administered subcutaneously.

Both doses of Somatuline Autogel gave similar prolonged release profiles with a serum level of > 1 µg/ml maintained for an average of 16 days (40 mg) and 23 days (60 mg). The $C_{\text{max}}$ (mean ± SD) for each dose was 4.4 ± 2.9 mg/l (40 mg) and 5.7 ± 3.5 mg/l (60 mg), as compared to 8.0 ± 2.1 mg/l for immediate release lanreotide. The levels decreased up to day 4 to 7 post-injection, at which point there was a slight increase and a “pseudo-plateau” or a continued slow decline.

The relative bioavailability was 0.9 (40 mg) and 0.81 (60 mg) for the Autogel formulations – the subcutaneous immediate release lanreotide being taken as the reference. The pharmacokinetic behaviour was linear within the dose range studied.

There were statistically significant differences in some parameters ($C_{\text{max}}$ and $C_{\text{max}}$/AUC) with respect to gender, indicating that women had a lower early release (“burst” effect) than men (see table 1).

Table 1
Mean (± sd) values of the main pharmacokinetic parameters per gender obtained after one single sc administration of either 40 mg or 60 mg lanreotide autogel.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>40 mg</th>
<th>60 mg</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ng.ml$^{-1}$)</td>
<td>5.826</td>
<td>6</td>
<td>2.636</td>
</tr>
<tr>
<td>$AUC^*$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ng.m$^{-1}$.d)</td>
<td>53.254</td>
<td>5</td>
<td>54.478</td>
</tr>
<tr>
<td>$C_{\text{max}}$/AUC$^*$</td>
<td>0.121</td>
<td>5</td>
<td>0.064</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>20.706</td>
<td>6</td>
<td>22.734</td>
</tr>
</tbody>
</table>

*For statistical comparisons the values were normalised by dose.
$^*$Volunteers with more than 20% of extrapolated AUC, were excluded from the mean.
N.S.: Not significant differences (p>0.05) by a Two-way GLM ANOVA

- Study ICHUV I-97: investigated the pharmacokinetics of 30, 40 and 60 mg of the autogel (0.287 mg/mg) given sc with the reference 30 mg microsphere preparation of lanreotide (given im) in 25 subjects (12 men, 12 women, 1 drop out).

The sc administration of Somatuline Autogel led to a lower and delayed early release than with im microspheres: $C_{\text{max}}$ (mean and 95% CI) 4.0 (1.6 – 6.4) vs. 23 (10 – 36) mg/l at the 30 mg dose; and $t_{\text{max}}$ (median and 95% CI) 5.7 (1.5 – 14) vs. 1.2 (0.7 – 2.1) h. The systemic bioavailability of lanreotide tended to be greater after sc autogel as compared to im.
microspheres, although this was not statistically significant: (mean and 95% CI) ~ 60% (40 – 80%) vs. ~ 47% (27 – 67%). The pharmacokinetics of the sc autogel were dose-proportional in the dose range studied.

The individual two-step compartmental analysis showed that the apparent terminal half-life (t1/2) of the sc autogel was longer than that of the microspheres. However, this was not confirmed by the population pharmacokinetic approach. Thus, the t1/2 of the two lanreotide formulations was comparable at between 15 to 30 days. Women had a significantly longer t1/2 than men (26 vs. 17 days) in the population approach, with only a tendency in this direction with the individual two-step analysis.

- **Study E33 52030 038**: different doses (60, 90 and 120 mg), formulations (0.205, 0.246 and 0.287 mg/mg) and routes of administration (sc or im) of lanreotide autogel were tested in 42 subjects (21 men, 21 women).

The lanreotide release profiles were similar regardless of the formulation, dose and route of administration of lanreotide autogel (except for 0.205 mg/mg 60 mg, im) and the absolute bioavailability was 60 to 70%. There was a linear relationship between the 60, 90 and 120 mg doses of 0.246 mg/mg lanreotide autogel im and serum lanreotide levels. The terminal half-life of 60 mg 0.246 mg/mg autogel was 23 ± 9 days after im administration and 33 ± 14 days after the sc route. The “apparent elimination” half-life appeared to be longer in women than men (27 vs. 21 days).

**Pharmacokinetics in patients**

**Study 00/PKR/051** is an interim report on the pivotal efficacy/safety study (E28 52030 709) and the subsequent long-term follow-up study (E28 52030 710). In study E28 52030 709, 144 acromegalic patients who had received at least 5 im doses of Somatuline LA 30 mg with a stable dose interval were then converted to deep sc lanreotide autogel (administered every 28 days at a fixed dose of 60, 90 or 120 mg for three doses). The follow-up study (E28 52030 710) took patients who had completed study 709 and continued lanreotide autogel for a period of one year.

Trough serum levels of lanreotide were similar after 3 doses of lanreotide autogel to those seen after equivalent doses of Somatuline LA 30 mg. Trough serum lanreotide levels were available after 7 consecutive monthly injections of the same dose of lanreotide autogel for 25, 13 and 18 patients taking 60, 90 and 120 mg of autogel, respectively (see table 2 below). Steady state serum lanreotide levels were reached after 4 injections in most patients and there was no evidence of accumulation of lanreotide.
**Table 2**
Comparative mean trough serum lanreotide levels at steady state in acromegalic patients following 5 *im* injections of lanreotide PR 30 mg at a dose frequency of 14, 10 and 7 days and following 7 deep subcutaneous injections of lanreotide autogel at doses of 60, 90 and 120 mg once monthly.

<table>
<thead>
<tr>
<th>Autogel Dose</th>
<th>60 mg</th>
<th>90 mg</th>
<th>120 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;minssPR 30&lt;/sub&gt;</td>
<td>1.94 (0.72)</td>
<td>2.95 (1.60)</td>
<td>3.06 (1.15)</td>
</tr>
<tr>
<td>C&lt;sub&gt;minssAutogel&lt;/sub&gt;</td>
<td>2.03 (0.62)</td>
<td>3.09 (1.22)</td>
<td>3.37 (1.53)</td>
</tr>
</tbody>
</table>

C<sub>minssPR 30</sub>: Trough serum lanreotide level at steady state after 5 doses of lanreotide PR 30mg
C<sub>minssAutogel</sub>: Trough serum lanreotide level after 7 doses of lanreotide autogel.

Note: All patients on 60mg lanreotide autogel are compared with lanreotide PR 30mg once every 14 days; all patients on lanreotide autogel 90 mg are compared with lanreotide PR 30mg once every 10 days; all patients on lanreotide autogel 120 mg are compared with lanreotide PR 30mg once every 7 days.

**Medical Assessor’s comments**
The data above support the use of the 0.246 mg/mg formulation of lanreotide autogel for 4-weekly dosing and administration by the deep *sc* route.

The apparent terminal half-life is consistently longer in women than men. Conflicting statements have been made as to whether this might be clinically relevant or not and this should be clarified. If available, data to resolve this issue should be provided from study E28 52030 710, which is due to be completed in June 2001.

Data should be provided concerning the possible effect of activity on the release profile of lanreotide from a deep *sc* gluteal injection. The applicant should discuss the relevance of the report in study ICHUV-1 of subject 216 KUB who indulged in strenuous exercise (marathon running) and who had an unusually short elimination half-life of 8 days.

**IV.3 Pharmacodynamics**
*Study 97/PKS/14*: this pharmacokinetic (PK)-pharmacodynamic (PD) study investigated the relationship between lanreotide serum levels and GH levels in 63 acromegalic patients from 5 studies that had responded to lanreotide (response was defined as: a decrease of ≥50% in basal GH levels or a normalisation of basal GH levels to ≤2.5 µg/l).

Lanreotide was administered subcutaneously (*sc*) or intramuscularly (*im*) as the immediate release formulation (IRF) or as prolonged release microspheres for periods of up to 12 months.

Individual analysis was performed in 54 patients. The EC<sub>50</sub> (the concentration of lanreotide required to reduce GH levels by at least 50%) for lanreotide was 0.5 µg/l and was not affected by the formulation or the route of administration. There was no evidence of tachyphylaxis as the EC<sub>50</sub> was stable in the long-term studies. The C<sub>2.5</sub> (the lanreotide concentration yielding GH levels less than 2.5 µg/l) were estimated from table 1 below: serum lanreotide levels up to 1.5 µg/l and 3.5 µg/l achieved GH levels below 2.5 µg/l in 46% and 81% of patients, respectively.
Table 3
FREQUENCY AND CUMULATIVE % OF PATIENTS WITH GH LEVELS INFERIOR TO 2.5 μg/l BY ESTIMATED LANREOTIDE LEVELS CATEGORIES

<table>
<thead>
<tr>
<th>Lanreotide levels (μg/l)</th>
<th>Number of patients</th>
<th>Number of patients % (frequency)</th>
<th>Cumulative number of patients</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5</td>
<td>2</td>
<td>4%</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>0.5-1</td>
<td>9</td>
<td>17%</td>
<td>11</td>
<td>20%</td>
</tr>
<tr>
<td>1-1.5</td>
<td>14</td>
<td>26%</td>
<td>25</td>
<td>46%</td>
</tr>
<tr>
<td>1.5-2</td>
<td>7</td>
<td>13%</td>
<td>32</td>
<td>59%</td>
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<td>2-2.5</td>
<td>4</td>
<td>7%</td>
<td>36</td>
<td>67%</td>
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<td>2.5-3</td>
<td>2</td>
<td>4%</td>
<td>38</td>
<td>70%</td>
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<tr>
<td>3-3.5</td>
<td>6</td>
<td>11%</td>
<td>44</td>
<td>81%</td>
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<td>3.5-4</td>
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<td>2%</td>
<td>45</td>
<td>83%</td>
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<td>4-5</td>
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<td>7%</td>
<td>49</td>
<td>91%</td>
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<td>5-6</td>
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<td>0%</td>
<td>49</td>
<td>91%</td>
</tr>
<tr>
<td>6-7</td>
<td>2</td>
<td>4%</td>
<td>51</td>
<td>94%</td>
</tr>
<tr>
<td>7-10</td>
<td>1</td>
<td>2%</td>
<td>52</td>
<td>96%</td>
</tr>
<tr>
<td>More</td>
<td>2</td>
<td>4%</td>
<td>54</td>
<td>100%</td>
</tr>
</tbody>
</table>

IV.4 Clinical efficacy
The efficacy data came from one study, the pivotal phase III study E28 52030 709 of lanreotide in acromegaly.

Study E28 52030 709: an “open, comparative multicentre phase III study evaluating the efficacy of three repeated deep subcutaneous administrations of lanreotide autogel (60, 90 or 120 mg) at fixed doses in acromegalic patients previously treated with lanreotide 30 mg PR”.

Patients were eligible if they had been treated with lanreotide PR 30 mg microspheres for at least 3 months and who had a diagnosis of active acromegaly made within the previous 5 years. Once enrolled, patients were to receive a further 5 doses of lanreotide 30 mg PR (the run-in period) at the same dose interval as before, followed by 3 deep sc injections of lanreotide autogel every 28 days. Patients receiving lanreotide PR at a dosing interval of between 12 and 16 days, 8 and 11 days or 5 and 7 days were switched to 60, 90 and 120 mg of lanreotide autogel, respectively (so patients continued to receive the same monthly total dose of lanreotide). The primary endpoint was the assessment of non-inferiority with respect to GH levels of 3 doses of lanreotide autogel as compared to lanreotide 30 mg PR, while a secondary endpoint was non-inferiority on insulin-like growth factor-1 (IGF-1) levels.

A total of 100 patients were planned and 144 patients (48% men, 52% women) were recruited from the 31 centres in 9 countries. The baseline characteristics of the per protocol (PP) and safety populations were similar. The results of the intention-to-treat (ITT) and PP populations were similar.

Non-inferiority analysis: the upper bound 95% confidence interval of the ratio of the geometric means of GH and IGF-1 levels at the end of the fourth interval of lanreotide 30 mg PR during the run-in period and after 3 doses of lanreotide autogel were 1.041 and 1.034, respectively (the lower bound limits were 0.926 and 0.961, respectively). These confidence intervals were lower than the limit of 1.25 and demonstrated the non-inferiority of lanreotide autogel (see table 3 below).
However, for all of the dose schedules of lanreotide autogel, at the end of the first dose interval, there was a decrease in the serum lanreotide level and an increase in the GH and IGF-1 levels (table 4).

**Table 4**
Mean trough GH and IGF-1 levels (µg/1) after treatment with lanreotide PR 30mg compared with mean GH and IGF-1 levels after treatment with lanreotide autogel every 28 days for 3 months (PP Population)

<table>
<thead>
<tr>
<th>Lanreotide Autogel dose</th>
<th>End 4th Interval Lanreotide 30mg PR N = 107</th>
<th>End 1st Interval Lanreotide Autogel N = 107</th>
<th>End 3rd Interval Lanreotide Autogel N = 107</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GH (µg / l)</td>
<td>GH (µg / l)</td>
<td>GH (µg / l)</td>
</tr>
<tr>
<td>All (no. of patients with data = 107)</td>
<td>2.82 ± 1.99</td>
<td>3.51 ± 2.90</td>
<td>2.87 ± 2.23</td>
</tr>
<tr>
<td>60mg (n=52)</td>
<td>2.59 ± 1.83</td>
<td>3.12 ± 2.38</td>
<td>2.33 ± 1.78</td>
</tr>
<tr>
<td>90mg (n=34)</td>
<td>2.57 ± 2.05</td>
<td>3.33 ± 3.28</td>
<td>3.03 ± 2.64</td>
</tr>
<tr>
<td>120mg (n=21)</td>
<td>3.78 ± 2.05</td>
<td>4.75 ± 3.21</td>
<td>3.92 ± 2.21</td>
</tr>
<tr>
<td></td>
<td>IGF-1 (µg / l)</td>
<td>IGF-1 (µg / l)</td>
<td>IGF-1 (µg / l)</td>
</tr>
<tr>
<td>All (no. of patients with data = 107)</td>
<td>322.6 ± 164.6</td>
<td>344.9 ± 169.6</td>
<td>316.6 ± 155.8</td>
</tr>
<tr>
<td>60mg (n = 52)</td>
<td>284.4 ± 159.7</td>
<td>306.3 ± 158.7</td>
<td>294.3 ± 160.7</td>
</tr>
<tr>
<td>90mg (n = 34)</td>
<td>328.0 ± 163.4</td>
<td>338.4 ± 149.6</td>
<td>301.9 ± 128.4</td>
</tr>
<tr>
<td>120mg (n = 21)</td>
<td>408.4 ± 151.3</td>
<td>451.0 ± 188.3</td>
<td>395.6 ± 165.6</td>
</tr>
</tbody>
</table>

Data Source: Table 56 in section 14.2

A summary of acromegalic symptoms is shown in table 4. The total numbers and percentages of patients with each symptom were similar at the end of the third interval of lanreotide autogel and at the end of the fourth interval of lanreotide 30 mg PR and most symptoms were mild or moderate in severity.

**Table 5**

Acromegaly Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>End 4th Interval Lanreotide 30 mg PR N = 107</th>
<th>End 3rd Interval Lanreotide Autogel N = 106</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>41 (38)</td>
<td>40 (38)</td>
</tr>
<tr>
<td>Swelling of extremities</td>
<td>36 (34)</td>
<td>29 (27)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>34 (32)</td>
<td>31 (29)</td>
</tr>
<tr>
<td>Headache</td>
<td>29 (27)</td>
<td>31 (29)</td>
</tr>
<tr>
<td>Night Sweats</td>
<td>25 (23)</td>
<td>22 (21)</td>
</tr>
</tbody>
</table>

Medical Assessor’s comments
The data provided demonstrate that 3 deep sc injections of lanreotide autogel are no less effective than lanreotide 30 mg PR with respect to GH, IGF-1 and symptoms in acromegaly.

At the end of the first dose interval of lanreotide autogel, serum lanreotide was lower and GH and IGF-1 levels were higher than after lanreotide 30 mg PR during the run-in period. In the absence of clinical data at the end of the first dose of lanreotide autogel, it is not possible to assess the relevance of these observations. The applicant should discuss this point and how it may impact on the dosing schedule: it may be preferable to give a larger first dose of lanreotide autogel when converting patients from Somatuline LA 30 mg.
No clinical data has been provided on the use of lanreotide autogel in neuroendocrine tumours, which is a licensed indication for Somatuline LA 30 mg. Nevertheless, the use of lanreotide autogel for this indication is justified given its pharmacokinetics (slightly greater bioavailability than lanreotide 30 mg PR microspheres and its half-life of 4 weeks) and its similar trough serum levels as compared to the same total monthly dose of lanreotide 30 mg PR when used for acromegaly. A clinical study of lanreotide autogel to relieve the symptoms of carcinoid neuroendocrine tumours is currently on going.

IV.5 Clinical safety
Overview of Safety Data
The clinical data for the assessment of the safety of lanreotide autogel in volunteers comes from the pharmacokinetic studies listed in section 6.2 as well as a study of the local tolerance of 60, 90 and 120 mg deep sc injections at different sites (study E55 52030 047). The safety data on lanreotide autogel in patients (with acromegaly) comes from the pivotal efficacy/safety study E28 52030 709 (144 patients) and allows comparison with lanreotide 30 mg PR in the same patients.

There were no clinically significant changes in any of these studies with respect to laboratory values, physical examination, heart rate or blood pressure. The observed ECG changes in study E92 52030 007 (decreased heart rate and QT prolongation) never exceeded normal limits.

Adverse events (AEs) can be divided into local reactions, those expected from the known properties of lanreotide (gastrointestinal tract, gall bladder and glucose metabolism) and unexpected adverse events. With respect to gastrointestinal events, cholelithiasis and changes in glucose metabolism, there were no new issues with lanreotide autogel as compared to the licensed Somatuline LA 30 mg microspheres (see table 5). The majority of these AEs were mild to moderate in severity.

Table 6 Number Of Patients Reporting AEs With An Incidence ≥ 5% (Safety Population)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Lanreotide 30 mg PR</th>
<th>Lanreotide Autogel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 144</td>
<td>N = 133</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Any AE</td>
<td>108 (75)</td>
<td>107 (80)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>55 (38)</td>
<td>38 (29)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31 (22)</td>
<td>23 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (18)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (10)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>5 (3)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (6)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Gall bladder sludge</td>
<td>4 (3)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3 (2)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (5)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>2 (1)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Hyperphosphataemia</td>
<td>4 (3)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>4 (3)</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>

Note: The denominator of each percentage is the number of patients who received at least one dose of lanreotide 30 mg PR or lanreotide autogel (N=144 and N=133, respectively)
The expected AEs that occurred with greater frequency with lanreotide autogel (hyperglycaemia, gall bladder sludge and cholelithiasis) were all mild in severity and not clinically significant.

**Adverse Reactions**

**Local Reactions**
Local tolerability was good in acromegalic patients with no significant differences in patients reporting pain, itching, erythema and indurations at the injection site between lanreotide 30 mg PR microspheres and lanreotide autogel. However, persistent palpable indurations were seen in 2/24 volunteers at 6 months post sc administration of lanreotide autogel (study E92 52030 007) and 20/27 volunteers at day 42 (study E55 52030 047). Retrospective ultrasound examination of volunteers in study E92 52030 007 showed that 6/19 had well-defined echogenic images 633 days (median) post injection. The clinical relevance of this finding is unclear but it is of note that animal data showed that some species could develop a granulomatous tissue reaction to sc lanreotide autogel. To-date, this has not been seen in acromegalic patients and the persistent palpable indurations in volunteers have not been associated with any other local or systemic AEs.

**Serious adverse events/deaths**
There were no drug-related serious AEs in acromegalic patients receiving lanreotide autogel and no deaths occurred during any of the studies. One serious AE of aseptic meningitis in a volunteer was observed 10 days following a sc injection of 60 mg of lanreotide. Although this was reported as possibly being related to the drug, the clinical details were in favour of a viral aetiology.

**Post-marketing experience**
There is considerable post-marketing experience with the current microsphere formulation of lanreotide (first licensed in France, 1994). The Periodic Safety Update Reports largely confirmed the expected side-effect profile. However, a number of rare, serious AEs were reported involving cardiovascular events and acute pancreatitis and assessed to be possibly or probably related to lanreotide.

**Conclusions on Safety**
The safety profile of these products is satisfactory and similar to that of Somatuline LA 30mg Powder for Suspension for Injection.

**IV.6 Risk Management Plan (RMP)**
The marketing authorisation holder has submitted an RMP in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to these products.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below.

**IV.7 Discussion on the clinical aspects**
The grant of marketing authorisations is recommended for these applications from a clinical perspective.
V  User consultation
Not applicable.

VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The currently approved labels are presented below:
### Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To add a new therapeutic indication &quot;The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease&quot;</td>
<td>UK/H/xxxx/WS/079</td>
<td>SmPC/PIL</td>
<td>02/07/2014</td>
<td>27/02/2015</td>
<td>Approval</td>
<td>Y</td>
</tr>
</tbody>
</table>
Annex I

Reference: PL 34926/0005-0019; PL 34926/0006-0020; PL 34926/0007-0021

Product: Somatuline Autogel 60, 90 & 120mg Solution for Injection

Marketing Authorisation Holder: Ipsen Limited

Active Ingredients: Lanreotide

Reason: To add a new therapeutic indication "The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease"

Background

The variation, classified as C.1.6a Type II extended, has been submitted by IPSEN PHARMA, France through a national worksharing procedure (the UK as Reference Authority with 24 Concerned Member States: AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK) according to Article 20 of Commission Regulation (EC) No 1234/2008. The variation affects several marketing authorisations in different EU Member States. All marketing authorisation holders have been confirmed as belonging to the same entity. Requirements for worksharing have been satisfied.

The scope of the variation is to add a new therapeutic indication, together with consequential changes to the Patient Information Leaflet, and changes in accordance with the updated QRD template.

Somatuline Autogel is currently indicated for:

- The treatment of individuals with acromegaly when the circulating levels of Growth Hormone (GH) and/or Insulin-like Growth Factor-1 (IGF-1) remain abnormal after surgery and/or radiotherapy, or in patients who otherwise require medical treatment. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalise these values.
- The treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours.

The variation application concerned a proposed additional indication (Section 4.1 of the SmPC) as follows:

- The treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adult patients with unresectable locally advanced or metastatic disease.

The proposed indication relates to an anti-tumour (growth inhibitory) action of the active substance, lanreotide, as distinct from a currently approved indication which relates to the provision of relief from carcinoid-like symptoms arising from the secretion of bioactive amines and hormones from functioning neuroendocrine tumours. To support the new indication, one pivotal Phase III study of clinical safety and efficacy, with a long term safety extension phase have been supplied in patients with GEP-NETs; in addition, supportive safety data have been derived from one double blind and three open label studies.

Supporting Evidence

A comprehensive clinical overview has been prepared by a suitably qualified physician and refers to 28 literature references published between 1997 and 2014.

Clinical studies were conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonisation (ICH) Consolidated Guideline on...
Good Clinical Practice (GCP). Multi-centre studies involved sites in the EU and in other countries including India and the USA. Studies adhered to all local regulatory requirements.

A tabular list of the studies submitted is provided below.

**Table 1: Listing of all clinical studies**

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Location of Study Report</th>
<th>Main Objective(s) of the Study</th>
<th>Study Design and Type of Control</th>
<th>Test Product(s); Dosage Regimen; Route of Administration</th>
<th>Number of Subjects</th>
<th>Healthy Subjects or Diagnosis of Patients</th>
<th>Duration of Treatment</th>
<th>Study Status; Type of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-55-52030-726</td>
<td></td>
<td>To assess the effect of lanreotide Autogel 120 mg compared to placebo on efficacy (progression free survival) and safety</td>
<td>Phase III, randomised, double blind, comparative, placebo controlled, parallel group, multicentre study</td>
<td>Lanreotide Autogel 120 mg; s.c. injections every 4 weeks</td>
<td>Randomised: 204</td>
<td>Well and moderately well differentiated nonfunctioning enteropancreatic neuroendocrine tumours</td>
<td>96 weeks</td>
<td>Full Study Report</td>
</tr>
<tr>
<td>2-55-52030-730</td>
<td></td>
<td>To assess the effect of lanreotide Autogel 120 mg compared to placebo on efficacy (use of rescue medication to control symptoms associated with carcinoid syndrome) and safety</td>
<td>Phase III, randomised, double blind, placebo controlled clinical study</td>
<td>Lanreotide Autogel 120 mg; s.c. injection every 4 weeks</td>
<td>Randomised: 115</td>
<td>History of carcinoid syndrome</td>
<td>Duration of the first two phases (double blind and IOL phases) was 48 weeks, LTOLE phase, up to two years after the last subject has completed his/her participation in the IOL phase</td>
<td>Data cut off date: 05 May 2013</td>
</tr>
<tr>
<td>2-55-52030-729</td>
<td></td>
<td>To assess the effect of lanreotide Autogel 120 mg on long term safety and efficacy (progression free survival)</td>
<td>Phase III, nonrandomised, multicentre, open label, extension study of Study 2-55-52030-726</td>
<td>Lanreotide Autogel 120 mg; s.c. injections every 4 weeks</td>
<td>Included: 88</td>
<td>Nonfunctioning enteropancreatic neuroendocrine tumours</td>
<td>Up to 3.9 years at the cut off date (planned for a maximum duration of approximately eight years)</td>
<td>Interim Full Study Report, Data cut off date: 30 March 2013</td>
</tr>
<tr>
<td>A-92-52030-166</td>
<td></td>
<td>To assess the effect of lanreotide Autogel 120 mg on efficacy (tumour growth stabilisation) and safety</td>
<td>Phase II, multi-centre, open label, noncontrolled, noncomparative study</td>
<td>Lanreotide Autogel 120 mg; s.c. injections every 4 weeks</td>
<td>Included: 30</td>
<td>Progressive neuroendocrine tumours</td>
<td>92 weeks</td>
<td>Full Study Report</td>
</tr>
<tr>
<td>E-47-52030-718</td>
<td></td>
<td>To assess the effects of lanreotide Autogel at doses of 60 mg, 90 mg or 120 mg on efficacy (relief of clinical symptoms) and safety</td>
<td>Phase II/III, open label, multicentre, dose titration study</td>
<td>Lanreotide Autogel 60, 90 and 120 mg; deep s.c. injection every 4 weeks</td>
<td>Included: 71</td>
<td>Carcinoid neuroendocrine tumours</td>
<td>Six months</td>
<td>Full Study Report</td>
</tr>
<tr>
<td>A-99-52030-216</td>
<td></td>
<td>To assess subject preference of two lanreotide Autogel administration practices; selfpartner or health care practitioner administration, efficacy and safety</td>
<td>Phase IV, open label; randomised, crossover, noncomparative study</td>
<td>Lanreotide Autogel 90 or 120 mg; deep s.c. injections every 4 weeks</td>
<td>Included: 20</td>
<td>Neuroendocrine tumours</td>
<td>Seven or eight months</td>
<td>Full Study Report</td>
</tr>
</tbody>
</table>

One pivotal clinical study, 2-55-52030-726 (Study 726) was conducted to demonstrate the efficacy and safety of lanreotide Autogel 120 mg in the treatment of subjects with asymptomatic GEP NETs. In this study, a total of 101 subjects were treated every 4 weeks with lanreotide Autogel 120 mg and 103 subjects received placebo, for a duration of 96 weeks. Additional evidence for the long term safety of lanreotide Autogel is provided by its extension phase, Study 2-55-52030-729 (Study 729, N=88). In addition to that provided in Studies 726 and 729, supportive safety data are derived from one double blind (DB) phase III trial (2-55-52030-730, Study 730) and three open label (OL) studies (Study A-92-52030-166 (Study 166); Study A-99-52030-216 (Study 216) and Study E-47-52030-718 (Study 718) of lanreotide Autogel administered using the intended dosing regimen in subjects with asymptomatic and symptomatic GEP NETs. A total of 378 unique subjects were treated with lanreotide Autogel in these studies and were included in the safety population. Of these 378 subjects,
159 were treated with lanreotide Autogel 120 mg in the DB, placebo controlled Studies 726 and 730. The remaining 219 subjects received lanreotide Autogel in the OL Studies 729 (N=47 previously treated with placebo in Study 726), 718 (N=71), 216 (N=26) and 166 (N=30), or in the OL phases of Study 730 (N=45 previously treated with placebo in Study 730).

A summary of the studies included in the safety population is provided below.

Table 2 – summary of studies included in the safety population

<table>
<thead>
<tr>
<th>Abbreviated number</th>
<th>Study design</th>
<th>Lanreotide Autogel dose (duration of treatment)</th>
<th>Number of subjects treated with lanreotide Autogel</th>
</tr>
</thead>
<tbody>
<tr>
<td>726</td>
<td>Phase III, randomised, double blind, comparative, placebo controlled, parallel group, multicentre study.</td>
<td>120 mg / 4 weeks (96 weeks)</td>
<td>Asymptomatic: 101, Symptomatic: 0</td>
</tr>
<tr>
<td>729</td>
<td>Phase III, open label extension of Study 726</td>
<td>120 mg / 4 weeks (maximum 8 years)</td>
<td>Asymptomatic: 41 LA:LA, Asymptomatic: 0</td>
</tr>
<tr>
<td>730</td>
<td>Phase III, double blind, randomised placebo controlled study followed by an initial open label phase and a long term open label extension phase [b]</td>
<td>120 mg / 4 weeks (48 weeks)</td>
<td>Asymptomatic: 0, Symptomatic: 103[c]</td>
</tr>
<tr>
<td>166</td>
<td>Phase II, open, single group multicentre study</td>
<td>120 mg / 4 weeks (92 weeks)</td>
<td>Asymptomatic: 11, Symptomatic: 19</td>
</tr>
<tr>
<td>216</td>
<td>Phase IV, international, open label, randomised, cross over study</td>
<td>90 or 120 mg / 4 weeks (7 or 8 months)</td>
<td>Asymptomatic: 0, Symptomatic: 26</td>
</tr>
<tr>
<td>718</td>
<td>Open phase II/III, multicentre, dose titration study</td>
<td>60, 90 or 120 mg / 4 weeks (6 months)</td>
<td>Asymptomatic: 0, Symptomatic: 71</td>
</tr>
</tbody>
</table>

CLINICAL PHARMACOLOGY

The currently approved formulation of lanreotide Autogel was used in all of the studies conducted to demonstrate efficacy and/or safety in support of this application. These were efficacy study 2-55-52030-726 (Study 726) and safety studies 2-55-52030-729 (Study 729), 2-55-52030-730 (Study 730), A-92-52030-166 (Study 166), A-99-52030-216 (Study 216) and E-47-52030-718 (Study 718). No new bioavailability or bioequivalence studies were, therefore, performed or necessary.

In the clinical studies presented in this dossier, pharmacokinetic (PK) data were obtained in four phase II and phase III studies in subjects with GEP NETs. These were the phase II/III study (Study 718), the phase II study (Study 166), and the phase III studies (Study 726 and Study 730).

BIOANALYTICAL METHODS:

Radioimmunoassays (RIAs) were used for both the quantification of lanreotide in serum and for the detection of antibodies to lanreotide in serum.

CLINICAL PHARMACOKINETICS - BACKGROUND:

No new dedicated clinical PK studies have been submitted with the application as the PK of lanreotide Autogel has been extensively studied in healthy volunteers and acromegalic subjects and was contributed as supportive data to the dossier.
PK in Healthy Subjects:
Lanreotide Autogel has a satisfactory prolonged release profile, compatible with a 4 week dosing interval. The release profile of lanreotide Autogel is characterised by an initial burst on the first day of administration that determines the maximum serum concentration \( (C_{\text{max}}) \) which is observed with a median time to maximum serum concentration \( (T_{\text{max}}) \) in the range of 0.29 to 0.50 days (7 to 12 h). This is followed by a more sustained release, to give a long apparent terminal half life \( (t_{\frac{1}{2}}) \) of 23 to 30 days, compared with approximately 2 h following i.v. administration of lanreotide IRF. The apparent terminal \( t_{\frac{1}{2}} \) of lanreotide Autogel is limited by the release from the depot and not by the disposition \( t_{\frac{1}{2}} \) of the peptide. The absorption from the depot site is therefore the rate limiting step.

A high variability in intra-individual \( C_{\text{max}} \) values was observed. Some variability was also seen in the \( T_{\text{max}} \) data, with most subjects having values ranging from 2 to 48 h. However, the interindividual variability in the area under the plasma concentration versus time curve (AUC) was moderate (24 to 28%).

Exposure was dose proportional with AUC values ranging from 1880±458 to 3620±922 ng.h/mL.

A population PK analysis was conducted in healthy subjects treated with IRF 7 μg/kg sc and 60, 90 and 120 mg sc lanreotide Autogel. A three compartment model parameterised in terms of clearance, central volume, two peripheral volumes, lag time and bioavailability was developed. The absorption rate was modelled as exponentially decreasing with time. Clearance, volume of distribution and bioavailability were 554 L/day, 15.1 L and 63%, respectively. A covariate analysis indicated no effect of age, weight and gender on the PK profile of lanreotide Autogel.

PK in Acromegalics:
PK in acromegalics is similar to that in healthy subjects. Repeat dose studies have shown that serum lanreotide concentrations reached steady state after 4 months (4 injections administered at 4 weekly intervals). The PK parameters were dose proportional over the dose range 60 to 120 mg.

Lanreotide Autogel exhibits an initial rapid release phase following injection, followed by a sustained release phase from the depot site. The Autogel formulation by deep subcutaneous administration considerably extends the apparent plasma elimination half life to 23 to 30 days, compared to approximately 7 to 12 h following IV administration of lanreotide immediate release formulation. Slow release from the site of injection is therefore the principal determinant of the extended elimination phase which is consistent with a 4 weekly administration schedule. Clearance, volume of distribution and bioavailability modelled from a population PK analysis were, respectively, 554 L.day, 15.1 L and 63% respectively. PK parameters are dose proportional over the range 60 to 120 mg. Covariate analysis showed no effect of age, weight or gender on the PK profile of lanreotide Autogel. The PK profile of lanreotide Autogel displays no particular features that would cause concern when extrapolating from these populations to patients with GEP-NETs.

Pharmacokinetics of Lanreotide Autogel in GEP-NET patients (Pooled Analysis)
In order to build a population PK model, sparse blood samples for the measurement of serum lanreotide concentrations and putative antibodies to lanreotide in subjects with GEP NETs were obtained in four phase II/III studies: Study 726, (phase III, pivotal for efficacy), the phase III Study 730, the phase II/III Study 718 and the phase II Study 166. In addition to the presentation of data from individual studies, the sponsor conducted a pooled population PK analysis from PK data collected in these four studies. The potential intrinsic sources of variability in lanreotide pharmacokinetics such as age, gender, race, body weight, and markers of renal and hepatic function were investigated using the population PK analysis.

An attempt to characterise the relationship between exposure following a dose of 120 mg lanreotide and efficacy markers (tumour size and biomarker endpoints (plasma chromogranin A, CgA)) and safety (e.g. adverse events (AEs), serious adverse events (SAEs), deaths) was made. In addition, the immunogenicity profile of lanreotide across studies was evaluated.
Pharmacokinetic Parameters in Subjects with GEP NETs

In subjects with GEP NETs, steady state serum lanreotide concentrations were reached after the 4th or 5th injection of lanreotide Autogel 120 mg. The mean observed trough serum lanreotide concentrations at steady state ranged from 5.3 to 8.6 ng/mL in Studies 726, 730 and 166 and were slightly lower in Study 718 (mean of 4.1 ng/mL). However, due to the titration design of Study 718, there were a limited number of subjects who received enough consecutive doses of lanreotide Autogel 120 mg to reach steady state. Non linear mixed effect modelling was used in order to define the structural PK model as well as the interindividual variability of the PK parameters. The analysis was performed on 290 subjects with asymptomatic or symptomatic GEP NETs across the four studies. A two compartment model parameterised on apparent total serum clearance (CL/F), apparent volume of distribution (V/F) and the first order rate constant of absorption (KA) best described the PK data in the pooled analysis.

The summary exposure PK parameters for the pooled PK analysis and the derived lanreotide Autogel 120 mg exposure parameters after a single injection, and at steady state, are shown in Table 3, Table 4 and Table 5, respectively:

Table 3: Summary statistics of lanreotide pooled pharmacokinetic model parameters

<table>
<thead>
<tr>
<th>Drug</th>
<th>CL/F (L/day)</th>
<th>V/F (L)</th>
<th>KA (day⁻¹)</th>
<th>t₁/₂ KA (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanreotide Autogel 120 mg (N=298)</td>
<td>519 (129)</td>
<td>26.3 (30.2)</td>
<td>0.0174 (0.009)</td>
<td>49.8 (28.0)</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>503</td>
<td>20.7</td>
<td>0.0156</td>
<td>44.4</td>
</tr>
<tr>
<td>Median</td>
<td>504</td>
<td>18.3</td>
<td>0.0157</td>
<td>44.3</td>
</tr>
<tr>
<td>5th and 95th percentiles</td>
<td>327 to 743</td>
<td>13.1 to 85.9</td>
<td>0.0075 to 0.0358</td>
<td>19.3 to 93.0</td>
</tr>
</tbody>
</table>

CL/F=apparent total plasma clearance; V/F=apparent volume of distribution; KA=constant of absorption; t₁/₂KA=absorption half life; SD=standard deviation

Table 4: Summary statistics of derived lanreotide Autogel 120 mg exposure parameters after a single dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC₀-28 (ng*day/mL)</th>
<th>Cmax (ng/mL)</th>
<th>Cmin (ng/mL)</th>
<th>Cavg (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>88.6 (40.1)</td>
<td>7.49 (7.58)</td>
<td>2.40 (0.93)</td>
<td>3.44 (1.57)</td>
</tr>
<tr>
<td>Geometric Mean</td>
<td>80.1</td>
<td>5.73</td>
<td>2.20</td>
<td>3.11</td>
</tr>
<tr>
<td>Median</td>
<td>83.8</td>
<td>5.39</td>
<td>2.38</td>
<td>3.24</td>
</tr>
<tr>
<td>5th and 95th percentiles</td>
<td>38.5 to 162</td>
<td>2.17 to 20.6</td>
<td>1.14 to 4.05</td>
<td>1.48 to 6.33</td>
</tr>
</tbody>
</table>

AUC=Area under the curve over the dosing interval (4 weeks); Cmax=maximum concentration; Cmin=concentration at the end of a dosing interval; Cavg=average concentration over the dosing interval (4 weeks); SD=standard deviation

Table 5: Summary statistics of derived lanreotide Autogel 120 mg exposure parameters at steady state

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC₀-28 (ng*day/mL)</th>
<th>Cmax (ng/mL)</th>
<th>Cmin (ng/mL)</th>
<th>Cavg (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>239 (64.8)</td>
<td>13.9 (7.44)</td>
<td>6.56 (1.99)</td>
<td>8.64 (2.36)</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>232</td>
<td>12.8</td>
<td>6.23</td>
<td>8.35</td>
</tr>
<tr>
<td>Median</td>
<td>231</td>
<td>11.9</td>
<td>6.49</td>
<td>8.41</td>
</tr>
<tr>
<td>5th and 95th percentiles</td>
<td>158 to 358</td>
<td>7.69 to 25.5</td>
<td>3.53 to 9.99</td>
<td>5.49 to 12.9</td>
</tr>
</tbody>
</table>

AUC=Area under the curve over the dosing interval (4 weeks); Cmax=maximum concentration; Cmin=concentration at the end of a dosing interval; Cavg=average concentration over the dosing interval (4 weeks); SD=standard deviation

After a single injection of lanreotide Autogel 120 mg, a mean Cmax value of 7.49±7.58 ng/mL was reached within the first day. At steady state, the mean Cmax value was 13.9±7.44 ng/mL and the mean trough serum value was 6.56±1.99 ng/mL. The mean apparent terminal half life was 49.8±28.0 days.

Cmax and AUC were higher at steady state compared to values following single dose administration but accumulation was not disproportionate for the length of elimination half life. It is noted however...
that mean plasma elimination half-life was somewhat longer (~50 days) in patients with GEP-NETs compared with healthy volunteers (23 – 30 days).

Clarification has been provided in section 5.2 of the SmPC that steady state is reached somewhat later than originally estimated (after 5 injections). It has been confirmed that although GEP-NET patients have a higher systemic exposure to lanreotide, dose for dose, compared with acromegalics (due to diminished renal clearance) this does not translate into a notably altered safety profile. There are however a few side effects that occur more commonly in GEP-NETs (asthenia, hyperglycaemia and diabetes mellitus); in the case of cholelithiasis however this is more common among acromegalics. This is now reflected in a revised table of side effects in section 4.8 which in all cases states the higher frequency categories whether for GEP-NETs or acromegaly.

**Influence of subject demographics**

In order to assess the effect of subject characteristics on the PK profile of lanreotide Autogel 120 mg, a number of covariates were evaluated using a population PK modelling approach. This analysis was conducted on a total of 290 subjects with symptomatic and asymptomatic GEP NETs included in the pooled PK analysis of Studies 726, 730, 718 and 166.

On the basis of this analysis, no dosage adjustment of lanreotide Autogel was considered to be necessary for age, gender, body weight, race, asymptomatic versus symptomatic GEP-NETs, renal impairment or hepatic impairment.

**Relationship Between Lanreotide Exposure and Pharmacodynamic Effects (Study 726)**

The relationship between pharmacodynamic parameters (plasma chromogranin A or tumour size) and serum lanreotide concentrations was examined in a non linear, mixed effect model of data obtained in Study 726.

A total of 1296 chromogranin A measurements obtained from 200 subjects were used in the PK/PD analysis. No correlation between plasma CgA levels and lanreotide exposure could be demonstrated.

A total of 1057 tumour size of target lesions (sum of largest diameters) measurements obtained from a total of 196 subjects were used in the PK/PD analysis. Measurements were obtained over a period of 96 weeks after the start of study treatment. Most of the subjects who showed an increase in tumour size were in the placebo group and the subjects experiencing a tumour size decrease were in the lanreotide Autogel 120 mg treatment arm. In the first step of PK/PD modelling the drug effect was captured. However, in a second step, it was not possible to relate the drug effect on tumour size of target lesions with lanreotide exposure using the current available data.

The relationship between drug related adverse events of special interest (serious and non-serious) and lanreotide PK descriptors was investigated. In the population PK analysis, sufficient data were available for analysis in four event categories (GI effects including and excluding diarrhoea, administration site reaction and pancreatitis). No trend in any plots in any of the four tested AE categories was observed and therefore no relationship between lanreotide PK descriptors and the occurrence of these adverse events was detected. In conclusion, there was overall no clear correlation between lanreotide exposure and pharmacodynamic readouts but this is limited by the nature of the analysis.

**Immunogenicity**

Low and variable rates of immunogenicity (development of anti-drug antibodies, ADA) were recorded in subjects with GEP-NETs treated with lanreotide Autogel in the four studies included in the population OK analysis. Incidence of ADA positivity ranged from 0.93% to 11% and there was no clear correlation with duration of treatment or dose. Comparisons of PK profiles from ADA positive and negative subjects in study 726 suggested no difference. There was also no correlation between development of ADAs and loss of efficacy. It is concluded that the presence of ADAs does not interfere with the PK profile or with the efficacy or safety of the drug.
Clinical efficacy

The primary efficacy data are derived from the pivotal, randomised, double blind, placebo controlled, multicentre, Study 726. The primary objective of Study 726 was to assess the effect of lanreotide Autogel 120 mg administered once every 4 weeks for a duration of 96 weeks, compared with placebo injections every 4 weeks, on progression-free survival (PFS) in subjects with well or moderately differentiated non functioning (asymptomatic) GEP NETs.

Study 729 is an ongoing, nonrandomised, multicentre, open label extension of Study 726. Eligible subjects either had stable disease after 96 weeks (irrespective of treatment received during Study 726) or had progressive disease (PD) during treatment with placebo in Study 726 that was confirmed by code break. All subjects received deep SC injections of lanreotide Autogel 120 mg every 4 weeks. Not all eligible subjects could be enrolled from Study 726 as some investigational sites elected not to participate in the extension study. The primary objective of Study 729 was assessment of the long term safety of lanreotide Autogel 120 mg. The long term efficacy of lanreotide Autogel 120 mg was assessed as a secondary objective.

Main study – Study 726

Methods

The pivotal efficacy and safety study, 726, was designed as a randomised, double blind, placebo controlled, multicentre study. Given the indolent nature of the disease, the study was conducted over a fixed duration (2 years) as opposed to an event-driven non-fixed duration study. A panel of independent experts recommended a fixed duration of 2 years as an adequate time for evaluating the safety and efficacy in this population of patients that would also permit a placebo control.

Inclusion criteria:

- Adults aged >18 years with histologically confirmed well or moderately differentiated nonfunctioning enteropancreatic endocrine tumours with primary localisation in the pancreas, midgut, hindgut or of unknown origin.
- No treatment with a SSTa at any time prior to study entry, except if that treatment was for less than 15 days and had been received more than 6 months before study entry;
- Metastatic disease and/or locally advanced inoperable tumours or had refused surgery;
- Absence of hormone related symptoms;
- ≥Grade 2 octreoscan assessed using the Krenning scale, during the Screening period or within 6 months prior to study entry (Visit 1) for the organ of target lesions;
- World Health Organisation (WHO) performance score ≤2,
- Biopsy performed within 6 months prior to the Screening visit if the subject had previous cancer, or evidence of clinical progression.

The screening process assessed whether subjects had progressive disease (PD) at baseline. Two computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed between 12 to 24 weeks after the Screening visit. The definition of PD was consistent with Response Evaluation Criteria in Solid Tumours [RECIST V1.0]) and based on central assessment of tumour progression. The presence or absence of tumour progression and previous therapies at study entry were included as stratification criteria. The inclusion of subjects with rapidly progressing tumours and those with symptoms requiring treatment with SSTas was avoided as they may have been randomised to receive placebo. It was considered unethical to maintain such subjects on placebo for the planned 2 year duration of the study.

Subjects with well or moderately differentiated tumours and with a proliferation index (Ki67) <10% or, in samples where the Ki67 antigen could not be reliably quantified, a mitotic index ≤2 mitosis/10 high power fields (HPF), were recruited. At the time of study design no active therapy had been shown to delay progression of disease in this subject population. Use of placebo as a comparator was therefore considered to be appropriate and acceptable.
Study 726 commenced enrolment in June 2006 and the study was completed in April 2013, consistent with a slow rate of recruitment due to the rarity of the condition. It is agreed that at the time of study design, the use of somatostatin analogues in the anti-proliferative treatment of gastroenteropancreatic tumours was not established; furthermore, somatostatin analogue therapy is currently authorised in Europe for tumours of mid-gut origin only and the study population in the case of the lanreotide pivotal trial was broader than this in including pancreatic and hindgut tumours. For the treatment of pancreatic NETs, other medical therapies including the mTOR inhibitor everolimus and the tyrosine kinase inhibitor sunitinib are authorised but clinical practice has to date not established any clear treatment hierarchy. In general it would be preferred for a pivotal study to compare an investigational product with an established therapy, in order to investigate non-inferiority at a minimum or superiority as an ideal, there is justification in these circumstances for a placebo-controlled study without an active comparator arm.

**Efficacy Endpoints:**

*Primary Endpoint*

The primary efficacy endpoint, progression free survival (PFS), was the time from randomisation to either disease progression (PD) or death occurring within 96 weeks after first treatment administration. All tumour assessments were based on an independent central review of radiological scans (CT or MRI) using the RECIST Version 1.0 and performed every 12 weeks during the first year of the Treatment Period and every 24 weeks during the second year of the Treatment Period. Only centrally assessed disease progression, and ‘on study’ deaths were included as events in the assessment of PFS. An on study death was defined as any death occurring during the course of the study, within 4 weeks of final study treatment or during the follow up period.

Secondary efficacy outcomes included a comparison of the proportion of subjects alive and without PD between treated and placebo groups at 48 and 96 weeks, a comparison of time to PD in subjects with progression, an evaluation of overall survival (OS), and change from baseline in circulating biomarkers – including CgA, 5-HIAA and pancreatic polypeptide. Additional secondary efficacy objectives were assessment of quality of life (QoL) using validated instruments and the pharmacokinetic profile of lanreotide Autogel 120 mg.

It is agreed that progression free survival can be an acceptable basis for drug approval in the case of an indolent tumour where expected survival after progression is long and where overall survival data could be confounded by subsequent therapies. The analysis of PFS has been determined using blinded radiological assessments and RECIST criteria. The Consensus report of the National Cancer Institute neuroendocrine tumour clinical trials planning meeting has also endorsed PFS as a primary endpoint for both phase III and phase II studies of these indolent tumours where survival is not a feasible endpoint, but where a delay in progression is clinically relevant and may be expected even for treatments not demonstrating objective responses.

**Dose selection rationale:**

The dose of lanreotide Autogel selected for development for this indication is 120 mg administered once every 4 weeks. The rationale for this dose selection includes reports that there is an SSTα concentration dependent inhibition of cell growth with optimum antiproliferative effects seen at higher doses than those doses required for suppression of symptoms due to hormonal effects. Given that the highest available dose that could be administered clinically also had an acceptable safety profile, this was used for the pivotal Study 726 in order to maximise efficacy without compromising subjects’ safety.

For provision of symptomatic relief in GEP-NETs, Somatuline Autogel is currently recommended at a starting dose of 60 to 120 mg every 28 days, with adjustment of dose according to response. In the treatment of acromegaly doses between 60 and 120 mg every 28 days are given and treatment is titrated according to response. Selection of a 120 mg dose for the anti-proliferative treatment of GEP-NETs is considered acceptable as there is sufficient patient experience at this dose from other indications; furthermore, dose escalation would not be recommended to reduce the risk of acquisition of tumour resistance by upregulation of anti-apoptotic and other tumour-promoting pathways. The proposed posology is therefore endorsed.
**Statistical Considerations**

**Sample Size**
The sample size was calculated based on assumptions supplied by an advisory board of independent experts consulted during the design of Study 726. These assumptions included:

- An expected rate of progression or death in the placebo group (based on known behaviour of the disease) of 0.80;
- An expected rate of progression or death in the active treatment group (based on a 20% improvement in PFS being considered clinically relevant) of 0.60,
- A constant hazard ratio (HR) of 0.57 over time,
- A Type I error 0.05, two sided test, 90% power.

A sample size of 100 subjects per group (i.e. 200 subjects in total) was therefore estimated to be necessary.

Based on an anticipated survival rate in the Placebo group at 4 years of 73.5%, HR of 0.57 and the number of deaths required to detect HR, the power of the overall survival (OS) analysis was estimated at only 44%. The comparison of OS was therefore planned as a supportive test in the event of a significant result for the primary efficacy endpoint (via a hierarchical testing procedure).

The study was adequately powered for the chosen primary endpoint of progression free survival. It is understood, given the indolent nature of the disease, a high expected proportion of survivors after 2 years even in the placebo group, and the low anticipated rate of recruitment, that the study could not be powered for overall survival. It is therefore acceptable that OS was considered as a secondary and not as a primary endpoint.

**Analysis of the Primary Endpoint**
All statistical tests (two sided) were performed with Statistical Analysis System (SAS)® (version 9.3) and with a type I error rate set at 5%. The primary analysis of PFS was based on all randomised subjects (intent to treat, ITT) and estimated using the stratified log rank test based on the Kaplan Meier (KM) method with the baseline stratification factors (presence/absence of tumour progression at Baseline and presence/absence of previous therapy at entry) as strata.

Due to the small number of subjects with progression at baseline, the stratum defined by presence of progression at baseline and presence of previous therapy at entry was combined with the stratum defined by presence of progression at baseline and absence of previous therapy at entry. The randomisation stratification factors therefore were represented by three strata in the analyses.

A supportive analysis of the primary efficacy parameter was performed based on the Cox proportional hazard (PH) model with the baseline stratification factors as covariates. The Cox PH model was also used to generate survival estimates for each treatment group, adjusted for the baseline stratification factors.

The analysis of the primary efficacy endpoint was repeated for the following prespecified subgroup according to the following variables: progression at baseline, previous therapy at entry, primary tumour type (pancreatic, midgut, hindgut and other/unknown) and whether or not subjects were enrolled within the United States (US versus non US). Due to the reduced sample sizes within subgroup categories, the unstratified log rank test was run.

Further exploratory analyses were performed in order to investigate the potential influence of preselected baseline covariates on the primary efficacy variable. These covariates included: location of the primary tumour, US versus non US, region (Western European, Eastern European and India, US), gender, age, BMI, ethnicity, time since diagnosis, hepatic tumour load, Baseline Ki67, tumour grade, Baseline CgA, previous chemotherapy for an asymptomatic NET and previous surgery for the primary tumour. The robustness of the analysis of the primary endpoint was investigated in five sensitivity analyses which evaluated the following:
1. withdrawals due to PD based on the investigator’s judgment (despite there being a central assessment of stable disease) considered as events;
2. all withdrawals (for disease progression or other reasons) considered as events;
3. correction of the primary analysis for potential bias in the follow up schedules;
4. the potential for bias due to the reduced frequency of CT/MRI scans in the second year of the study.
5. calculation of PFS from the start of treatment rather than from the time of randomisation.

The analyses of the primary efficacy endpoint (including KM plots with the stratified log rank test, the KM summary table and the Cox PH model) were repeated for these five sensitivity analyses.

Results

Patient Population
A total of 264 subjects were screened in Study 726 from 70 open sites. Of these, 204 subjects were randomised from 48 active sites in 14 countries to form the intention to treat (ITT) population: 101 subjects randomised to receive lanreotide Autogel 120 mg and 103 subjects randomised to receive placebo.

Of the 204 subjects enrolled in the study, 30 were in the US, 167 were in the EU and the remaining 7 subjects were recruited in India. The majority of subjects were recruited in the EU. There was no significant imbalance between placebo and lanreotide treated groups in the different geographical regions.

The median duration of exposure to study treatment for the Safety population was 95.86 weeks in the lanreotide Autogel 120 mg group and 60.14 weeks in the placebo group. Subjects received a median of 24 injections in the lanreotide Autogel 120 mg group and a median of 15 injections in the placebo group. The lower median number of injections in the placebo group was due to the withdrawal from the study of subjects who progressed. Safety data were collected at each assessment visit according to the assessment schedule at each study site.

Study Completion and Withdrawals
Randomised subjects who completed all specified assessments of Study 726 or were withdrawn from the study because of tumour progression or death were defined as study completed subjects. In total, 83.8% (171/204) of subjects completed the study with nearly the same number of subjects completing in both treatment groups: 84.2% (85/101) in the lanreotide Autogel 120 mg group and 83.5% (86/103) in the placebo group. More than twice as many subjects treated with lanreotide Autogel 120 mg completed the study without an event (centrally assessed PD or death) compared with subjects treated with placebo (52%, 53/101 subjects versus 25%, 26/103 subjects). In total, 18 subject withdrawals occurred in the lanreotide Autogel 120 mg group compared with a total of 21 subject withdrawals in the placebo group. Reasons for withdrawals in both groups included investigator assessment of PD, daverse events (AEs), consent withdrawal, protocol violation, and other reasons. Withdrawals due to investigator’s judgement of PD were similar in both groups. The proportions of subjects who withdrew due to AEs were low in both groups: 3.0% (3/101 subjects) in the lanreotide Autogel 120 mg group versus 2.9% (3/103 subjects) in the placebo group.

Demographic and Baseline Characteristics
The demographic and baseline characteristics of the ITT population were well balanced between the treatment groups. In the ITT population, 52.5% (107/204) were male, and the mean (standard deviation, SD) age was 62.7 (10.5) years (range: 30 to 92 years). The majority of subjects (82.4%) had a WHO performance status score of 0 (normal activity) and no subjects reported a WHO performance status score of ≥2. All subjects had a positive octreoscan with a mean Krenning scale score of 3.2 (0.7) and no subject had a score of ≤1. The demographic characteristics, WHO performance status score and Krenning scale score were well balanced between the two treatment groups.
**Disease History**

Mean (SD) time since diagnosis was 33.46 (43.65) months and was similar between the two treatment groups. The large majority of subjects (80.9%, 165/204) had no PD and were naïve to medical treatment, and 14.7% (30/204) had no PD and had received prior medical treatment; 3.4% (7/204) of subjects had PD but were naïve to medical treatment, and only 1% (two subjects in the lanreotide Autogel 120 mg group) had PD and had received prior medical treatment.

**Tumour Characteristics**

The majority of subjects (99.5%, 203/204) had well differentiated tumours. One subject had a moderately well differentiated tumour. All tumours had a low proliferation index (Ki67 <10%). Most subjects (80.4%, 164/204) had primary tumours originating in the pancreas (44.6%, 91/204) or midgut (35.8%, 73/204) and more subjects had Grade 1 than Grade 2 tumours (Grade 1: 69.1%, 141/204; Grade 2: 29.9%, 61/204; two subjects without tumour grade). The hepatic tumour load (HTL) was ≤25% in 62 (61.3%) subjects and >25% in 39 (38.7%) subjects. A higher proportion of subjects with a HTL >25% were treated with lanreotide Autogel 120 mg (39/101 (38.6%)), compared with placebo (28/103 (27.2%)). With the exception of four gastrinomas which were well controlled by proton pump inhibitors (PPIs), they had no hormone related symptoms.

Location of primary tumour was not a stratification criterion which resulted in some imbalance between treated and placebo groups: pancreatic NET (42/101 (41.6%) in the lanreotide group compared with those in the placebo group (49/103 (47.6%)); midgut (33/101 (32.7%) lanreotide versus 40/103 (38.8%) placebo) and hindgut (11/101 (10.9%) lanreotide versus 3/103 (2.9%) placebo).

In Study 726 the vast majority of tumours were recorded at baseline as well differentiated (99%) versus moderately differentiated (1%). Furthermore, although tumour grades G1 and G2 appeared to be well represented at baseline (50.5% and 29.9% respectively, with Ki67 unknown in 20% of patients), tumours were graded as G2 with a proliferation index (Ki67) of 2 - <10% whereas according to the WHO classification, G2 grade spans a Ki67 index of 3 – 20%, suggesting that patients were not fully reflective of the G2 stage.

The indication should make it sufficiently clear that lanreotide should only be recommended for a subset of Grade 2 GEP-NETs as defined by a Ki 67 index up to 10%. It is important to reflect in the indication that lanreotide cannot currently be recommended for all Grade 2 GEP-NETs that span the range of Ki 67 index from 3 – 20% as the data do not support this.

It is reiterated that the vast majority of patients included in the pivotal study were classed as having “well differentiated” disease. It is however accepted that a sizeable proportion of the patient population (~30%) fell into the Grade 2 subset, Ki 67 index >2 - < 10% and therefore it is justified to include at least a proportion of Grade 2 patients in the indication.

Given that higher proliferation indices may be critical in identifying patients with a greater need for systemic cytotoxic therapy or targeted inhibitors of kinase pathways which, although overall likely to be more toxic than somatostatin analogues, may be justified to slow the course of the disease at a point where prognosis may still be relatively good. It is therefore considered that further clinical studies of patients with higher Ki 67 indices would be required before it could be insinuated that all Grade 2 GEP-NETs are suitable for first line therapy with lanreotide.

Therefore, the final approved wording of “The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs)” is considered acceptable.
Primary efficacy endpoint

The results of the primary efficacy analysis demonstrated a highly statistically significant difference in PFS between the two treatment groups in favour of lanreotide Autogel 120 mg (stratified logrank test p=0.0002) and almost twice the number of events or deaths in the placebo group.

Table 6: Analysis of the Primary Efficacy Endpoint: Study 726, Intention to Treat Population (ITT)

<table>
<thead>
<tr>
<th>Efficacy Variable</th>
<th>Lanreotide Autogel</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of progression events, n (%)</td>
<td>32 (31.6%)</td>
<td>60 (58.2%)</td>
</tr>
<tr>
<td>Median PFS (95% CI) (weeks)</td>
<td>&gt;96 weeks</td>
<td>72.0 (48.6, 96.0)</td>
</tr>
<tr>
<td>p value</td>
<td>0.0002[a]</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.47 (0.30, 0.73)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0007[b]</td>
<td></td>
</tr>
</tbody>
</table>

PFS=progression free survival; CI=confidence interval; N=number of subjects in the treatment group

Figure 1: PFS (Kaplan Meier Curves) – Study 726, ITT Population

The median PFS was 72 weeks (95% CI: 48.6, 96.0) in the placebo group but had not been attained in the lanreotide Autogel 120 mg group at the end of the study and was, therefore, determined to be >96 weeks.

Treatment with lanreotide Autogel 120 mg for 96 weeks reduced the risk of PD or death by 53% compared with placebo (Cox PH model, HR=0.47, 95% CI: 0.30, 0.73). Based on the KM estimates at the time of the last scan performed in the study, 78% of the subjects had progressed or died in the placebo group, compared with 38% of those in the lanreotide Autogel 120 mg group.
Sensitivity Analyses

All five sensitivity analyses showed results consistent with the primary efficacy analysis, indicating that even after consideration of some preplanned adjustments for potential bias, the effect of lanreotide Autogel 120 mg in improving PFS was statistically significantly superior to that of placebo.

Table 7: PFS: Overview of Results for Sensitivity Analyses of the Primary Outcome – ITT Population

<table>
<thead>
<tr>
<th>Sensitivity Analysis</th>
<th>Median PFS (95% CI) (weeks)</th>
<th>p value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Withdrawals due to Investigator judgment of PD despite central assessment of stable disease</td>
<td>Not reached</td>
<td>60.1 (48.1, 73.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>2: Any withdrawal considered as an event</td>
<td>Not reached</td>
<td>52.0 (48.0, 72.1)</td>
<td>0.0007</td>
</tr>
<tr>
<td>3: Assessments mapped to the time of the scheduled radiological assessments</td>
<td>Not reached</td>
<td>72.1 (48.1, 96.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>4: Assessments mapped to 3 months schedule in year 2 for lanreotide</td>
<td>Not reached</td>
<td>72.1 (48.1, 96.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td>5: PFS calculated from start of treatment</td>
<td>Not reached</td>
<td>72.0 (48.4, 96.0)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

The primary efficacy endpoint was clearly met in the pivotal study 726 and showed a high level of statistically significant difference in PFS between lanreotide Autogel treated and placebo treated patients.

Exploratory Analyses

In the exploratory analyses, there was a highly statistically significant effect of treatment on PFS adjusted for progression status at baseline, previous therapy status at entry, hepatic tumour load, primary tumour type and BMI.

Analysis by Baseline characteristics: The results of a Cox PH model subgroup analysis of PFS in the ITT Population demonstrated a consistent effect of treatment in favour of lanreotide Autogel 120 mg (Figure 2). Potential prognostic factors identified were included in a further multivariate Cox PH model. This analysis demonstrated a clinically meaningful reduction in the risk of progression or death after 96 weeks of treatment with lanreotide Autogel 120 mg compared with placebo (HR=0.40, 95% CI: 0.25, 0.63) adjusting for the covariates HTL, primary tumour location and BMI.

Demographic factors:

A consistent and clinically meaningful benefit of treatment with lanreotide Autogel 120 mg was seen in analysis by demographic subgroups (age, race, gender, BMI, geographical region and time since diagnosis). No analyses were performed by centre as the sample size in many centres was too small to permit this. Centres were therefore pooled based on geographical region (i.e. Western European, Eastern European and India, and US). The effect on PFS was consistent across the different geographical regions, in all cases favouring lanreotide over placebo.

Figure 2: Cox Proportional Hazards Covariate Analysis of Progression Free Survival: Consistent Treatment Effect by Baseline Characteristics – Study 726 ITT Population
Disease Characteristics: A consistent and clinically meaningful benefit of treatment with lanreotide Autogel 120 mg was seen in an analysis by disease characteristics (Baseline CgA, Ki67, tumour grade, hepatic tumour load, previous chemotherapy and previous surgery (Figure 3).

There was a clinically meaningful benefit of treatment with lanreotide Autogel 120 mg on PFS adjusted for progression status at Baseline, previous therapy status at entry, hepatic tumour load (≤25% or >25%), and BMI. In the multivariate analysis, treatment with lanreotide Autogel for 96 weeks reduced the risk of progression or death by 60% in comparison with placebo (HR=0.40, 95% CI: 0.25, 0.63).

Benefit-risk evaluation in GEP-NETs of pancreatic origin:
Although the results of a Cox PH model subgroup analysis of PFS in the ITT Population demonstrated a clear effect of treatment in favour of lanreotide Autogel 120 mg following overall adjustment for primary tumour location (Figure 2), further exploratory subgroup analysis from study 726 of progression-free survival according to location of primary tumour (tumour site having been pre-specified as a baseline covariate) suggested some difference in magnitude of treatment effect depending on location of the primary tumour (Figure 3). This analysis appeared to show a lesser effect on pancreatic NETs compared with those of mid-gut origin although the result still favours lanreotide over placebo. Given that somatostatin analogues are not currently routinely recommended for treatment of non-functioning pancreatic NETs, the Applicant has provided further discussion around the effect of lanreotide Autogel on pancreatic NETs in the context of currently available treatment options for pancreatic NETs.

The RMS acknowledges that there appears to be a very encouraging clinical benefit of lanreotide in patients with pancreatic NETs compared with patients treated with placebo as median PFS was greater than 96 weeks compared with 48.6 weeks in the placebo group. The study was not powered for the subgroup analysis however as patient numbers were not high enough in each subgroup and therefore the failure to reach statistical significance can be understood; there was nonetheless
borderline significance in the pancreatic subgroup with a point estimate for the Hazard Ratio clearly in favour of lanreotide. The Applicant presents Kaplan Meier curves for the pancreatic NET subgroup treated with lanreotide compared with placebo which suggest a progressive separation of the curves towards the end of the study, suggesting that an even greater benefit with lanreotide might be observed over a longer time period than 96 weeks (at which point median PFS had not been reached). The ENETs guidelines recognise treatment of functioning (symptomatic) pancreatic NETs with SSTAs (somatostatin analogues) as well established but treatment of non-functioning pancreatic NETs (to achieve an anti-proliferative effect) is less so. This is largely due however to the fact that the only existing SSTA therapy for anti-proliferative treatment of GEP-NETs is octreotide LAR and this is restricted to GEP-NETs of mid-gut origin. This restriction can be understood however by the fact that the pivotal study populations for the octreotide anti-proliferative authorisation was restricted to patients with GEP-NETs of mid-gut origin and therefore to date there have been no available data from randomised clinical trials investigating the anti-tumour effect of SSTA therapy in patients with pancreatic NETs.

The ENETs guidelines also discuss the potential place of everolimus and sunitinib in the anti-tumour treatment of pancreatic NETs. Although everolimus has been shown to have a statistically significant benefit compared with placebo in medically naïve as well previously treated patients, given the lack of long term toxicity data for everolimus, it is not recommended as first-line therapy in patients with pancreatic NETs. Therefore everolimus, is currently recommended only in second and subsequent line treatment of pancreatic NETs and furthermore this should be disease that is progressive.

With regard to the potential place of sunitinib in anti-proliferative treatment of pancreatic NETs, randomised clinical trial data are only available for patients in whom the majority had undergone prior systemic therapy including cytotoxic treatment. Therefore, as for everolimus, sunitinib is recommended only for second and third line therapy of progressive pancreatic NETs and should only be offered as first line therapy in pancreatic NETs in special cases where SSTAs, chemotherapy and/or locoregional therapies are not feasible or not likely to be effective.

By contrast, the pivotal study for lanreotide enrolled a patient population suitable for a first line therapeutic indication as the majority were those with non-progressive disease and only a small number of patients had progressive disease and had previously received medical treatment. Therefore the population of patients with pancreatic NETs in the lanreotide study very largely excluded patients who would have been candidates for everolimus or sunitinib which was an appropriate approach for an investigational agent.

The availability of long term safety data for lanreotide in a number of patient populations, which overall indicates a drug with low toxicity - compared to the paucity of long term safety data for everolimus - also attests to its greater suitability for a first-line therapeutic indication compared with other targeted therapies.

The RMS therefore acknowledges that there is justification for the indication – which relates to first-line treatment of GEP-NETs - to include the subgroup of pancreatic NETs along with mid-gut NETs.

Benefit-risk evaluation in GEP-NETs of hind-gut origin:

In subgroup analysis according to primary tumour location, progression-free survival appeared more favourable with placebo compared with lanreotide in the case of tumours of hind gut origin. It is acknowledged that patient numbers in this subgroup were small due to the overall lower incidence of this type of GEP-NET, resulting in a very wide confidence interval, which renders interpretation difficult.

There was also marked imbalance in the numbers of patients receiving lanreotide versus placebo (10.9% lanreotide versus 2.9% placebo) which could have confounded the data. This nonetheless raised the question of sensitivity of large intestinal tumours to lanreotide treatment and whether any biological/clinical differences in this subset of the disease could account for a difference in treatment effect.
Further discussion has been provided in relation to the potential inclusion of tumours of hind gut origin within the indication. The RMS accepts that owing to the small number of included patients with hindgut tumours in the pivotal study it was therefore poorly powered to come to any definitive conclusion regarding an effect of lanreotide in this group of patients. As they stand, the data suggest a better effect with placebo over lanreotide although the imbalance in the treatment arms also contributes to difficulty in interpretation.

Justification by extrapolation from other types of GEP-NETs on the basis of no substantive biological difference between hind-gut GEP-NETs and those of other origins has been provided. The high unmet need is also highlighted.

It is accepted that by the time rectal or colonic GEP-NETs have reached a stage where they are locally unresectable or metastatic, they generally have a poor prognosis and as there is no clear treatment algorithm for this group of patients (owing to lack of data) there is therefore a high unmet need.

The RMS does not agree that there is no evidence of biological difference, as hindgut GEP-NETs at the point of unresectability or metastasis have a lower expected survival than GEP-NETs overall; this may be due to in part to later diagnosis but it is also suggested in the literature that they may behave more aggressively than other GEP-NETs. Also, the majority of colorectal GEP-NETs are not only asymptomatic but also apparently non-secretory (are not associated with elevated levels of chromogranin and other secretory markers associated with other types of GEP-NETs). Furthermore, the tumours can display distinct patterns of peptide hormone staining that are different from GEP-NETs of other origin. It might have been reassuring if it was known whether hindgut GEP-NETs have a similar profile of SSTR subtype expression to other groups of GEP-NETS, and in particular expression of SSTR 2 and SSTR 5 for which lanreotide displays the greatest binding affinities. However, this information doesn’t appear to be available. It therefore cannot be accepted that on balance there is no substantive biological difference between hindgut GEP-NETs and other GEP-NETs.

Although NANETs (North American) guidelines suggest that SSTAs might be considered in some circumstances for SSTAs in treatment of colorectal NETs, no clear recommendations are provided in ENETs guidelines which state that there is very limited evidence for use of SSTA as anti-tumour agents in non-functioning colorectal GEP-NETs. Instead, a range of treatment options are suggested for G1 and G2 colorectal GEP-NETs including anti-angiogenic drugs, mTOR inhibitors and potentially temozolomide based regimes. SSTR-targeted radiotherapy (using isotopes linked to octreotide) is also suggested. Thus, although this is a condition of high unmet need, there are a number of treatment possibilities.

It is therefore considered that further clinical trial data would be needed before a positive recommendation could be made for inclusion of hind-gut tumours within the therapeutic indication.

A justification for the inclusion of the tumour subgroup of unknown primary origin has been provided and stems from post-hoc subgroup analysis of the 13% of patients in study 726 that were classified as having GEP-NETs of “unknown/other primary origin” and post-hoc analysis of this subgroup showed a statistically significant improvement in median PFS for lanreotide versus placebo (median PFS was beyond 96 weeks in the lanreotide group versus 15 months in the placebo group. Logrank test: p=0.0341; HR 0.20 (95% CI: 0.04,1.03).

Kaplan Meier survival curves for GEP-NET patients with tumours of unknown origin are given below:
It has been conceded that it is evident from the broader literature that for a substantial proportion of GEP-NETs, available imaging modalities are unable to identify the primary site of the tumour. In such cases, a variety of features (peptide hormone secretion, clinical characteristics and histopathological features) can provide clues to where the tumour originated from, which helps to determine treatment. It also appears that tumours of the foregut (gastrinomas and those from the proximal duodenum for example), and pancreatic tumours also, can be particularly difficult to localise by imaging techniques. It is reasonable therefore to assume that of the patients included in the lanreotide trials, tumours defined as of unknown/other origin were more likely to be in these categories than to be of hind gut origin. It is also undeniable that the response demonstrated in the “unknown subgroup” was similar to that in tumours confirmed to be of pancreatic origin where the RMS has provided a positive opinion.

In recognition of the fact that in the present state of clinical practice, imaging modalities can for a significant proportion of GEP-NETs be insufficient to localise the primary site of the tumour, and given that such tumours are more likely to be of foregut (including pancreatic) origin, the RMS is prepared to the worded indication that includes tumours of unknown origin but excludes tumours of hind gut origin for which there is at present no evidence of clinical benefit and for which other treatment options do exist. The inference of the re-worded indication would be that it includes GEP-NETs where imaging has not precisely localised the primary tumour site but where other clinical features point to tumours of foregut, midgut or pancreatic origin and not to hind gut origin. This is considered to be helpful to clinical practice.

Figure 3: PFS Subgroup Analysis: Treatment Effect Across Subgroups (Disease Characteristics) in the ITT Population
Secondary efficacy analyses

*The Proportion of Subjects Alive and Without PD (Disease Progression Assessed via Centralised Scan) at Weeks 48 and 96*

The treatment effects at Weeks 48 and 96 were statistically significant (p=0.0110 and p<0.0001, respectively). At Week 48, subjects in the lanreotide Autogel group had twice the odds of being alive and progression free compared with subjects in the placebo group (OR) of 2.11 (95% CI: 1.19, 3.76). By Week 96, the subjects in the lanreotide Autogel 120 mg group had more than three times the odds of being alive and progression free (OR: 3.27, 95% CI: 1.81, 5.92) compared with those in the placebo group.

Consistent with the observation that the median PFS in the lanreotide Autogel 120 mg group had not been reached by the end of the study, the separation of the KM curves appeared to be still increasing at the 96 week timepoint, suggesting that there had been no loss of efficacy over the duration of the study.

*Overall Survival*

Overall survival was added as a secondary efficacy endpoint in February 2011. By this time (i.e. more than 5 years after study initiation), some subjects had already left the study and were unreachable (lost to follow up); additionally some of the subjects contacted declined to participate in the post study follow up for OS. In total, OS data were available for 83 subjects treated with lanreotide Autogel 120 mg and 78 subjects who received placebo. Furthermore, the study was not powered to evaluate OS. With respect to the limited survival data collected, 19 deaths were observed in the lanreotide Autogel 120 mg group compared with 17 deaths in the placebo group.

Only four deaths (two in each treatment group), occurred during the double-blind study and none of these were considered to be related to treatment. The remaining 32 deaths occurred during the post study follow up period.
While survival data were collected after the double blind study, interpretation of these data is, as previously stated, confounded by factors such as challenges encountered in collecting OS data, the low number of deaths observed and crossover to other therapies after completion of the study or its open label extension. The low number of deaths was consistent with the indolent nature of the disease. Given these caveats, the confidence intervals of the nominal hazard ratio for OS were wide (HR=1.05, (95% CI: 0.55, 2.03) and the result of the analysis of OS gives little meaningful information.

The study was not powered for analysis of overall survival which was added as a secondary endpoint 5 years after study initiation. Two deaths in each treatment group occurred during the double blind phase, which were not considered treatment-related, and the remaining 32 deaths occurred during the post-study follow up. The data may therefore have been confounded by crossover to other therapies after completion of the study or its open label extension. The point estimate for the hazard ratio for OS was 1.05 (in favour of placebo) but the confidence interval was extremely wide (95% CI: 0.55,2.03) and is therefore difficult to interpret. Given the doubt about the reliability of the OS data, this result is overall not considered to detract from the clear result on PFS in the primary efficacy analysis.

Quality of Life
Treatment with lanreotide Autogel 120 mg did not have a deleterious effect on subjects’ QoL when compared with placebo. There were no major differences between the lanreotide Autogel 120 mg and placebo groups in transformed scores for the EORTC QLQ-C30 and the EORTC QLQ-G.I.NET2.1 questionnaires from baseline to last visit.

Change in Tumour Markers
Chromogranin A
The pre-specified analysis was conducted on the ITT population. Throughout the study, more subjects in the lanreotide Autogel group had a >50% decrease in CgA compared to the placebo group. At the last available post baseline value, 42.2% of lanreotide Autogel subjects compared to 4.7% of placebo subjects had a >50% reduction in CgA. The odds of having a ≥50% decrease in plasma CgA were significantly greater in the lanreotide group at each post baseline assessment. At the last available post baseline value, the odds of having a 50% or more decrease in plasma CgA were 15 times greater with lanreotide than with placebo (OR: 15.2, 95% CI: 4.29, 53.9; p value from logistic regression model: <0.0001).

Subjects with gastrinomas were allowed to participate in the study if they were well controlled on PPIs, although it is known that PPIs cause elevations in CgA. Therefore, in a post hoc modification, the analysis was repeated using the subgroup of subjects with elevated baseline CgA values and with exclusion of subjects with gastrinomas. Compared with placebo, a significant decrease in CgA in subjects treated with lanreotide Autogel 120 mg was also seen in this population. At the last post baseline value, the odds of having a 50% or more decrease in plasma CgA from baseline were 15 times greater with lanreotide Autogel than placebo (OR=15.95% CI: 4.29-53.9), logistic regression p<0.0001).

The results of the two analyses were, therefore, entirely consistent.

Approximately 10 times as many lanreotide-treated (42.2%) patients compared to placebo treated (4.7%) patients had demonstrated declines in circulating chromogranin A >50% from baseline at the last available post-baseline assessment. This was selected as a pre-specified analysis as it can be considered reflective of a response in a meaningful biological parameter for this tumour type and it was confirmed as not confounded by proton pump inhibitor medication in patients with gastrinomas.

Other Tumour Markers
Tumour markers above normal range at baseline (pancreatic polypeptide, gastrin, and urinary 5-hydroxyindolacetic acid (5-HIAA) were assessed. There were significant reductions in 5-HIAA and pancreatic polypeptide at each post baseline assessment (and at the last post baseline value available),
in the lanreotide Autogel group compared with the placebo group. There were no significant differences between the treatment groups for gastrin. The subgroup of subjects with elevated gastrin was small and differences were not expected due to the use of PPIs as concomitant medication.

**Association Between Tumour Markers and PFS**

In a post hoc Cox PH model analysis of subjects with secreting tumours and elevated CgA (63.2%, 129/204), as well as in subjects with any elevated peptide (or tumour markers >1 x ULN) at baseline (Study 726). The effect of lanreotide Autogel 120 mg on extending PFS was consistent with that observed in subjects with normal baseline values.

The inclusion criteria for study 726 specified inclusion of “non-functioning” tumours whereas a high percentage of patients had tumours with secretory properties. It is assumed therefore that “non-functioning” tumours referred to asymptomatic tumours (patients without carcinoid-like symptoms) and could therefore include tumours associated with elevated levels at baseline of circulating secretory proteins including chromogranin and neuroendocrine hormones, but without carcinoid-like symptoms.

It has been clarified that for Study 726, the term “non-functioning tumours” referred to those not associated with a hormone-related clinical syndrome. However, some could still be associated with elevated levels of secretory proteins (such as chromogranin A (CgA) and pancreatic polypeptide).

Despite the different terms used to describe them, these tumour types are indistinguishable histopathologically, and both exhibit classic secretory granules that determine their classification as neuroendocrine tumours. The population of patients with no hormone-related clinical syndrome included in Study 726 was comprised of patients with tumours associated with elevated levels of secretory proteins, as well as of patients with non-secreting tumours. The efficacy of lanreotide on PFS was clinically significant and consistent across all (secretory and non-secretory) GEP-NETs.

**Long Term Efficacy, Development of Tolerance and Withdrawal Effects**

Consistent with the observation that the median PFS in the lanreotide Autogel 120 mg group had not been reached by the end of Study 726, the separation of the KM curves appeared to be still increasing at the 96 week timepoint (Figure 1), suggesting that there had been no loss of efficacy over the two year duration of the study. Further evidence for the maintenance of efficacy of lanreotide Autogel 120 mg is provided by data from Study 729, the long term extension of study 726.

To date, supportive data on the long term safety and efficacy of lanreotide Autogel 120 mg have been evaluated in 88 subjects enrolled directly from Study 726 from 24 investigational sites. This included 41 subjects treated with lanreotide Autogel in Study 726 who were subsequently treated with lanreotide Autogel in Study 729, (LA:LA) and 47 subjects treated with placebo in Study 726 and lanreotide Autogel in Study 729 (PB:LA). In LA:LA subjects, a median PFS of 131.14 weeks (95% CI: 123.57, 271.86) was determined and represented an improvement in PFS of 59.1 weeks compared with a median PFS of 72.00 weeks (95% CI: 48.43, 84.57) in the placebo group. The results of the KM analysis are shown in Figure 4.

**Figure 4: Progression Free Survival in Study 726 and Study 729 by Randomised Treatment in Study 726 (ITT)** (Tumour assessments prior to the vertical line were performed centrally within Study 726; those after the vertical line were performed locally within Study 729. Tumour assessments for the placebo group after switch to open label lanreotide Autogel are excluded)
Efficacy Conclusions

Study 726 enrolled 204 subjects with well or moderately well differentiated GEP NETs. Overall, 95.6% of subjects were not progressing (as per RECIST v1.0) during the 12 to 24 week screening period prior to initiation of treatment. The hepatic tumour load was ≤25% in 62 (61.3%) subjects and >25% in 39 (38.7%) subjects treated with lanreotide Autogel.

After 96 weeks of treatment, median PFS was not reached in the lanreotide Autogel 120 mg treatment group compared with a median PFS of 72 weeks in the placebo treated group (HR: 0.47; 95% CI 0.30, 0.73; p=0.0002). Based on the KM estimates at the time of the last scan performed in the study, 78% of the subjects had progressed or died in the placebo group, compared with 38% of those in the lanreotide Autogel 120 mg group.

A statistically significant effect of lanreotide Autogel 120 mg on PFS compared to placebo treated patients was therefore demonstrated.

The baseline characteristics of subjects treated in Study 726 were comparable in both treatment arms. The robustness of the analysis of the primary efficacy endpoint was confirmed by the results of five separate sensitivity analyses supporting that even after consideration of some preplanned adjustments for potential bias, the effect of lanreotide Autogel 120 mg in improving PFS was statistically and significantly superior to that of placebo.

Treatment with lanreotide Autogel 120 mg demonstrated a consistent prolongation of PFS in subjects with both elevated and normal biomarker values. Additionally, it significantly reduced elevated CgA values and resulted in a statistically significant reduction in 5-HIAA and pancreatic polypeptide, demonstrating a strong biochemical response to treatment with lanreotide Autogel 120 mg.

Clinical safety

Safety Population and Patient Exposure

Safety data are derived from six clinical studies which recruited subjects with asymptomatic or symptomatic GEP NETs and in which lanreotide Autogel was administered by deep sc injection once every 4 weeks. The categorisation of clinical studies with respect to the level of safety information reported considered the targeted indications, study design, the legacy nature of the studies and the completeness of the data and documentation collected. The key safety data (Category 1) are derived from the pivotal, DB, placebo controlled Study 726. Supportive safety data (Category 2) are derived from five phase II/III studies conducted between 2001 and 2013 which evaluated the efficacy and safety of lanreotide Autogel administered by deep sc injection once every 4 weeks in subjects with asymptomatic and symptomatic GEP NETs. They were the DB, placebo controlled, Study 730, and the OL studies 166, 729 (the OL extension of Study 726), 216 and 718.
In the safety analysis, data from Category 2 studies were pooled with data from the Category 1 study. Given that the tumours in asymptomatic and symptomatic GEP NETs are structurally the same these two clinical populations are combined in the safety population.

All postmarketing surveillance (PMS) data associated with the administration of any lanreotide formulation, at any dose, in the targeted indication are included in the PMS category. Safety in this category is based on subjects treated with lanreotide at any dose and who reported at least one serious adverse event (SAE) or adverse event (AE). This includes spontaneous reports (from all sources e.g. healthcare professionals, patients), literature reports, reports from registries and reports from externally sponsored studies.

Patient exposure:
A total of 378 subjects were included in the All Subjects population of the pooled safety analyses. Of these 378 subjects, 159 were treated with lanreotide Autogel 120 mg in the DB, placebo controlled Studies 726 and 730. The remaining 219 subjects received lanreotide Autogel in the OL Studies 729, 718, 216 and 166, or in the OL phases of Study 730.

There were 159 subjects with asymptomatic GEP NETs (Asymptomatic population) and 219 subjects with symptomatic GEP NETs (Symptomatic population).

Extent of Exposure:
Overall, the mean duration of treatment with lanreotide Autogel in the All Subjects pooled population was shorter than that in the Asymptomatic population, primarily due to the shorter duration of studies which investigated the treatment of subjects with symptomatic GEP NETs. In the Asymptomatic and All Subjects pooled populations, the majority of subjects were treated for >6 months.

Safety Evaluations
Subjects were evaluated for AEs, deaths and other SAEs, vital signs, physical measurements, laboratory test parameters (haematology and biochemistry), electrocardiograms (ECGs), gallbladder echography (the presence of gallstones and sludge were recorded), local injection site tolerance, symptom assessment and antibodies to lanreotide. Additionally, adverse events of special interest (AESIs) were defined based on the nature, mechanism of action, and known safety profile of lanreotide. The AESIs evaluated were: GI effects, cholelithiasis, effects on glycoregulation, effects on thyroid function, bradycardia, administration site reaction, headache or dizziness (central nervous system (CNS)), allergic reaction, hepatic dysfunction and pancreatitis.

For all Category 1 and 2 subjects with asymptomatic GEP NETs, all AEs were collected on the AE page of the Case Report Form. In the case of some Category 2 subjects with symptomatic GEP NETs, specific safety information related to diarrhoea, flushing events and injection site tolerance were collected.

Adverse events
GI system:
Consistent with the known pharmacological actions of SSTAs, the adverse events observed during treatment with lanreotide Autogel most commonly affected the GI system and included diarrhoea, abdominal pain, nausea, vomiting and constipation.

Glucose regulation:
The observed effects of lanreotide Autogel on glycoregulation in subjects with GEP NETs were consistent with the known pharmacological actions of SSTAs (modulation of insulin and/or glucagon release may result in hypoglycaemia or hyperglycaemia). It is recommended that blood glucose levels are monitored when lanreotide treatment is initiated and that antidiabetic treatment is adjusted accordingly.

Thyroid function:
There have been no changes in thyroid function seen in the GEP NET population described in this application. However, slight decreases in thyroid function have been seen during treatment with
SSTas in other indications, though clinical hypothyroidism is rare (<1%). Thyroid function tests are recommended where clinically indicated.

Gallbladder motility:
The effects of lanreotide on gallbladder motility are consistent with the expected pharmacological actions of SSTas. Because of the effects of lanreotide on gallbladder motility, subjects may need to be periodically monitored.

Cardiovascular:
Although the number of subjects experiencing bradycardia following lanreotide treatment was small (2/378), given data from the use of SSTas in other indications, care should be taken when initiating treatment with lanreotide in subjects with bradycardia.

Injection site
As for other parenteral treatments injection site reactions (mostly pain) were commonly reported.

CNS:
Review of the clinical pharmacology and safety data did not indicate any potential of lanreotide to affect the patient's ability to drive or operate machines. However, given that dizziness has been reported following treatment with lanreotide Autogel, if a subject is affected, he/she should not drive or operate machinery.

Safety in special populations:
Demographic factors such as gender, age and race do not affect the safety profile of lanreotide. Pregnancies that have occurred during lanreotide treatment did not raise any obvious safety concerns, however, lanreotide Autogel should only be used in pregnant women if clearly needed, and caution should be exercised when lanreotide Autogel is administered to nursing women.

In renally impaired, hepatically impaired and elderly subjects, no clinically relevant differences in the PK of lanreotide Autogel were observed in subjects with GEP NETs. Therefore, no dose adjustments are considered necessary. Similarly, no adjustments of dosing are required based on subjects’ demographic characteristics. There was no evidence of any changes in AE profile, vital signs or laboratory data relevant to the administration of lanreotide Autogel in special populations.

Drug interactions:
No new information on drug interactions has become available. Interactions expected with lanreotide Autogel reflect those already known for SSTas.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
A single pivotal clinical study (study 726) has been submitted, a randomised, double blind, placebo-controlled design, in support of the new therapeutic indication. In this circumstance where the product has been authorised for other indications, including an overlapping indication (relief of carcinoid-like symptoms in patients with neuroendocrine tumours), coupled with the pragmatic difficulty of rate of recruitment due to the rarity of the condition, a single pivotal study can in principle be considered acceptable; however, the data obtained in support of the new indication should be compelling.

Study 726 commenced enrolment in June 2006 and the study was completed in April 2013, consistent with a slow rate of recruitment due to the rarity of the condition. At the time of study design, the use of somatostatin analogues in the anti-proliferative treatment of gastroenteropancreatic tumours was not established; furthermore, somatostatin analogue therapy is currently authorised in Europe for tumours of mid-gut origin only and the study population in the case of the lanreotide pivotal trial was broader than this in including pancreatic and hindgut tumours. For the treatment of pancreatic NETs, other medical therapies including the mTOR inhibitor everolimus and the tyrosine kinase inhibitor sunitinib are authorised but clinical practice has to date not established any clear treatment hierarchy. In general it would be preferred for a pivotal study to compare an investigational product with an
established therapy, in order to investigate non-inferiority at a minimum or superiority as an ideal, there is justification in these circumstances for a placebo-controlled study without an active comparator arm.

The single pivotal study 726 clearly met the single primary efficacy endpoint of statistically significant difference in PFS up to 96 weeks in lanreotide Autogel treated compared to placebo treated patients (p=0.0002). Robustness of the primary efficacy endpoint analysis was demonstrated by appropriate sensitivity analyses and by statistical analysis that adjusted for a range of baseline covariates.

The PFS data were supported by reductions in circulating biomarkers reflective of neuroendocrine secretion from this tumour type.

There was no effect on overall survival (OS), a secondary efficacy endpoint. The study was not powered to evaluate OS due to the indolent nature of the disease and the low recruitment; furthermore, OS was confounded by crossover to other therapies after completion of the study. The failure to demonstrate an effect on OS is therefore not considered to affect the overall conclusion of efficacy benefit demonstrated by PFS which, as a primary efficacy parameter in clinical trials of GEP-NETs, is endorsed by international experts in the field.

It was proposed to specify the target population according to WHO Classification Grade 1 and 2 (up to Ki 67 10%). Although this is in principle acceptable, the proposed wording did not make it sufficiently clear that lanreotide should only be recommended for a subset of Grade 2 GEP-NETs as defined by a Ki 67 index up to 10%. It is important to reflect in the indication that lanreotide cannot currently be recommended for all Grade 2 GEP-NETs that span the range of Ki 67 index from 3 – 20% as the data do not support this.

Given that higher proliferation indices may be critical in identifying patients with a greater need for systemic cytotoxic therapy or targeted inhibitors of kinase pathways which, although overall likely to be more toxic than somatostatin analogues, may be justified to slow the course of the disease at a point where prognosis may still be relatively good. It is therefore considered that further clinical studies of patients with higher Ki 67 indices would be required before it could be insinuated that all Grade 2 GEP-NETs are suitable for first line therapy with lanreotide.

In relation to clarification of the scope of the therapeutic indication regarding degree of disease severity, the following specification is acceptable:

The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs)...

Post-hoc exploratory subgroup analysis of PFS according to location of primary tumour appeared to suggest some differences. The difference in PFS for lanreotide compared to placebo appeared less marked in tumours of pancreatic origin compared to those of mid-gut origin but in both cases favoured lanreotide over placebo. In the case of hindgut tumours, effect on PFS appeared to favour placebo. However, this subset was confounded by small patient numbers and imbalance between treated and placebo arms.

An evaluation of the benefit-risk for the different tumour subsets can be summarised as follows: The benefit-risk is clearly positive in GEP-NETs of mid-gut origin and does not require further discussion.

Benefit-risk evaluation in GEP-NETs of pancreatic origin:
Subgroup analysis appeared to show a lesser effect on pancreatic NETs compared with those of mid-gut origin although the result still favours lanreotide over placebo. The RMS acknowledges that there appears to be a very encouraging clinical benefit of lanreotide in patients with pancreatic NETs compared with patients treated with placebo as median PFS was greater than 96 weeks compared with 48.6 weeks in the placebo group. The study was not powered for the subgroup analysis however as patient numbers were not high enough in each subgroup and
therefore the failure to reach statistical significance can be understood; there was nonetheless borderline significance in the pancreatic subgroup with a point estimate for the Hazard Ratio clearly in favour of lanreotide. The Applicant presents Kaplan Meier curves for the pancreatic NET subgroup treated with lanreotide compared with placebo which suggest a progressive separation of the curves towards the end of the study, suggesting that an even greater benefit with lanreotide might be observed over a longer time period than 96 weeks (at which point median PFS had not been reached).

The ENETs guidelines recognise treatment of functioning (symptomatic) pancreatic NETs with SSTAs (somatostatin analogues) as well established but treatment of non-functioning pancreatic NETs (to achieve an anti-proliferative effect) is less so. This is largely due however to the fact that the only existing SSTA therapy for anti-proliferative treatment of GEP-NETs is octreotide LAR and this is restricted to GEP-NETs of mid-gut origin. This restriction can be understood however by the fact that the pivotal study populations for the octreotide anti-proliferative authorisation was restricted to patients with GEP-NETs of mid-gut origin and therefore to date there have been no available data from randomised clinical trials investigating the anti-tumour effect of SSTA therapy in patients with pancreatic NETs.

The ENETs guidelines also discuss the potential place of everolimus and sunitinib in the anti-tumour treatment of pancreatic NETs. Although everolimus has been shown to have a statistically significant benefit compared with placebo in medically naïve as well previously treated patients, given the lack of long term toxicity data for everolimus, it is not recommended as first-line therapy in patients with pancreatic NETs. Therefore everolimus, is currently recommended only in second and subsequent line treatment of pancreatic NETs and furthermore this should be disease that is progressive.

With regard to the potential place of sunitinib in anti-proliferative treatment of pancreatic NETs, randomised clinical trial data are only available for patients in whom the majority had undergone prior systemic therapy including cytotoxic treatment. Therefore, as for everolimus, sunitinib is recommended only for second and third line therapy of progressive pancreatic NETs and should only be offered as first line therapy in pancreatic NETs in special cases where SSTAs, chemotherapy and/or locoregional therapies are not feasible or not likely to be effective.

By contrast, the pivotal study for lanreotide enrolled a patient population suitable for a first line therapeutic indication as the majority were those with non-progressive disease and only a small number of patients had progressive disease and had previously received medical treatment. Therefore the population of patients with pancreatic NETs in the lanreotide study very largely excluded patients who would have been candidates for everolimus or sunitinib which was an appropriate approach for an investigational agent.

The availability of long term safety data for lanreotide in a number of patient populations, which overall indicates a drug with low toxicity - compared to the paucity of long term safety data for everolimus - also attests to its greater suitability for a first-line therapeutic indication compared with other targeted therapies.

The RMS therefore acknowledges that there is justification for the indication – which relates to first-line treatment of GEP-NETs - to include the subgroup of pancreatic NETs along with mid-gut NETs.

Benefit-risk evaluation in GEP-NETs of hind-gut and those of unknown primary origin:
In subgroup analysis according to primary tumour location, progression-free survival appeared more favourable with placebo compared with lanreotide in the case of tumours of hind gut origin. It is acknowledged that patient numbers in this subgroup were small due to the overall lower incidence of this type of GEP-NET, resulting in a very wide confidence interval, which renders interpretation difficult. There was also marked imbalance in the numbers of patients receiving lanreotide versus placebo (10.9% lanreotide versus 2.9% placebo) which could have confounded the data. This nonetheless raised the question of sensitivity of large intestinal tumours to lanreotide treatment and whether any biological/clinical differences in this subset of the disease could account for a difference in treatment effect.
The RMS accepts that owing to the small number of included patients with hindgut tumours in the pivotal study it was therefore poorly powered to come to any definitive conclusion regarding an effect of lanreotide in this group of patients. As they stand, the data suggest a better effect with placebo over lanreotide although the imbalance in the treatment arms also contributes to difficulty in interpretation.

Justification has been provided by extrapolation from other types of GEP-NETs on the basis of no substantive biological difference between hind-gut GEP-NETs and those of other origins. The high unmet need is also highlighted.

It is accepted that by the time rectal or colonic GEP-NETs have reached a stage where they are locally unresectable or metastatic, they generally have a poor prognosis and as there is no clear treatment algorithm for this group of patients (owing to lack of data) there is therefore a high unmet need.

The RMS does not agree that there is no evidence of biological difference, as hindgut GEP-NETs at the point of unresectability or metastasis have a lower expected survival than GEP-NETs overall; this may be due to in part to later diagnosis but it is also suggested in the literature that they may behave more aggressively than other GEP-NETs. Also, the majority of colorectal GEP-NETs are not only asymptomatic but also apparently non-secretory (are not associated with elevated levels of chromogranin and other secretory markers associated with other types of GEP-NETs). Furthermore, the tumours can display distinct patterns of peptide hormone staining that are different from GEP-NETs of other origin. It might have been reassuring if it was known whether hindgut GEP-NETs have a similar profile of SSTR subtype expression to other groups of GEP-NETS, and in particular expression of SSTR 2 and SSTR 5 for which lanreotide displays the greatest binding affinities. However, this information doesn’t appear to be available. It therefore cannot be accepted that on balance there is no substantive biological difference between hindgut GEP-NETs and other GEP-NETs.

The RMS also does not accept that the preclinical data provide support as the rectal xenograft model cited is said to have revealed an anti-angiogenic effect of octreotide but this effect is not intrinsic to the tumour cell type and instead reflects a secondary effect on the tumour from inhibition of the vasculature. Whilst it is potentially interesting that SSTAs may have anti-angiogenic effects, these data only suggest a possible benefit arising from anti-angiogenesis which would apply to a number of anti-angiogenic drugs that are already known to have a place in treatment of some colorectal tumours.

Although NANETs (North American) guidelines suggest that SSTAs might be considered in some circumstances for SSTAs in treatment of colorectal NETs, no clear recommendations are provided in ENETs guidelines which state that there is very limited evidence for use of SSTAs as anti-tumour agents in non-functioning colorectal GEP-NETs. Instead, a range of treatment options are suggested for G1 and G2 colorectal GEP-NETs including anti-angiogenic drugs, mTOR inhibitors and potentially temozolomide based regimes. SSTR-targeted radiotherapy (using isotopes linked to octreotide) is also suggested. Thus, although this is a condition of high unmet need, there are a number of treatment possibilities.

It is therefore considered that further clinical trial data would be needed before a positive recommendation could be made for inclusion of hind-gut tumours within the therapeutic indication.

It has been proposed to re-word the therapeutic indication to include GEP-NETs of unknown origin but excludes tumours of hind-gut origin. The justification for the inclusion of the tumour subgroup of unknown primary origin stems from post-hoc subgroup analysis of the 13% of patients in study 726 that were classified as having GEP-NETs of “unknown/other primary origin” and post-hoc analysis of this subgroup showed a statistically significant improvement in median PFS for lanreotide versus placebo (median PFS was beyond 96 weeks in the lanreotide group versus 15 months in the placebo group. Logrank test: p=0.0341; HR 0.20 [95% CI: 0.04,1.03]).

Based on this, the following wording is considered to be appropriate:
The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or of unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease (see section 5.1).

In recognition of the fact that in the present state of clinical practice, imaging modalities can for a significant proportion of GEP-NETs be insufficient to localise the primary site of the tumour, and given that such tumours are more likely to be of foregut (including pancreatic) origin, the RMS finds acceptable the re-worded indication that includes tumours of unknown origin but excludes tumours of hind gut origin for which there is at present no evidence of a clinical benefit and for which other treatment options do exist. The inference of the re-worded indication would be that it includes GEP-NETs where imaging has not precisely localised the primary tumour site but where other clinical features point to tumours of foregut, midgut or pancreatic origin and not to hind gut origin. This is considered to be helpful to clinical practice.

There were no notable differences in subjects’ Quality of life as measured by validated instruments between lanreotide and placebo groups.

Overall the benefit-risk is considered to be favourable and the variation to be approvable.

In addition, the following conditions were met with regards to one-year’s additional data exclusivity:

- **Well established substance:** the active substance lanreotide has been authorised in the EU for more than 20 years and as the formulation lanreotide Autogel for 13 years. The product is currently marketed in more than 60 countries world-wide for the treatment of acromegaly and relief from carcinoid symptoms associated with neuroendocrine tumours. The estimated cumulative patient exposure is approximately 1.9 million treatment months across all populations and all indications.

- **New therapeutic indication:** the proposed indication can be considered a new therapeutic indication (with respect to those currently authorised for the product):

  1) It concerns a different mechanism of action for the product – tumour growth inhibition – as opposed to relief from carcinoid-like symptoms from neuroendocrine tumours. It therefore concerns an extended target population of asymptomatic gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in addition to symptomatic GEP-NETs. This is in contrast to the currently authorised indication that concerns symptomatic, particularly carcinoid, NETs. Patients with symptomatic and asymptomatic GEP-NETs are recognised as distinct patient populations that are defined respectively by the presence or absence of carcinoid-like symptoms. The Applicant has also provided clear evidence of slowing of disease progression in GEP-NETs with lanreotide Autogel compared with placebo whereas the currently approved indication in NETs (in particular carcinoid tumours) is for treatment of symptoms only.

  2) The new indication concerns a target population that is distinct from patients suffering from the condition of acromegaly, for which lanreotide is also currently indicated. Acromegaly is a condition arising from an anterior pituitary tumour. Such tumours, like GEP-NETs, can be considered in the broad group of neuroendocrine tumours. Importantly, however, GEP-NETs and pituitary tumours represent distinct tumour subgroups with different clinical characteristics and disease course (for example, pituitary tumours don’t metastasise whereas GEP-NETs do). Furthermore, lanreotide has a high degree of selectivity for particular somatostatin receptor subtypes (of which there are 5 in total) and therefore clinical response will depend on profile of somatostatin receptor subtype expression which may not be the same across different tumour subtypes. The patient population defined in the new indication therefore does not overlap with the acromegaly patient population; furthermore, the drug’s mechanism of action would not predict clinical response in one patient population from the response in the other.
Significant clinical studies have been carried out in relation to the new indication: a confirmatory Phase III study was conducted over 96 weeks in 204 patients with asymptomatic (non-functioning) GEP-NETs who had unresectable or metastatic disease. Lanreotide treated patients demonstrated significantly longer time to disease progression or death compared with the placebo group, consistent with slowing of tumour growth. Placebo was a suitable comparator as at the Somatuline Autogel, UK/H/xxxx/WS/079 4/8 FVAR addendum – confirmation of data protection time study enrolment commenced (some 7 years prior to study completion owing to the slow rate of recruitment in this rare disease) there were no licensed therapies for this group of patients. The double blind period of 96 weeks was followed by an open label active treatment extension phase up to 3.9 years to study long term efficacy and safety of lanreotide Autogel in patients with non-functioning GEP-NETs. This revealed maintenance of efficacy and an acceptable safety profile over the longer term. The demonstration of an approximate doubling of time to tumour progression or death (131 versus 72 weeks) for lanreotide over placebo in an extended target population of GEP-NETs is considered to satisfy the criterion of a significant clinical study in relation to the new therapeutic indication.

Background concerning the decision of the one-year’s data exclusivity
Somatostatin analogues, of which lanreotide is one, are recognised in the treatment of symptomatic GEP-NETs where they are used to provide relief from carcinoid symptoms. Somatostatin analogues are also recognised to exert an anti-proliferative effect in neuroendocrine tumours and the somatostatin analogue octreotide is authorised for the treatment of NETs of mid-gut origin; this authorisation post-dated the design of the lanreotide trial. The study population in the case of the lanreotide pivotal trial was broader than this as it included pancreatic and hindgut tumours. For the treatment of pancreatic NETs, other medical therapies including the mTOR inhibitor everolimus and the tyrosine kinase inhibitor sunitinib are authorised but clinical practice to date has not established a clear treatment hierarchy. Systemic cytotoxics are indicated in rapidly progressive GEP-NETs with a high cellular proliferation index but such patients were excluded from the pivotal study as it would have been unethical to randomise them to a placebo arm for a period of up to 2 years.

Paragraph 1 of Article 10(5) of Directive 2001/83/EC sets out provisions for granting of a one year period of data exclusivity where an application is made for a new indication for a well established substance. In this context, the new indication is assessed in comparison with indications previously approved for the well established substance. A European Commission guidance document (Brussels November 2007, Guidance on a New Therapeutic Indication for a Well-established substance) describes the features that would normally allow a new indication to be specified as such: these include “an extended target population for the same disease” and “change from treatment to prevention of progression of a disease”. The new indication proposed for lanreotide Autogel is considered to fully satisfy the criterion of an extended target population for the same disease and in part to satisfy the criterion of change from treatment to prevention of progression of a disease. In the context of data protection (exclusivity) the indication applied for can be considered to fulfil the definition of a new indication.

A data exclusivity award requires the support of significant preclinical and/or clinical studies in relation to the new indication. According to the European Commission guidance, in principle it would be expected that a significant clinical study would compare the medicinal product with a suitable comparator in the new therapeutic indication. The clinical study in support of the data exclusivity request for lanreotide Autogel was a two-armed study in which the comparator arm was placebo as no authorised therapies for the wider group of well and moderately differentiated asymptomatic GEP-NETs (including pancreas, mid-gut and hind-gut) were available at the time of study commencement; even now, no clear treatment hierarchy is in place and for the most indolent (well differentiated) tumours, placebo treatment with regular monitoring for tumour progression would be acceptable. The design of the clinical study therefore satisfies the criterion of a significant clinical study in the context of a data exclusivity request.

Clinical efficacy and safety:
The proposed indication relates to an anti-tumour (growth inhibitory) action of the active substance, lanreotide, as distinct from the currently approved indication which relates to the provision of relief
from carcinoid-like symptoms arising from the secretion of bioactive amines and hormones from functioning neuroendocrine tumours. One pivotal clinical study (Study 726) was conducted to demonstrate the efficacy and safety of lanreotide Autogel 120 mg in the treatment of subjects with asymptomatic GEP NETs. In this study, a total of 101 subjects were treated every 4 weeks with lanreotide Autogel 120 mg and 103 subjects received placebo, for a duration of 96 weeks. Additional evidence for the long term safety of lanreotide Autogel is provided by its extension phase (Study 729). In addition to that provided in Studies 726 and 729, supportive safety data are derived from one double blind (DB) phase III trial (Study 730) and three open label (OL) studies (Study 166, Study 216 and Study 718) of lanreotide Autogel administered using the intended dosing regimen in subjects with asymptomatic and symptomatic GEP NETs. A total of 378 unique subjects were treated with lanreotide Autogel in these studies and were included in the safety population.

Efficacy
The single primary efficacy endpoint, progression free survival (PFS), was the time from randomisation to either disease progression (PD) or death occurring within 96 weeks after first treatment administration.

The single pivotal study 726 clearly met the primary efficacy endpoint of statistically significant difference in PFS in lanreotide Autogel treated compared to placebo treated patients (p=0.0002). Robustness of the primary efficacy endpoint analysis was demonstrated by appropriate sensitivity analyses and by statistical analysis that adjusted for a range of baseline covariates.

The PFS data were supported by reductions in circulating biomarkers reflective of neuroendocrine secretion from this tumour type.

There was no effect on overall survival (OS), a secondary efficacy endpoint. The study was not powered to evaluate OS due to the indolent nature of the disease and the low recruitment; furthermore, OS was confounded by crossover to other therapies after completion of the study. The failure to demonstrate an effect on OS is therefore not considered to affect the overall conclusion of efficacy benefit demonstrated by PFS which, as a primary efficacy parameter in clinical trials of GEP-NETs, is endorsed by international experts in the field.

Post-hoc exploratory subgroup analysis of PFS according to location of primary tumour appeared to suggest some differences which the Applicant has been asked to discuss in the response to the Day 70 RMS and Day 85 CMS questions. The difference in PFS for lanreotide compared to placebo appeared less marked in tumours of pancreatic origin compared to those of mid-gut origin but in both cases favoured lanreotide over placebo. In the case of hindgut tumours, effect on PFS appeared to favour placebo. However, this subset was confounded by small patient numbers and imbalance between treated and placebo arms. The Applicant has been asked to discuss the significance of any apparent differences in sensitivity according to tumour location in the context of available therapies for these tumour subsets.

There were no notable differences in subjects’ Quality of life as measured by validated instruments between lanreotide and placebo groups. However, the sensitivity of the instruments to detect difference in patients with good performance scores has been queried.

A detailed justification for inclusion of moderately differentiated disease in the indication was also requested. In the pivotal efficacy and safety trial (study 726) the vast majority of tumours were recorded at baseline as well differentiated (99%) versus moderately differentiated (1%). Furthermore, although tumour grades G1 and G2 appeared to be well represented at baseline (69.1% and 29.9% respectively), tumours were graded as G2 with a proliferation index (Ki67) of 2 - <10% whereas according to the WHO classification, G2 grade spans a Ki67 index of 3 – 20%, suggesting that patients were not fully reflective of the G2 stage.

In the context of the data exclusivity request for these products, it is considered appropriate that the comparator arm was placebo as no authorised therapies for the wider group of well and moderately differentiated asymptomatic GEP-NETs (including pancreas, mid-gut and hind-gut) were available at the time of study commencement; even now, no clear treatment hierarchy is in place and for the most
indolent (well differentiated) tumours, placebo treatment with regular monitoring for tumour progression would be acceptable. The pivotal study demonstrated overall superiority for lanreotide compared with placebo as evidenced by the primary endpoint of progression free survival. However, subgroup analysis revealed differences in the degree of response according to location of primary tumour, with mid-gut the most responsive, hind gut showing the least and pancreas an intermediate response. Further justification for inclusion of pancreas and hindgut tumours in the indication which at present encompasses the broad group of GEP-NETs was requested; also, to discuss the response in the context of available therapies for these tumour subgroups (such as everolimus and sunitinib which are authorised for pancreatic NETs).

The RMS considers that sufficient justification have been provided for the inclusion of GEP-NETs of pancreatic, mid-gut and unknown origin where hind gut sites of origin have been excluded. Clarity has been provided to the therapeutic indication to reflect disease severity in terms of tumour classification grade and the magnitude of the Ki67 cellular proliferation index which is widely recognised by clinical practitioners in Europe as a tool for assessing disease severity in GEP-NETs.

Safety
Safety data are derived from six clinical studies in patients with GEP-NET, acromegaly and studies of symptomatic relief in GEP-NET. These products have an acceptable safety profile in patients for the indication of treatment of GEP-NET and no new safety signals have emerged to suggest that this patient population is at special risk compared to those previously treated for the indications of acromegaly and symptomatic GEP-NETs. The warnings in the product information are adequate and have been amended where necessary to reflect the proposed new indication.

Conclusions concerning the one-year’s data exclusivity
Based on the review of the data provided, it is considered that Ipsen Pharma’s request for an additional one year period of data exclusivity in accordance with Article 10(5) of Directive 2001/83/EC, as amended by Directive 2004/27/EC, for a new therapeutic indication for these products of:

The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or of unknown origin where hindgut sites

is approvable as the therapeutic indication has been agreed by the involved Member States and the following conditions of data exclusivity are considered to have been met:

- **Well established substance:** The active substance lanreotide has been authorised in the EU for more than 20 years and as the formulation lanreotide Autogel for 13 years.
- **New therapeutic indication:** The proposed indication can be considered a new therapeutic indication as it concerns an extended target population that includes asymptomatic gastro-enteropancreatic neuroendocrine tumours (GEP-NETs) as well as symptomatic GEP-NETs. It also concerns a distinct target population compared with an acromegalic patient population.
- **Significant clinical studies have been carried out in relation to the new indication:** A positive confirmatory trial in patients with asymptomatic (non-functioning) GEP-NETs has been supplied. Lanreotide demonstrated clear superiority over placebo, an acceptable comparator, in the population of GEP-NETs overall. The scope of data exclusivity will correspond with the final indication.

Further, CMDh agreed to the request for one year of data exclusivity for Somatuline (lanreotide) Autogel, the scope of which corresponds with the agreed new therapeutic indication: The treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or of unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease (see section 5.1).