Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Octreotide

## Proprietary Product Name: Sandostatin LAR

## Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

**February 2012**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

# About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents



# I. Introduction to product submission

### Submission details

| | |
|---|---|
| *Type of submission:* | Extension of Indications |
| *Decision*: | Approved |
| *Date of decision:* | 15 December 2011 |
| *Active ingredient:* | Octreotide |
| *Product name:* | Sandostatin LAR |

| | |
|---|---|
| *Sponsor's name and address:* | Novartis Pharmaceuticals Australia Pty Ltd |
| *Dose form:* | Powder for Injection |
| *Strengths:* | 10 mg, 20 mg and 30 mg |
| *Container:* | Glass vial |
| *Approved therapeutic use:* | Treatment of patients with progression of well-differentiated, advanced neuroendocrine tumours of the midgut or suspected midgut origin.[1] |
| *Route of administration:* | Intramuscular (IM) |
| *Dosage:* | 30 mg every 4 weeks |
| *ARTG numbers:* | 69413, 69210 and 69376 |

## Product background

Octreotide is an analogue of the natural short half-life hormone somatostatin. There are two registered formulations, the short acting Sandostatin and the slow release Sandostatin LAR. Neuroendocrine tumours (NETs) may be associated with hormone hypersecretion (so called "functional" NETs) as well as mass effects. Octreotide inhibits many hormones including growth hormone, gastrin, insulin, glucagon and other gastrointestinal hormones.

Octreotide is registered for the relief of symptoms associated with functional gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs). It is proposed to extend the indication to include an anti-tumour effect as well as relief of symptoms. A related drug lanreotide (Somatuline Autogel) is registered for the relief of symptoms associated with one GEP-NET, carcinoid tumour.

This AusPAR describes the application by the sponsor to obtain approval for Sandostatin LAR dosed at 30 mg every 28 days for the "*treatment of patients with advanced Neuroendocrine Tumours of the midgut or unknown primary location*."

The proposed indication was granted orphan designation status by the TGA on 15 September 2009 and the current Australian submission is restricted to long-acting Sandostatin LAR.

Neuroendocrine tumours (NETs) are rare solid tumours which form heterogeneous group of neoplasms characterized by embryological, biological and histopathological differences. Most endocrine tumours are well differentiated, non functioning and slow growing.

[1] The full indications are now:
*Acromegaly*: For the symptomatic control and reduction of growth hormone and IGF-1 plasma levels in patients with acromegaly, including those who are inadequately controlled by surgery, radiotherapy, or dopamine agonist treatment but who are adequately controlled on subcutaneous (SC) treatment with Sandostatin. Sandostatin LAR is also indicated in acromegalic patients unfit or unwilling to undergo surgery, or in the interim period until radiotherapy becomes fully effective.
*Gastro-Entero-Pancreatic Tumours*: For the relief of symptoms associated with the following functional tumours of the gastro-entero-pancreatic endocrine system: - Carcinoid tumours with features of the carcinoid syndrome; and Vasoactive intestinal peptide secreting tumours (VIPomas) in patients who are adequately controlled on subcutaneous treatment with Sandostatin. Sandostatin LAR is not curative in these patients
*Advanced Neuroendocrine Tumours Of The Midgut*: Treatment of patients with progression of well differentiated, advanced neuroendocrine tumours of the midgut or suspected midgut origin.

A classification of NETs has been proposed by the WHO in 2000 which is based on a series of histopathological and biological characteristics: cellular grading, primary tumour size and site, cell proliferation markers, local and vascular invasivity and the production of biologically active substances. [2]

Tumours are classified into one of the four main categories: well differentiated endocrine tumours characterised by a low grade malignancy and well differentiated endocrine carcinomas which are more aggressive because of the presence of metastases; poorly differentiated endocrine carcinomas with a high grade of malignancy and a poor prognosis; and mixed exocrine-endocrine tumours.

A few moderately differentiated tumours with cellular and structural types intermediate between well and poorly differentiated NETs have also been found among GEP-NETs. The main difference between poorly differentiated and well-differentiated endocrine carcinoma is evaluated by means of histological preparations, and in general it is reasonable to treat the former by chemotherapy, and the later with hormone/biotherapy.

Based on the WHO classification, the terminology "NETs" is used for neuroendocrine tumours and well differentiated neuroendocrine carcinomas. A distinction between foregut, midgut and hindgut tumours was used in the past to describe carcinoids.

This traditionally based classification according to the point of origin in the embryonic development classifies NETs as foregut (thymus, lung, stomach, proximal duodenum and pancreas), midgut, or hindgut tumours (distal colon and rectum).

The current submission refers specifically to midgut NETs, which includes tumours of the distal duodenum, jejunum, ileum, cecum, appendix, ascending colon, hepatic flexure and proximal colon.

Tumours of the lower jejunum and ileum account for 23 - 28 % of all gastrointestinal endocrine tumours and are more frequent than those of the appendix. The majority of tumours are located in the terminal ileum close to the ileocaecal valve (ENETS Guidelines [3]).

The prognosis of tumours arising in the distal small intestine is generally unfavourable compared to other GI endocrine tumours of comparable size. These tumours can behave very aggressively since they have a tendency to spread to the adjacent lymph nodes and later to the liver and elsewhere.

Endocrine tumours of the appendix are not discussed here as they were not represented in the clinical trials. Most patients with appendiceal carcinoids have a favourable prognosis, carcinoids < 2 cm in size, confined to the appendiceal wall and not angio invasive are completely cured by appendicectomy.

From a clinical viewpoint, endocrine tumors can be divided into functioning, and non functioning tumors. The term "non functioning" refers to the absence of clinical symptoms of hormonal hypersecretion.

Although both functioning and non functioning NETs frequently secrete one or more peptides, in most of the cases, those peptides do not result in a specific clinical syndrome. The carcinoid syndrome is usually seen in patients with liver metastases (95 % of patients).

Non functioning NETs are diagnosed late in the course of the disease, at the onset of clinical signs and symptoms due to tumour mass or metastatic disease. Patients with

[2] Modlin IM *et al* (2010). Gastrointestinal neuroendocrine (carcinoid) tumours: current diagnosis and management. *Med J Aust* 2010; 193: 46 - 52
[3] Plöckinger U *et al* (2004). *Neuroendocrinology* 2004; 80: 394 – 1424.

malignant tumours may present with mixed syndromes, or tumours may change clinically over time.

### Well differentiated jejunal-ileal tumours/carcinomas

The majority of tumours belong to WHO Group 2. European Neuroendocrine Tumour Society (ENETS) Guidelines.[4]

NETs of the lower jejunum and ileum have the reported incidence rates of 0.28 - 0.8/100,000 population/year. Most of these tumours are well differentiated and have an indolent course. As a consequence of the long delay between onset of symptoms and final diagnosis many patients have advanced disease at the time of diagnosis. Clinical incidence is probably higher than stated in the literature.

Non Functioning tumours: Asymptomatic NETs in the distal small intestine are discovered while searching for a primary in patients with newly discovered liver metastases from an endocrine tumour or incidentally during colonoscopy. Typical symptoms include intermittent abdominal discomfort misinterpreted as irritable bowel disease, intestinal bowel obstruction and non-secretory diarrhoea due to bacterial overgrowth.

Functioning tumours: Up to 18 % of patients with liver metastases due to an endocrine tumour of the jejunum-ileum present with the carcinoid syndrome. The rate of functionality and presence of the carcinoid syndrome in this patient group is about 20 - 30 %, that is, higher than previously stated.

Regional lymph node metastases are present at the time of diagnosis in 36 - 39 %, and non localized disease is evident in 64.1 % of the patients. The 5 year survival rate of patients with hepatic tumour spread is 18 - 32 %. If all stages are combined, the 5 year survival rate of NETs of jejunum-ileum is 60.5 % .The presence of the carcinoid syndrome has been described to decrease survival.

### Regulatory status

A similar application was lodged in many European countries . The product has been approved for this indication in several EU countries.

Sandostatin (octreotide acetate for SC or IV use) was first registered in New Zealand in December 1987 and in Australia in 1993. Sandostatin LAR was first registered in France in 1995 and in Australia in 1999. Novartis is currently the Marketing Authorization Holder for Sandostatin LAR in 95 countries worldwide.

### Product information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

Each vial of the product contains 10, 20, or 30 mg octreotide (present as acetate) and the excipients polyglactin and mannitol. The powder is a white to off-white colour. The vehicle

[4] Eriksson et al (2008). Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors - Well-Differentiated Jejunal-Ileal Tumor/Carcinoma Neuroendocrinology 87: 8 - 19. <http://www.enets.org/pdf/guidelines/Well-differentiated%20jejunal-ileal%20tumors.pdf>

contains carmellose sodium, mannitol and water for injections and is a clear, colourless solution.

# III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

# IV. Clinical findings

### Introduction

This literature based submission (LBS) submission contains only one study supporting the application (PROMID publication [5]), a series of reference studies and a large amount of background reading material including a number of nonclinical references. A total of 54 published references were submitted.

The *PROMID trial*, which represents the pivotal study for this submission was the first, placebo controlled, double blind, multicenter, prospective, randomised study assessing the antiproliferative effect of Sandostatin LAR in patients with metastatic, well differentiated midgut NETs.

The core data for the current Australian submission was derived from the planned Interim Analysis (IA) of the pivotal study, which was halted due to the efficacy claim, just after over half (52 %) of its intended participants were enrolled (85/162). The IA was based on 85 randomised patients: 42 to Sandostatin LAR arm and 43 to placebo.

The reference studies included a series of open, mostly uncontrolled trials conducted in a heterogeneous population involving a small number of participants, and some retrospective series using historical controls, pertaining to the antiproliferative effect of octreotide in NETs.

Some of these studies were evaluated by the TGA as part of the previous LBA application relating to rare functional GEP-NETs. The other submitted references included international guidelines/consensus statements and review articles.

The current submission also included the postmarketing data from Product Safety Update Report (PSUR) for Sandostatin/Sandostatin LAR. This report has been evaluated by the TGA for the rare GET-NETs submission. The PSUR has been evaluated for current submission.

### Pharmacokinetics

There were no new clinical pharmacokinetic data.

### Pharmacodynamics

There were no new clinical pharmacodynamic data.

[5] Rinke A *et al* (2009). Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. *J Clin Oncol* 27: 4656-4663.

## Efficacy

### PROMID study as reported by PROMID study group

A report from the PROMID Study Group was published by Rinke *et al* in 2009[5] and endorsed by the European Neuroendocrine Tumor Society. It also resulted in presentations at the American Society of Oncology (ASCO) annual meeting in 2009.[6]

#### *Design*

Phase IIIB, multi center (18 academic centres in Germany), prospective, placebo controlled, double blind, randomised (1:1) study, assessing the antiproliferative efficacy of Sandostatin LAR in treatment-naive patients with advanced well differentiated NETs of the midgut, or unknown primary tumour location.

Main inclusion criteria included locally inoperable or metastatic NETs of the midgut (primary tumour of midgut origin or tumour of unknown origin believed to originate in midgut; if pancreas, chest or elsewhere excluded by CT/MRI), Karnofsky performance status (KPS) > 60 %, and no curative therapeutic options.

Patients with either functioning or non functioning tumours were eligible for the study. All patients were required to have a measurable disease by Computerized axial tomography (CT)/Magnetic Resonance Imaging (MRI), and proof of well differentiated histology. For symptomatic patients to be eligible for the study, they were not to require treatment with somatostatin analogues (SSAs) for symptom management.

The randomization scheme used stratification with respect to the possible prognostic factors of tumour functionality, presence of distant metastases (liver or elsewhere), Ki-67[7] index, and age.

A total of 85 patients were randomised: 42 to Sandostatin LAR and 43 to placebo.

*Interventions*: Sandostatin LAR 30 mg IM (market form) or placebo (NaCl) every 28 days for 18 months, or until tumour progression, documented by CT/MRI, or death.

Due to the differences in appearance of octreotide and placebo, additional measures were taken to minimize the bias.

During the study, additional anti cancer therapy was not allowed. Further treatment, on disease progression was at the discretion of the physician, including placebo recipients' crossing-over to Sandostatin LAR.

*Sponsor comments: Considering the good tolerability of Sandostatin LAR, the choice of the maximal labelled dose of 30 mg Sandostatin LAR every 28 days was considered appropriate for the study. The use of placebo in this setting was also considered justified, as NETs are relatively slow growing tumours with limited data on the natural course of the disease. At the time of the study, there were no therapies with demonstrated efficacy in interfering with disease progression in midgut NETs.*

#### *Endpoints*

The primary objective was to demonstrate if the time to progression( TTP is lengthened in patients who receive Sandostatin LAR treatment compared to patients who receive placebo.

[6] R. Arnold, ASCO 2009. The results of *PROMID study* were first presented at the ASCO-Gastrointestinal (GI) in January 2009 (Arnold et al), and data from an update analysis with additional follow up to May 2009 were presented at ASCO annual meeting in June 2009.

[7] The Ki-67 protein (also known as MKI67) is a cellular marker for proliferation. Ki-67 is an excellent marker to determine the growth fraction of a given cell population. The fraction of Ki-67-positive tumor cells (the *Ki-67 labeling index*) is often correlated with the clinical course of cancer.

The *primary endpoint* was time to progression (TTP) defined as time from randomization to tumour progression or tumour-related death.

*Sponsor comments: While Progression Free Survival (PFS) is preferred over TTP in the Phase III settings, the two endpoints only differ in the way they define Progressive disease (PD). PFS includes deaths unrelated to tumour, while TTP disregards them.*

*In trials where the majority of deaths are expected to be related to cancer, PFS may be preferable to TTP as a correlate of OS. However, this is not the case for midgut NETs and consequently, deaths not related to tumour were expected to be a confounder for a PFS analysis. Therefore, TTP was considered a more appropriate primary endpoint for the PROMID study.*

*Secondary endpoints* were survival time, Quality of Life (QoL), and clinical (objective response rate judged by blinded central reader according to the WHO criteria), and biochemical response, at 6 months after study entry.

The blinded central reader judged tumour response according o the WHO criteria. Assessments were planned at 3 monthly intervals up to Month 18.

Complete Response (CR) = disappearance of all known tumour manifestations, in 2 examinations at least 14 days apart.

Partial Response (PR) = at least 50 % decrease in the total tumour burden of all lesions, measured in at least 2 examinations, at least 4 weeks apart.

Stable Disease (SD) = neither a decrease of at least 50 % nor an increase of at least 25 %.

Disease Progression (DP) = increase of at least 25 % in the size of ≥ 1 measurable lesions, or the appearance of new lesions.

*Sponsor comments: Tumor response evaluation was conducted according to the established methodology at the time the PROMID study was designed (2000/2001); namely the WHO criteria. While the RECIST criteria is now the preferred methodology for tumour assessment in the Phase III setting, evaluation according to the WHO criteria in the PROMID study is still considered adequate.*

Moreover, for cytostatic drugs, like Sandostatin, the most favourable response is expected to be SD. In such circumstances the evaluation of disease progression according to either the WHO or to the RECIST criteria are likely to yield very similar results.

### *Statistical methods*

The study tested the hypothesis that octreotide LAR prolongs TTP and survival.

The study was designed as a group sequential with one interim analysis after observation of 64 events and the final analysis after observation of 124 events. The confirmatory analyses encompassed the 2 efficacy endpoint: TTP and survival time. The primary confirmatory analysis was a conservative analysis based on the Intent to Treat (ITT) principle (cITT).

A median Time to Progression (TTP) of 9 months was assumed for the placebo group. A Hazard ratio (HR) of 0.6 was postulated as a clinically meaningful difference to be detected with a power of 80 %.

Assuming a 3 year recruitment period with 18 months follow up and lost to follow up rate of 10 %, a minimum number of 162 patients needed to be recruited according to Schoenfeld and Richter[8]. A nominal Type I error level of 0.0122 at interim and 0.044 at the

[8]Schoenfeld and Richter 1982. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* 38:163-170.

final analyses was planned. The α-spending was based on Lan and DeMets (1994)[9] to control the overall Type I error rate at 2 sided α = 0.05.

Statistical analyses were performed using log rank test, univariate and multivariate Cox regression models, Fisher's exact test, and Wilcoxon-Mann-Whitney test, with or without stratification. Per protocol, a 2 sided log rank test stratified by tumour functioning status (functioning versus non functioning) was used to compare the primary endpoint TTP in the 2 treatment groups at the overall 2 sided α = 0.05 level.

For survival time, a fixed sample test based on 121 observed deaths was defined in the protocol. Controlling the family wise error rate at the level of 5 %, this test was planned as a confirmatory test in the event of a significant result for the primary endpoint, with the option of redesign.

A sensitivity analysis was performed on a Per Protocol (PP) basis. Exploratory analyses were performed to investigate potential prognostic factors. During the study, hepatic tumour involvement was recognized as a further important factor.

ITT population: All randomised patients; Sandostatin LAR (n = 42) and placebo (n = 43).

cITT population: The primary confirmatory analysis of the *PROMID study* as reported by Rinke *et al* 2009[5]; included all 85 randomised patients although 3 patients were censored at randomization (2 in the Sandostatin LAR arm and 1 in the placebo group).

PP population: all 85 patients but with further censoring as compared to the cITT analysis.

The results of the pre-planned IA on TTP were highly significant in favour of Sandostatin LAR and the study was stopped. At that time a total of 85 patients *(*52 % of the intended population*)* were randomised and 9 patients continued to receive study medication in a blinded fashion; follow up of this population will continue without unblinding, on yearly basis, until death.

### *Patient enrolment, characteristics and disposition*

Of the 85 randomised patients 43 were male and 42 were female. The median age was 62 years (range: 38 - 82). The median time since diagnosis was 4.3 months. Almost all patients enrolled in the study had newly diagnosed tumour disease; in 21 patients, the site of primary was unknown; 5 of these patients had carcinoid syndrome.

Baseline characteristics of the 85 randomised patients:

A total of 33 patients (39 %) had symptoms of carcinoid syndrome. The primary tumour had been removed in 56 patients (66 %); 73 patients (86 %) had liver metastases, and hepatic tumour load was ≤ 10 % in 64 patients (75 %); 81 patients had Ki-67 values up to 2 %; 73 patients underwent Octreoscan[10], of whom 63 (86 %) had a positive result.

Overall, the baseline characteristics of the 2 treatment arms appear to be well balanced except for the time since diagnosis; the median time since diagnosis was longer in the Sandostatin LAR arm than in the placebo arm (7.5 versus 3.3 months; p = 0.0096).

For 64 patients included in the *PROMID study*, the initial diagnosis was locally inoperable or metastatic midgut NET, and 21 patients had locally inoperable or metastatic NET of unknown origin.

[9] DeMets DL, Lan KK: Interim analysis: The alpha spending function approach. Stat Med 13: 1341-1352, 1994.
[10] An Octreotide scan or Octreoscan is a type of scintigraphy used to find carcinoid and other types of tumors and to localise sarcoidosis. Octreotide, a drug similar to somatostatin, is radiolabelled with indium-111 and is injected into a vein and the radioactive octreotide attaches to tumor cells that have receptors for somatostatin. A radiation measuring device detects the radioactive octreotide and makes pictures showing where the tumor cells are in the body. It is also called *somatostatin receptor scintigraphy* and SRS.

Post study treatment in the octreotide LAR and placebo groups included octreotide LAR (25 versus 33 patients, respectively), hepatic chemoembolisation (4 versus 9 patients, respectively), radioligand therapy (4 versus 6 patients, respectively), and chemotherapy (3 versus 3 patients, respectively).

### *Primary efficacy results*

Patients were registered between March 2001 and January 2008.The Interim Analysis was performed (June 2008) after 67 events and the p-value boundary was recalculated to 0.0125 (up from 0.0122 based on pre-planned 64 events) to account for the number of events higher than initially planned.

The data from 67 patients with tumour progression and 16 deaths (n = 7 octreotide LAR, 9 placebo) were included in the analysis. Based on the results of the IA, the recruitment into the study was stopped, due to the significant clinical benefit provided by Sandostatin LAR and the slow enrollment rate.

*TTP*

The results of the IA showed a benefit of Sandostatin LAR in prolonging TTP as compared to placebo across all 3 efficacy analyzed populations (Table 1).

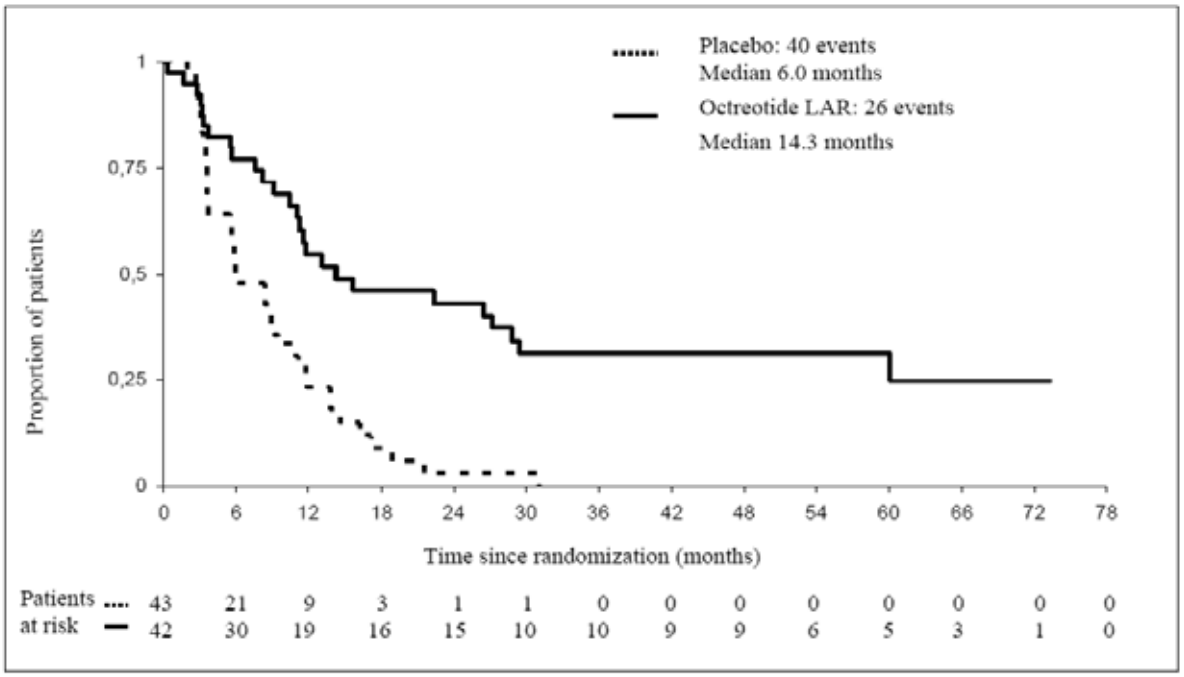
**Table 1. PROMID study. TTP results by analysis populations.**

| | TTP Events | | Median TTP months [95% C.I.] | | HR [95% C.I.] p-value * |
|---|---|---|---|---|---|
| | Sandostatin LAR | Placebo | Sandostatin LAR | Placebo | |
| ITT | 26 | 41 | NR | NR | 0.32 [ 0.19 to 0.55] p-value*=0.000015 |
| cITT | 26 | 40 | 14.3 [ 11.0 to 28.8] | 6.0 [ 3.7 to 9.4] | 0.34 [0.20 to 0.59] p-value*=.000072 |
| PP | 19 | 38 | NR | NR | 0.24 [ 0.13 to 0.45] p-value* =0.0000036 |

NR=not reported; HR=hazard ratio; TTP=time to tumor progression; ITT=intention to treat; cITT=conservative ITT; PP=per protocol
*Logrank test stratified by functional activity
Source: Rinke et al. 2009[5]

In the planned confirmatory cITT analysis, 26 and 40 progressions or tumour related deaths were observed in the octreotide LAR and placebo groups, respectively (HR = 0.34; 95 % CI: 0.20 - 0.59; p = 0.000072) (Figure 1).

**Figure 1. PROMID study. Kaplan-Meier estimates of TTP comparing Sandostatin LAR with placebo (conservative ITT population)**




Logrank test stratified by functional activity: P=0.000072, HR= 0.34 [95%-CI: 0.20–0.59]

Median TTP was 14.3 months in the Sandostatin LAR group and 6.0 months in the placebo group. This difference was considered not only statistically significant but also clinically meaningful.

In the planned ITT analysis, 26 and 41 progressions were seen in the octreotide LAR and placebo groups, respectively (HR = 0.32; 95 % CI: 0.19 - 0.55; p = 0.000015).

For the ASCO presentation, the ITT analysis was updated (May 2009) and only marginal changes were seen for the primary endpoint, with 27 and 41 progressions seen, respectively (HR = 0.33; 95 % CI: 0.19 - 0.55; p = 0.000017).

The presented data were based on ITT population and included 68 tumour progressions. Median TTP was 15.6 months in the Sandostatin LAR group and 5.9 months in the placebo group. These latter results continued to demonstrate the benefit of Sandostatin LAR therapy to midgut NET patients.

Analysis of the PP population showed that tumour progression or tumour related death was observed in 19 and 38 Sandostatin LAR and placebo recipients, respectively (HR = 0.24; 95 % CI: 0.13 - 0.45; p = 0.0000036).

*TTP subgroup analyses results (exploratory analyses)*

Subgroup analyses of TTP based on PP population were performed to explore the influence of some potential prognostic factors on the treatment effect. The results showed that for all sub-groups explored, the HRs trend is in the direction of favoring Sandostatin LAR (Table 2).

**Table 2. PROMID study. Per protocol subgroup analyses of treatment effect for TTP.**

| | Per-protocol analysis | | | |
|---|---|---|---|---|
| | | Sandostatin LAR | Placebo | |
| | N | Median (months) | Median (months) | HR; 95% CI |
| Functioning tumours | 33 | 14.3 | 5.5 | 0.23 [0.09 to 0.57] |
| Non-functioning tumor | 52 | 28.8 | 5.9 | 0.25 [0.10 to 0.59] |
| Liver involvement 0% | 12 | 13.1 | 8.2 | 0.55 [0.10 to 3.09] |
| Liver involvement 0-10% | 52 | 29.4 | 6.1 | 0.17 [0.08 to 0.40] |
| Liver involvement 10-50% | 14 | 11.2 | 5.5 | 0.40 [0.10 to 1.67] |
| Liver involvement >50% | 7 | 4.6 | 2.8 | 0.71 [0.11 to 4.45] |
| Chromogranin A elevated* | 56 | 14.3 | 5.6 | 0.26 [0.13 to 0.54] |
| Chromogranin A not elevated | 27 | 28.8 | 8.5 | 0.26 [0.08 to 0.85] |
| Karnofsky Index ≤80% | 12 | 11.5 | 6.1 | 0.32 [0.05 to 1.98] |
| Karnofsky Index >80% | 73 | 27.1 | 5.8 | 0.23 [0.12 to 0.45] |
| Age <63 yrs | 43 | 28.8 | 8.3 | 0.23 [0.08 to 0.63] |
| Age ≥63 yrs | 42 | 14.3 | 5.7 | 0.23 [0.10 to 0.53] |
| Primary tumor resected | 56 | 29.4 | 5.9 | 0.16 [0.07 to 0.36] |
| Primary tumor not resected | 29 | 10.3 | 5.6 | 0.84 [0.35 to 2.06] |
| Time since diagnosis <4.3 mo | 43 | 11.5 | 5.6 | 0.34 [0.15 to 0.76] |
| Time since diagnosis ≥4.3 mo | 42 | 28.8 | 8.3 | 0.22 [0.09 to 0.56] |

* Plasma CgA levels were determined in the participating study centers. Since assay conditions varied between centers, the respective absolute values were transformed. Elevated if above the upper limit of normal controls.
Source: (Rinke et al. 2009[5])

However, due to small sample size for some of those sub groups, these data should be interpreted with caution (upper bound of the 95 % CI exceeded 1).

The treatment effect was similar in patients with functioning (HR = 0.23; 95 % CI: 0.09 - 0.57) or non functioning tumours (HR = 0.25; 95 % CI: 0.10 - 0.59).

*Evaluator's comment: In fact, the study compared minimally symptomatic patients (carcinoid syndrome) with those having "non functional tumours" (also see comments on inclusion criteria). Midgut NETs are strongly associated with carcinoids.*

The subgroup analyses also suggested that the antiproliferative effect may be influenced by resection of the primary tumour and hepatic tumour burden. The benefit of Sandostatin LAR appeared to be greater in patients whose primary tumour was resected than in those without resection (HR = 0.16 versus HR = 0.84). The extent of hepatic tumour burden seemed to be important prognostic factor.

To further explore the impact of tumour burden, an additional analysis was performed using a threshold of 10 % liver involvement. Factors exploring heterogeneity of the effect size are listed in Table 3 and bivariate and multivariate analyses for possible prognostic factors are shown in Table 4.

**Table 3. PROMID study.**

**Table 2.** Per-Protocol Subgroup Analyses of Treatment Effects for Time to Progression or Tumor-Related Death

| Factor | No. of Patients | Per-Protocol Analysis: Median Time to Progression or Tumor-Related Death (months) Octreotide LAR | Placebo | HR | 95% CI |
|---|---|---|---|---|---|
| Carcinoid syndrome | 33 | 14.3 | 5.5 | 0.23 | 0.09 to 0.57 |
| Inactive tumor | 52 | 28.8 | 5.9 | 0.26 | 0.10 to 0.69 |
| Liver involvement | | | | | |
| 0% | 12 | 13.1 | 8.2 | 0.55 | 0.10 to 3.09 |
| 0%-10% | 52 | 29.4 | 6.1 | 0.17 | 0.08 to 0.40 |
| 10%-50% | 14 | 11.2 | 5.5 | 0.40 | 0.10 to 1.67 |
| > 50% | 7 | 4.6 | 2.8 | 0.71 | 0.11 to 4.45 |
| Chromogranin A* | | | | | |
| Elevated | 56 | 14.3 | 5.6 | 0.26 | 0.13 to 0.54 |
| Not elevated | 27 | 28.8 | 8.5 | 0.26 | 0.08 to 0.85 |
| Karnofsky performance status | | | | | |
| ≤ 80% | 12 | 11.5 | 6.1 | 0.32 | 0.05 to 1.98 |
| > 80% | 73 | 27.1 | 5.8 | 0.23 | 0.12 to 0.45 |
| Age, years | | | | | |
| < 63 | 43 | 28.8 | 8.3 | 0.23 | 0.08 to 0.63 |
| ≥ 63 | 42 | 14.3 | 5.7 | 0.23 | 0.10 to 0.53 |
| Primary tumor resection | | | | | |
| Yes | 56 | 29.4 | 5.9 | 0.16 | 0.07 to 0.36 |
| No | 29 | 10.3 | 5.6 | 0.84 | 0.35 to 2.06 |
| Time since diagnosis, months | | | | | |
| < 4.3 | 43 | 11.5 | 5.6 | 0.34 | 0.15 to 0.76 |
| ≥ 4.3 | 42 | 28.8 | 8.3 | 0.22 | 0.09 to 0.56 |

Abbreviation: HR, hazard ratio.
*Plasma chromogranin A levels were determined at the participating study centers. Because assay conditions varied between centers, the respective absolute values were transformed. Levels were considered elevated if greater than the upper limit of normal controls.

**Table 4. PROMID study.**

**Table 3.** Prognostic Factors for Time to Progression or Tumor-Related Death Adjusted for Treatment Based on the Per-Protocol Analysis

| Factor | Bivariate Analysis P | HR | 95% CI | Multivariate Analysis P | HR | 95% CI |
|---|---|---|---|---|---|---|
| Octreotide LAR v placebo* | | | | < .0001 | 0.27 | 0.14 to 0.49 |
| Functional active tumor v inactive tumor | .2420 | 1.36 | 0.81 to 2.37 | | | |
| Liver involvement > v ≤ 10% | .0009 | 2.81 | 1.53 to 5.18 | .0023 | 2.63 | 1.41 to 4.90 |
| Chromogranin A elevated v not elevated | .3098 | 1.36 | 0.75 to 2.48 | | | |
| Karnofsky performance status ≤ v > 80% | .6518 | 1.21 | 0.54 to 2.71 | | | |
| Age ≥ v < 63 years | .1709 | 1.47 | 0.85 to 2.56 | | | |
| Primary tumor not resected v resected | .1040 | 1.60 | 0.91 to 2.80 | .6784 | 1.45 | 0.60 to 2.20 |
| Time since diagnosis ≥ v < 4.3 months | .0806 | 0.62 | 0.38 to 1.06 | .2883 | 0.71 | 0.38 to 1.34 |

Abbreviation: HR, hazard ratio.
*P value and effect size are only presented for multivariate analysis.

At baseline, 32/42 Sandostatin LAR recipients (76 %) and 32/43 placebo recipients (74 %) had a hepatic tumour load ≤ 10 %. Median TTP in these patients was 27.14 months when treated with Sandostatin LAR and 7.21 months when given placebo; p < 0.0001.

In patients with a hepatic tumour load >10 % (24 % of Sandostatin LAR and 26 % of placebo recipients), TTP was 10.35 months versus 5.45 months, respectively (p = 0.345).

The benefit of Sandostatin LAR appeared to be greater in patients with a hepatic tumour burden of ≤ 10 %, than in those patients with a larger tumour burden. However, the number of patients in these subgroups were small, and although the difference in TTP between Sandostatin LAR and placebo in patients with a hepatic tumour load >10 % did not achieve statistical significance; there was also a trend for that subgroup of patients.

TTP was extended with Sandostatin LAR irrespective of baseline Chromogranin A (CgA) levels (elevated or not) or age (< or > 63 years).*Comment: The decline of tumour markers, like CgA is due to the anti secretory effect of SSAs and should not be interpreted as evidence for tumour volume reduction.*[11]

The analysis of prognostic factors showed that the influence of time since diagnosis lead to only a slight reduction in therapeutic effect. There were no significant differences between groups in other baseline characteristics including: sex, KPS (> or < 80 %), or Ki-67 level (> or < 2 %).

### *Secondary efficacy results*

*Overall Survival (OS)*

The important study aim, of whether or not the favorable effect of octreotide LAR on TTP indicated prolonged OS could not be determined.

In total, 7 and 9 deaths were observed in the Sandostatin LAR and the placebo groups, respectively.

Given the small number of deaths, the median survival time could not be estimated in the Sandostatin LAR group, and the estimation of 73.7 months in the placebo group is not robust; HR = 0.81; 95 % CI: 0.30 - 2.18; p = 0.77.

These results, however, should be considered with caution, as in addition the influence of other therapies after disease progression on OS cannot be ruled out.

*WHO response*

Tumor progression after 6 months occurred in 24 % (10/42) of Sandostatin LAR and 53 % (23/43) of placebo recipients.

SD was observed in 66.7 % (28/42) and 37.2 % (16/43) of Sandostatin LAR and placebo recipients, respectively.

Only one partial remission was seen in either group. No complete response occurred. In 6/85 patients, tumour response was unknown.

Comparison by the Wilcoxon-Mann-Whitney test showed a difference in favour of Sandostatin LAR; p = 0.0079.

Although widely accepted, it is of note that the definition of SD includes quite a wide range of tumour responses; (SD = neither a decrease of at least 50 % nor an increase of at least 25 %).

*Symptomatic and biochemical response, QoL*

The eligibility criteria of the study excluded symptomatic patients if they required treatment with SSA for symptom management. Consequently, even though almost 40 % of

[11]Plöckinger U and Wiedenmann B (2007). *Virchow's Arch* 451 (Suppl 1): S 71 - S 80.

the patients enrolled in the study were considered symptomatic, most had mild symptoms.

While the efficacy of Sandostatin LAR in controlling symptoms of GEP-NETs is well established, the small number of patients with more pronounced symptomatology in both arms did not allow any significant difference to be observed.

Both treatment groups had comparable levels of global QoL at random assignment and after 6 months of follow up.

In the Sandostatin LAR group, 63.4 % (26/41) of patients had elevated CgA levels at study entry, which declined to 43.3 % (13/30) of patients at 6 months. In the placebo group, these percentages were 71.4 % (30/42) and 60 % (12/20), respectively. Normalisation of elevated CgA levels was observed in 9 Sandostatin LAR and 4 placebo recipients at 6 months.

***Discussion of the results by study authors***

The study provides evidence that octreotide LAR inhibits tumour growth in patients with metastatic well-differentiated midgut NETs. The recruited patients represented the typical population of this tumour entity.

The most favourable outcome was stabilisation of tumour growth. Patients with functionally active and inactive tumours responded similarly. The extent of hepatic tumour burden seemed to be an important prognostic factor. The anti proliferative response was more pronounced in patients with resected primary tumour and patients with low (≤ 10 %) hepatic tumour load.

Additional studies with higher patient numbers are necessary to identify further parameters that may influence the anti proliferative effect of octreotide LAR.

Only treatment naïve patients were included in this trial and therefore almost all patients had newly diagnosed tumour disease.

Patients with a high tumour load had a poorer prognosis than patients with few liver metastases. Therefore it was suggested that newly diagnosed patients with low hepatic tumour burden and a resected primary tumour are candidates for treatment with octreotide LAR.

Further studies are needed to determine whether patients with a high hepatic tumour burden that developed slowly respond to biotherapy more favourably.

Although prolongation of TTP by antiproliferative therapy may influence overall survival, no conclusions in this regard can be drawn from current study.

Long term observation of patients not receiving octreotide LAR is difficult; most patients from the placebo group received SSAs and many patients in the active group continued with octreotide LAR.

*Author's overall conclusion[12]:*

Octreotide LAR significantly lengthens median time to tumour progression compared with placebo in patients with metastatic NETs of the midgut. Because of the low number of observed deaths, survival analysis was not confirmatory.

Patients treated with octreotide LAR had a 67 % risk reduction of tumour progression compared with patients receiving placebo.

[12] Paper by Rinke *et al* 2009 and ASCO presentation by Arnold *et al* 2009.

Octreotide LAR demonstrates substantial tumour control and shows a more favorable anti proliferative response than placebo, as nearly 2/3 of patients treated with octreotide LAR achieved SD at 6 months.[1 & 2]

"We believe that biotherapy with octreotide LAR is the treatment of choice in patients with newly diagnosed, functionally active or inactive, well-differentiated metastatic midgut NETs and with a low hepatic burden. Additionally, octreotide LAR may be an attractive treatment option for patients after cytoreductive surgery with few remaining metastases.

We propose that impact of biotherapy on time to tumour progression and overall survival should be investigated further in clinical trials, in addition to studies including NETs of other origins."

**Novartis supportive analysis of PROMID study.**

Title of the report: "Placebo-controlled prospective randomised study on the antiproliferative efficacy of octreotide in patients with metastasized neuroendocrine tumours of the midgut."

***Design***

The objective of this independent analysis was to assess whether the positive findings from Rinke *et al* (2009)[5] still hold when analysis was performed on Novartis re derived TTP.

The Novartis analysis reproduced as close as feasible the methodology as described in the protocol by Rinke *et al* (2009). As some of the methodology could not be retrieved, some assumptions were made.

The database received by Novartis had the same data cut off date (June 2008) as that used to generate results for Rinke *et al* (2009). The two databases may, however, present some differences, because after the initial interim database lock, additional checks were applied to both safety and efficacy variables by Novartis; resolutions of the queries were independently incorporated into both databases.

***Endpoints***

The primary endpoint in the Novartis assessment was the same as per study protocol, and that used by Rinke *et al* (2009), that is, TTP.

In the Novartis analysis, assessment of the efficacy data was based on the measurements as well as comments, recorded in the central radiologist review panel, in the database provided to Novartis. Individual CT or MRI-films were not evaluated.

When comments were used in assessing the progression status/measurable disease, this was done manually by a Novartis physician; nine patients had a non measurable disease at baseline. The assessment of tumour progression was similarly based on WHO criteria.

Since treatments given to patients after study discontinuation were not well controlled and closely tracked, censoring was implemented when assessing efficacy. Tumour measurements taken more than 56 days after study discontinuation were not considered in assessing progression. The same applied to deaths beyond the same time window, regardless of tumour relationship (Table 5).

**Table 5. Novartis analysis. Per-protocol subgroup analyses of treatment effect for TTP.**

| | Sandostatin LAR N=42 | Placebo N=43 |
|---|---|---|
| **TTP events** | | |
| 25% or more increase in size of one or more measurable lesions comparing to the baseline | 19 | 33 |
| Appearance of new lesion in the comments field of the central review data panel | 1 | 2 |
| Comments in the central review data panel supported tumor progression[1] | 4 | 1 |
| Tumor-related death | 1 | 0 |
| **Censoring** | | |
| Censoring at last adequate tumor assessment[2] | 12 | 4 |
| Censoring at last adequate tumor assessment prior to date of study discontinuation + 56 days[2,3] | 2 | 2 |
| Censoring at randomization[4] | 3 | 1 |

[1] This does not include new lesions in the comments field.
[2] The last adequate tumor assessment must be performed on the same lesion measured at baseline.
[3] These patients have tumor measurements or other tumor related information 56 days after study discontinuation.
[4] Three patients (2 in Sandostatin LAR and 1 in placebo) did not have any tumor measurement nor tumor related information documented in the comments field. One patient (Sandostatin LAR) had only one baseline tumor measurement record showing non-measurable disease with no post-baseline records.

### *Statistical methods*

The Novartis analysis focused only on the primary endpoint of TTP in the ITT population, referred to as Full Analysis Set (FAS).

The FAS consisted of all randomised patients (n = 85) analysed according to the treatment they were assigned to at randomisation.

Similar to the original analyses, a 2 sided log rank test stratified by tumour functioning status was used to compare the primary endpoint in the 2 treatment groups, at the overall 2 sided $\alpha = 0.05$ level.

Since the exact method used by Rinke *et al* 2009 to determine significance p value boundary could not be obtained from the authors; the significance level in its IA was

determined using Wang and Tsiatis (1987)[13] power family boundary with the shape parameter set to 0.17 in order to match the p value boundary specified in the protocol.

A more conservative approach, the O'Brien-Fleming boundary, was also calculated. As specified in the protocol, the IA was planned when 64 tumour progressions or tumour related deaths occurred, out of the planned 124 events. The p value boundary from Wang and Tsiatis power family for the planned IA is 0.0122, while that from the O'Brien-Fleming method is 0.0036.

From the Novartis assessment, there were 61 tumour progressions or tumour related deaths observed in the dataset; 25 (including 1 tumour related death) in the Sandostatin LAR arm and 36 in the placebo arm. Based on this number of events, the significance boundaries according to the Wang and Tsiatis power family and the O'Brien-Fleming method are 0.0111 and 0.0028, respectively.

### *Primary efficacy results*

TTP differed significantly between the Sandostatin LAR and the placebo treatment arm.

The median TTP in the ITT analysis was 11.3 months (95 % CI: 6.7 - 14.3) in patients receiving Sandostatin LAR versus 5.6 months (95 % CI: 3.5 - 6.2) for placebo patients, the difference being statistically significant (HR 0.41; 95 % CI: 0.24 - 0.70; p = 0.0008) (Table 6 and Figure 2).

**Table 6. Novartis analysis. Stratified log-rank test and Cox regression model for time to progression (months), comparison of Sandostatin LAR with placebo - overall and by tumour functioning status (Novartis full analysis set, N = 85).**

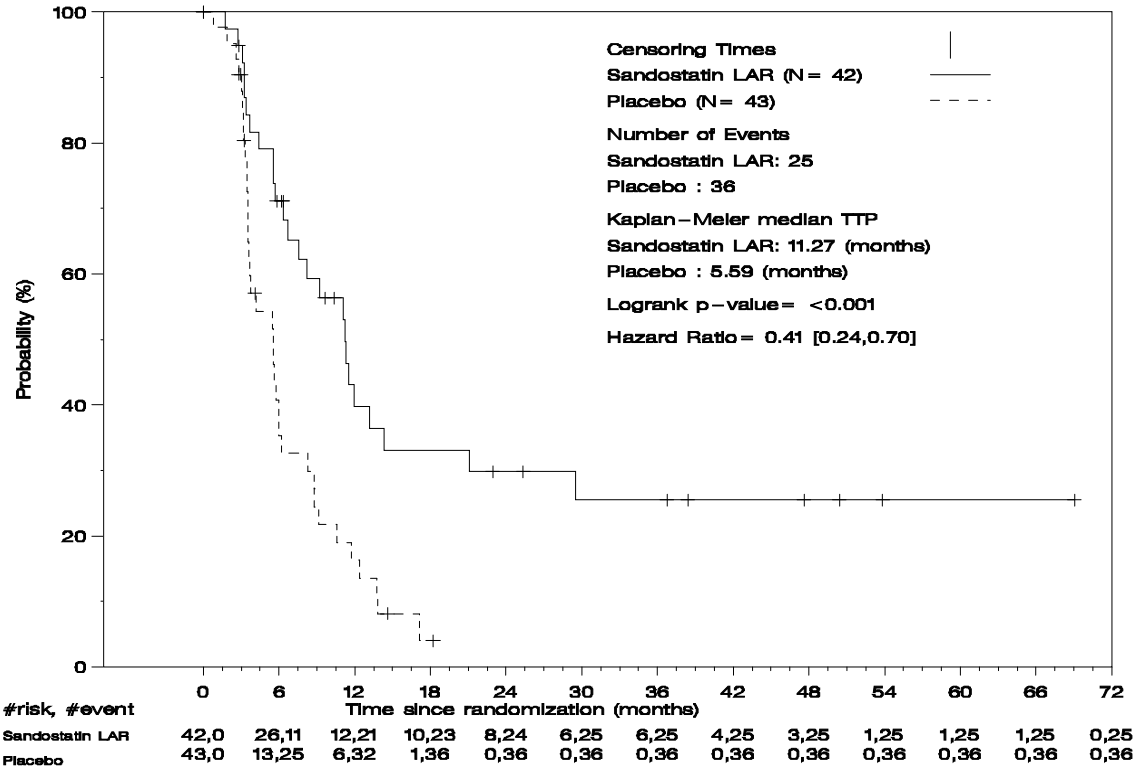
| | | | Cox Model | Log-rank test |
|---|---|---|---|---|
| | **Event/N (%)** | **Median TTP (95% CI) (months)** | **Hazard ratio (95% CI)** | ***P*-value** |
| **All patients** | | | | |
| Sandostatin LAR | 25/85 (29.4) | 11.3 (6.7, 14.3) | 0.41 ( 0.24, 0.70) | 0.0008 |
| Placebo | 36/85 (42.4) | 5.6 (3.5, 6.2) | | |
| **Functioning (stratum 1)** | | | | |
| Sandostatin LAR | 12/33 (36.4) | 11.9 (4.4, 21.1) | 0.41 ( 0.18, 0.95) | |
| Placebo | 13/33 (39.4) | 3.7 (3.5, 8.8) | | |
| Non-functioning (stratum 2) | | | | |

[13] Wang SK and Tsiatis AA (1987). Approximately Optimal One-ParameterBoundaries for Group Sequential Trials. *Biometrics* 43:193-199.

| | | | Cox Model | Log-rank test |
|---|---|---|---|---|
| | **Event/N (%)** | **Median TTP (95% CI) (months)** | **Hazard ratio (95% CI)** | ***P*-value** |
| Sandostatin LAR | 13/52 (25.0) | 9.2 (6.3, N/A) | 0.41 ( 0.20, 0.82) | |
| Placebo | 23/52 (44.2) | 5.6 (3.5, 8.3) | | |

- TTP = time from randomization to tumor progression or tumor-related death (months)
- Median TTP and the corresponding 95% CI are generated by Kaplan-Meier estimation
- For "All patients", both the log-rank test and Cox model are stratified by tumor functioning status (functioning vs. non-functioning)
- Hazard ratio is the hazard of the Sandostatin LAR arm with respect to the placebo arm.
- N/A= not available

**Figure 2. Novartis analysis. Kaplan-Meier plot of TTP by treatment - Novartis full analysis set (N = 85)**




This significant delay of progression was consistently observed in the subsets according to functional status; HR 0.41 (95 % CI: 0.18 - 0.95) and 0.41 (95 % CI: 0.20 - 0.82) in functioning and non functioning tumours, respectively.

Although PFS was not formally derived in Novartis analysis, PFS and TTP are expected to yield the same results.

The number of observed deaths was 7 and 9 in the Sandostatin LAR and placebo groups, respectively.

According to the database received by Novartis all deaths unrelated to tumour occurred after tumour progression, except for 1 patient whose cause of death is unknown, and who did not receive any study medication. By applying the 56 day post study discontinuation rule, TTP and PFS both censored this patient at date of randomisation. Therefore, TTP and PFS would be identical.

*Sponsor's conclusion:*

*The Novartis analysis of the data from PROMID study and the analysis performed by Rinke et al 2009 are congruent.*

*The analysis performed by Novartis further supports the validity of the original analysis by Rinke et al and confirms the antiproliferative effect of Sandostatin LAR 30 mg.*

### *Other efficacy evidence*

Additional clinical data presented in support of this application includes a series of open label, uncontrolled, published studies pertaining to the antiproliferative effect of octreotide in patients with NETs.

*According to the aim of the sponsor's submission, this report is centred on evidence relating to treating the disease progression in patients with NETs, including those with non functional disease. SSAs are already established in the treatment of symptoms associated with functional NETs. Therefore, symptoms control and biochemical data are not included in the report.*

## Case series/observational studies

### *Study by Aaron Vinik and Ali Reza Moattari 1989*

Title: "Use of Somatostatin Analog in Management of Carcinoid syndrome." *Dig Dis Sci* 34:14S-27S.

Observational study from the University Hospital in Michigan, USA, evaluating the effects of octreotide *(SMS 201-995)* on clinical symptoms, biochemical outcomes and tumour growth in carcinoid patients (n = 14).

Patients with histologically proven carcinoid were enrolled in the study. There were no selection criteria as far as symptoms or extent of the disease. The population included heterogeneous group of highly symptomatic patients with carcinoid (13/14 had CT evidence of liver metastases). The primary tumour was in the ileum (8), pancreas (2), and not identified (4).

There were 8 males and 6 females with a mean age of 60 years (range: 46 - 80). A total of 10 patients had resection of primary tumour/debulking of metastases and 5 had chemotherapy. The time from initial diagnosis to initiation of octreotide therapy ranged from 2 - 96 months.

*Intervention*

Octreotide at an initial dose of 100 µg SC BD, increased to maximum maintenance dose of 250 µg every 6 hours "to control symptoms and correct paraclinical abnormalities." Octreotide was continued as long as the patients wished and had evidence of clinical and biochemical improvement.

*Results*

"Tumour growth appeared to be slowed in 2/3 of cases treated for up to 4 years."

Follow up CT scans were available for 10 patients: 2 cases showed "some regression of the tumour" (one of these cases showed tumour infarction), 4 cases showed progression and 5 showed no changes (including one case followed up for up to 2 years).

The authors commented that "the relationship between tumour size and growth and the biochemistry is not a simple one" describing a patient in whom "the tumour is clearly shrinking, but ACTH[14] levels have risen", and a case of "progression of tumour growth after 18 months of SMS *(octreotide)* therapy" accompanied by "dramatic fall in blood serotonin values and asymptomatic patient", and a case of "the opposite situation of unchanged tumour size, a very well patient and hormonal levels that were unaffected by SMS even in doses as high as 1000 µg/day".

The authors commented that the studied population included a "heterogeneous group with advanced carcinoid tumours refractory to conventional chemotherapeutic agents who were tried on somatostatin analog with variable clinical and biological response".

Due to the slow growth of carcinoid tumours it is difficult to assess the effect of octreotide on the rate of tumour growth or regression. "Tumours, in general, continue to grow, but this may be slowed or in rare cases tumour growth arrested. In individual cases the tumour may even infarct, leading to spontaneous cure."

"The effect of SMS on tumour growth needs to be further evaluated in relation to the slow progression and indolent nature of these tumours."

*Evaluator's note: In reference to Table 7; the number of participants in the study should be 14. On bases of this paper, the evaluator cannot comment on the numbers (%) presented in the table representing tumour response.*

**Table 7. Summary of submitted studies (as presented by the sponsor). Tumour response after treatment with Sandostatin or Sandostatin LAR in patients with GEP-NETs.**

| Author/ year | N | Product | Dose | Evidence of tumor response (% of patients) PR | SD | Duration | Diagnosis Inclusion Criteria | Primary endpoint(s) | Comments |
|---|---|---|---|---|---|---|---|---|---|
| (Vinik and Moattari 1989) | 11 | SMS | 100 µg b.i.d to 250 µg q.i.d | 18 | 45 | 6-24 mo | Metastatic carcinoid or pNET | Symptom control, biochemical control, tumor growth | PR was defined as any tumor regression |
| (Anthony et al. 1993) | 13 | SMS | 500-2000 µg t.i.d | 31 | 15 | Until tumor progression | Metastatic fore-, mid-, or hindgut NET | Symptom control, tumor growth | PR defined as 50% reduction in tumor diameter, evaluated by CT. One patient (PR) received concomitant 5-FU |

Of note: In study by Vinik and Moatari (1989) the correct number of study participants should be 14; 10 patients had follow up CT scans. The evaluator cannot comment on the numbers (%) presented in the table representing tumour response.

### *Study by Anthony et al 1993*

Title: "Somatostatin Analogue Phase I Trials in Neuroendocrine Neoplasms." *Acta Oncol* 32:217-223.

[14] Adrenocorticotropic Hormone

The paper describes 2 trials conducted in Nashville Veterans Affairs Medical Center, USA, investigating the antineoplastic efficacy of somatostatin analogues; Sandostatin (n = 14) and Lanreotide (n = 13).

All patients had pathologically confirmed carcinoid tumours of the foregut, midgut, or hindgut origin. A total of 14 patients underwent octreotide dose escalation; 11 patients treated with octreotide had midgut carcinoid. The majority of patients had liver metastases. All patients had been previously treated with octreotide for a period of 1.5 months to 3.5 years.

*Intervention*

Sandostatin was escalated in doses ranging from 1500 µg - 6000 µg daily in patients with carcinoid; all patients completed the dose escalation.

To assess tumour response, patients were monitored during 6 weekly admissions with abdominal/chest CT or ultrasound (US).

PR was defined as 50 % reduction in the product of perpendicular tumour diameters without any signs of new metastases; SD as < 50 % reduction, but not > 25 % increase in the product of perpendicular diameters; and PD as > 25 % increase in the product of perpendicular diameters.

*Results (octreotide)*

A total of 13 patients were evaluable for octreotide anti tumour efficacy (1 patient received concomitant 5-FU): PR was observed in 4 (31 %), SD in 2 and PD in 7 patients. Radiographic changes of tumour necrosis occurred in 5 patients and were independent of response (Table 8).

**Table 8. Study by Anthony at al. 1993. Response rate by treatment.**

| Response | Octreotide | | Somatuline | |
|---|---|---|---|---|
| | n | % | n | % |
| PR | 4 | 31 | 4 | 31 |
| SD | 2 | 15 | 1 | 8 |
| PD | 7 | 54 | 8 | 62 |
| Total assessable | 13 | | 13 | |
| Increased necrosis | 5 | 38 | 6 | 46 |

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease

A total of 11 patients continued to receive octreotide 6000 µg/day for 1 - 2 years (one patient with PR continued to receive additional 5-FU). Two patients died of PD 15 and 16 months respectively, after octreotide dose escalation.

*Comments*

Dose escalation of SSAs is well tolerated and may be associated with antitumour activity in some neuroendocrine neoplasms.

### *Study by Saltz et al 1993*

Title: "Octreotide as an antineoplastic agent in the treatment of functional and non functional neuroendocrine tumours." *Cancer* 72(1):244–248.

Phase II, single center, prospective, non blinded study performed at USA Tertiary Comprehensive Cancer Centre evaluating the antineoplastic activity of patients (n = 34) with advanced, progressive NETs with metastases to various organs.

Patients were classified as having functional (n = 21), or non functional (n = 13) tumours, and further clustered as carcinoid (n = 20), or islet cell tumours (n = 13), one patient had a non functional NEC of unknown primary.

The population included 59 % patients (n = 20) with carcinoid, 6 of which were non functional tumours. *The origin of the carcinoid tumour is not stated.*

All patients had advanced incurable NETs with confirmed pathologic status. Strict objective tumour growth was the basis of study entry; most patients had measurable disease in the liver. All patients with bi dimensionally measurable tumour masses were imaged at the beginning of octreotide therapy and again after 6 to 8 weeks of treatment. Further measurements were obtained at approximately 8 to 10 weeks intervals thereafter.

Progression of the disease was defined as > 25 % tumour growth on serial CT scans over 2 to 4 month interval, or unequivocal development of new lesion.

*Intervention*

Octreotide administered at a median dose of 250 µg SC TDS for a median duration of 29 months (range: 1 - 47), commenced only after clear, objective progression of the disease.

*Results*

No patients had a complete or partial tumour response. Overall, 50 % (95 % CI: 33 - 67 %) of patients (17/34) experienced a CT documented SD maintainable for a minimum of 2 months (median 5 months; range: 0 - 27); "one of these patients exhibited some minimal regression on tumour size."

SD was achieved in 47 % (10/21) of patients with functional tumours and 54 % (7/13) of patients with non functional tumours.

Of the 3 patients who had octreotide dose increased after treatment failure, none demonstrated benefit to the increased dose.

Of the total 34 patients entered, 12 have died. The median survival for this patient population has not been reached, with a median follow up of 29 months (range: 1 - 47 months). This preliminary data compared favourably with historical controls.

Additionally, 19/20 patients with documented PD, who received octreotide as initial anti-neoplastic therapy, survived for ≥ 1 year from the start of therapy. Median survival was 23 months for patients with islet cell tumours, while median survival for patients with carcinoid tumours had not been reached after a median follow up of 29 months (Figures 3 and 4).

**Figure 3. From paper by Saltz *et al* 1993.**

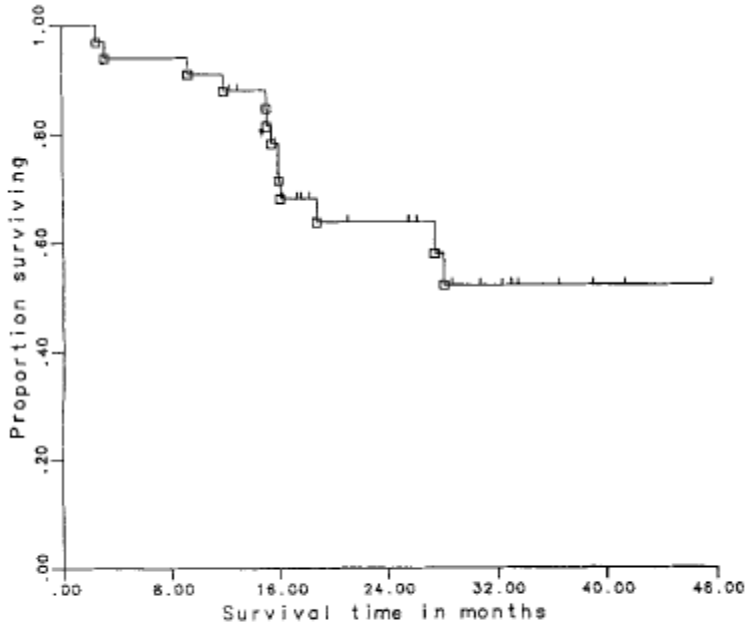



Figure 1. Survival from start of octreotide in patients receiving octreotide as antineoplastic therapy for neuroendocrine tumors. Tick mark indicates last follow-up.

**Figure 4. From paper by Saltz et al 1993.**

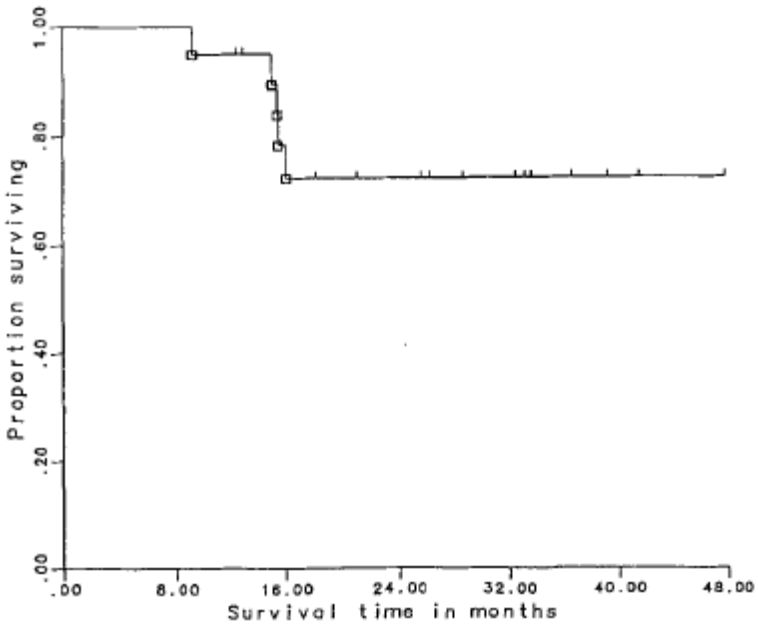



Figure 3. Survival from start of octreotide in patients receiving octreotide as initial antineoplastic therapy. Tick mark indicates last follow-up.

*Authors' conclusion*

Octreotide may influence the natural history of NETs. Survival in patients treated with octreotide, as measured from the time of progression of the disease, compared favourably with historical controls. Proof of a survival advantage would require a multi centre, randomised trial.

### *Study by Arnold et al 1996*

Title: "Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroentropancreatic tumours." *Gut* 38:430-438.

German, Phase II, prospective, multicentre, non blinded, trial investigating the effects of octreotide administered for 1 year on tumour growth and endocrine abnormalities in patients (n = 103) with advanced, incurable GEP-NETs.

There were 64 functional tumours (48 carcinoids) and 39 non functional tumours of which most originated from the pancreas and the small intestine. In total there were 43 tumours originating from the small intestine; 34 functional and 9 non functional; small intestine was the site of the primary tumour in 34/48 patients with carcinoid (Table 9).

**Table 9. From paper by Arnold *et al* 1996. Distribution of functional and non functional tumours within the three subgroups of patients.**

| | *Tumour growth before octreotide* | | | |
|---|---|---|---|---|
| | *Progression* | *Stable disease* | *Unknown* | *Total* |
| Functional tumours | | | | |
| Insulinoma | | 1 | | 1 |
| Glucagonoma | 3 | | 1 | 4 |
| Gastrinoma | 8 | | 3 | 11 |
| Carcinoid syndrome originating from: | | | | |
| Small intestine | 14 | 3 | 17 | 34 |
| Pancreas | 1 | 1 | 1 | 3 |
| Stomach | 1 | | | 1 |
| Colon | 1 | | | 1 |
| Lung | 1 | | | 1 |
| Unknown | 2 | 1 | 5 | 8 |
| Total | 31 | 6 | 27 | 64 |
| Non-functional tumours originating from: | | | | |
| Small intestine | 3 | 3 | 3 | 9 |
| Pancreas | 8 | 3 | 4 | 15 |
| Stomach | 2 | 1 | 2 | 5 |
| Colon/rectum | 2 | | 1 | 3 |
| Lung | 1 | | 1 | 2 |
| Unknown | 5 | | | 5 |
| Total | 21 | 7 | 11 | 39 |

All patients had histologically confirmed GEP-NETs. Patients with confirmed tumour progression within the preceding 6 months and those with endocrine symptoms requiring octreotide therapy and showing a measurable indicator of response to treatment (indicated by CT) were regarded as eligible for participation; 89 patients had CT confirmed measurable disease in liver.

According to protocol, responders were evaluated at 12 months. Follow up investigations were performed every 3 months for a year, and then 6 monthly in responders. Patients with CT confirmed PD (n = 52), SD (n = 13), and no information on pre entry tumour growth (n = 38) were analysed separately.

Tumour growth was assessed by CT of pertinent indicator lesion in a blind fashion without knowledge of the clinical data.

*Intervention*

Octreotide SC titrated to a dose of 200 µg administered TDS for at least 6 months; continued in responders until tumour progression. The dose of octreotide was increased to 500 µg TDS in 28 of patients with PD. During octreotide treatment patients did not receive other antiproliferative therapy.

Only 55.7 % (59/103) patients could be followed over the entire study period of 12 months; the total number of deaths within 12 months was 31 (30.1 %). The mortality

within the study was high, which may reflect the Karnofsky performance status (KPS) of ≤ 80 in 47/103 patients at study entry.

*Results*

No objective tumour regression could be seen in patients with PD before treatment, or any other group.

Stabilisation of the disease occurring in 19/52 patients (36.5 %) with confirmed tumour progression before octreotide treatment was the most favourable therapeutic effect. Median duration of SD was 18 months (Table 10).

**Table 10. From paper by Arnold *et al* 1996. Effect of octreotide on tumour growth in 52 patients with confirmed progression before treatment.**

| | | | Month 6–12 | | | |
|---|---|---|---|---|---|---|
| | | *No* | *Death* | *Progression* | *Stable disease* | *Tumour regression* |
| Month 3 | Death | 8 | 8 | | | |
| | Progression | 30 | 11† | 14 | 5* | 0 |
| | Stable disease | 14* | 3 | 4 | 7 | 0 |
| | Tumour regression | 0 | 0 | 0 | 0 | 0 |
| | Total | 52 | 22 | 18 | 12 | 0 |

*Response to octreotide occurred in 19 patients according to the study protocol, †one death from heart infarction.

At Month 12, SD continued in 12 patients, declined after 24 months in 9 patients, and after 36 months in 5 patients.

In the subgroup with SD before octreotide, SD continued in 53.8 % of patients over 12 months (Tables 11 (SD at baseline) and 12 (no information on tumour growth before treatment).

**Table 11. From paper by Arnold et al 1996.**

TABLE VII *Effect of octreotide on tumour growth in 13 patients with confirmed stable disease before treatment*

| | | | Month 6–12 | | | |
|---|---|---|---|---|---|---|
| | | *No* | *Progression* | *Stable disease* | *Tumour regression* | *No evaluation possible* |
| Month 3 | No evaluation possible* | 1 | | | | 1 |
| | Progression | 2 | 2 | | 0 | 1 |
| | Stable disease | 10 | 2 | 7 | 0 | 1 |
| | Tumour regression | 0 | 0 | 0 | 0 | 0 |
| | Total | 13 | 4 | 7 | 0 | 2 |

*Because of discontinuation of treatment during the first month.

**Table 12. From paper by Arnold *et al* 1996.**

TABLE VIII *Effect of octreotide on tumour growth in 38 patients with no information on spontaneous tumour growth before treatment*

| | | | Month 6–12 | | | | |
|---|---|---|---|---|---|---|---|
| | | *No* | *Death* | *Progression* | *Stable disease* | *Tumour regression* | *No evaluation possible* |
| Month 3 | No evaluation possible* | 1 | | | | | 1 |
| | Death | 2 | 2 | | | | |
| | Progression | 15 | 6 | 8 | 0 | 0 | 1 |
| | Stable disease | 20 | 2 | 5 | 13 | 0 | |
| | Tumour regression | 0 | 0 | 0 | 0 | 0 | |
| | Total | 38 | 10 | 13 | 13 | 0 | 2 |

*Because of discontinuation of treatment during the first month.

Increasing the dose to 500 µg SC TDS had no further effect with the exception of one patient (tumour progression changed to SD). No association of tumour size and patient's

characteristics could be detected. Endocrine response and tumour size have not been found to be related. Patients with better KPS responded significantly better to octreotide.

Although the numbers were small, there was a tendency of tumours originating from the small intestine and of patients with carcinoid syndrome to respond better to octreotide compared with pancreatic tumours and non functional tumours (Table 13).

**Table 13. From paper by Arnold *et al* 1996.**

TABLE VI *Inhibition of tumour growth according to patients' characteristics (n=52)*

| *Characteristics* | *No of patients* | *No with objective growth inhibition (%)* | *p Value* |
|---|---|---|---|
| Sex | | | |
| Male | 34 | 14 (41·2) | 0·514 |
| Female | 18 | 5 (27·8) | |
| Age (y) | | | |
| <60 | 37 | 12 (32·4) | 0·517 |
| ≥60 | 15 | 7 (46·7) | |
| Karnofsky Index | | | |
| <80 | 25 | 5 (20·0) | 0·039 |
| ≥80 | 25 | 13 (52·0) | |
| Tumour type | | | |
| Gastrinoma | 8 | 3 (37·5) | |
| Carcinoid syndrome | 20 | 11 (55·0) | 0·122 |
| Non-functional tumour | 21 | 5 (23·8) | |
| Glucagonoma | 3 | 0 | |
| Origin of primary | | | |
| Small intestine | 19 | 10 (52·6) | 0·229 |
| Pancreas | 18 | 5 (27·8) | |
| Somatostatin receptors | | | |
| Present | 13 | 8 (61·5) | |
| Absent | 0 | 0 | |
| Previous chemotherapy | | | |
| Yes | 20 | 5 (25·0) | 0·285 |
| No | 32 | 14 (43·8) | |
| Improvement of flushing* | | | |
| Yes | 12 | 9 (75·0) | 0·547 |
| No | 4 | 2 (50·0) | |
| Improvement of diarrhoea* | | | |
| Yes | 7 | 4 (57·1) | 1·0 |
| No | 5 | 3 (60·0) | |
| Hormone suppression* | | | |
| Yes | 2 | 1 (50·0) | 1·0 |
| No | 14 | 9 (64·3) | |

*Carcinoid syndrome only.

The authors commented that their data do not permit any conclusions with respect to a survival advantage but the beneficial effect of octreotide were at least in some patients long lasting.

"This trial does not exclude the possibility that patients with stable disease before octreotide may profit from the drug by extending the interval of stable disease", as well as "the results of this prospective Phase II trial are strong enough to generate the hypothesis that octreotide inhibits the tumour growth in patients with metastatic endocrine GEP tumours."

"The presented results do not exclude the possibility that at least short lasting stabilization of tumour growth during octreotide treatment after preceding tumour progression mirrors phases of spontaneous tumour growth behaviour and could also occur without treatment."

*Authors' conclusion*

Currently, octreotide can only be recommended as an antiproliferative drug if patients with clearly progressive disease show stabilization after treatment for 3 to 6 months.

### *Study by Di Bartolomeo et al 1996*

Title: "Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumours." *Cancer* 77:402-408.

An Italian, Phase II, multicentre, prospective, open label study aimed to "determine the safety and efficacy of octreotide in controlling carcinoids and other neuroendocrine tumours" and investigating the possible role of octreotide as a cytoreductive agent.

The study enrolled patients (n = 58) with metastatic NETs and disease progression. All patients were required to have a histological confirmation of diagnosis (carcinoid or other NET), DP and at least one clearly measurable lesion visible on CT or US.

The eligibility criteria are not entirely clear, as in another part of the paper the authors also stated: "Patients with disease progression and also those with symptomatic carcinoids without tumour progression were included."

The predominant histotype was carcinoid (n = 31); 15 had carcinoid syndrome. The carcinoid group included: foregut carcinoids (11), midgut carcinoids (2), hindgut carcinoids (2), and 9 with unknown primary. Other tumours included: islet cell carcinoma (12), Merkel cell carcinoma (3), and medullary thyroid cancer (12).

The liver was the most frequent site of metastatic disease (38/58), 35 patients had multiple lesions and 23 had single lesions. All were outpatients, and most were capable of full or part time work.

*Intervention*

Two sequel doses of SC octreotide was used; octreotide 500 µg TDS (first 23 patients) and octreotide 1000 µg TDS (remaining 35 patients), until tumour progression. Median treatment duration was 5 months (range: 2 - 31).

Octreotide was administered as first line treatment in 46 patients. Patients with PD were eligible to receive concomitant chemotherapy (n = 25).

The study assessed tumour growth control, symptomatic and biochemical response. The main tumour response efficacy variable was the proportion of patients with PR and CR. Follow up CT/radiography was performed every 2 months; tumour growth control was defined according to the International Union against Cancer.

*Statistical analysis*

All of the enrolled patients were considered evaluable. Patients with carcinoids and with other histopathological subgroups were considered separately in the analyses. The survival function for TTF and time to death was estimated using the Kaplan-Meier method. Response duration was calculated from the time the tumour became evident to the time of progression.

According to the 2 stage design, the study was planned to compare a response probability of 10 % under the null hypothesis with a response probability of 25 % under the alternative hypothesis, with a 0.05 α level and a power of 80 %. The treatment had to be rejected if no more than 2 and 7 responses were observed at the end of first (18 patients) and second stages (43 patients) of the trial, respectively.

*Results:*

In terms of tumour regression, octreotide was disappointing (PR 3 %).

After a median treatment duration of 5 months (range: 2 - 32+), 2 carcinoid patients showed an objective response. These individuals had liver metastases with an unknown primary and partial regressions were documented by ultrasound after 4 months of treatment. The duration of response was 14 and 10 months, respectively. One of these patients was in the first group treated with 500 µg, the other in the second group.

SD of at least 6 months duration was observed in 27 cases (47 %) and the disease was stable for > 1 year in 13 patients (22 %) (Table 14).

**Table 14. From paper by Di Bartolomeo *et al* 1996.**

**Characteristics of 13 Patients with Stable Disease Lasting Longer Than 1 Year**

| | No. of patients | |
|---|---|---|
| Characteristic | Observed | Stabilized (%) |
| Median age | 55 | 49 |
| Histology | | |
| Carcinoid | 31 | 9 (29) |
| MTC | 12 | 4 (33) |
| Octreotide dose | | |
| 500 μg | 11 | 6 (54) |
| 1000 μg | 20 | 7 (35) |
| Disease sites | | |
| Liver | 38 | 7 (18) |
| Lung | 11 | 3 (27) |
| Nodes | 30 | 3 (10) |

MTC: medullary thyroid carcinoma.

PD was observed in 29 patients after a median time of 6 months (Figure 5).

**Figure 5. From paper by Di Bartolomeo *et al* 1996.**

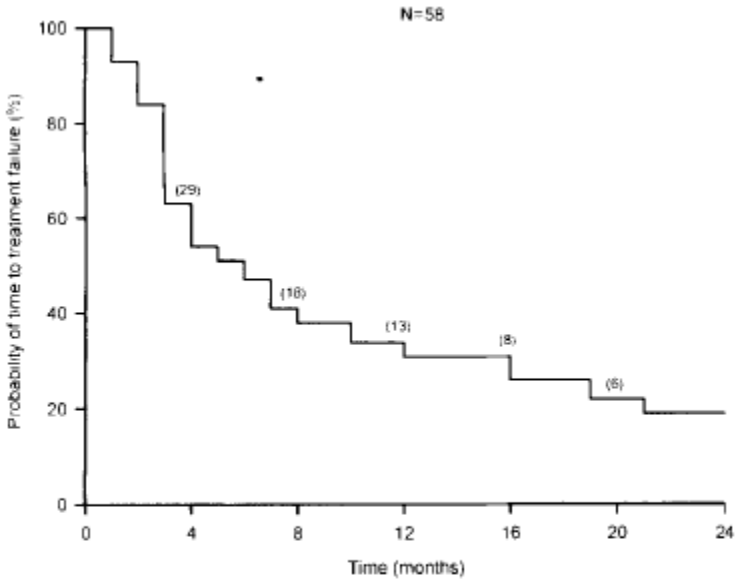



**FIGURE 1.** Treatment failure free survival. Patients who remain at risk of treatment are shown in parenthesis.

There were no complete tumour responses and 13 patients had SD for at least a year (carcinoids and medullary thyroid carcinomas).

The median survival of the patients as a whole group was 22 months (range: 1- 32) but only 12 months if patients with carcinoid tumours were excluded (the median survival for carcinoids has not been reached after a median follow up of 12 months) (Figures 6 and 7).

**Figure 6. From paper by Di Bartolomeo *et al* 1996**

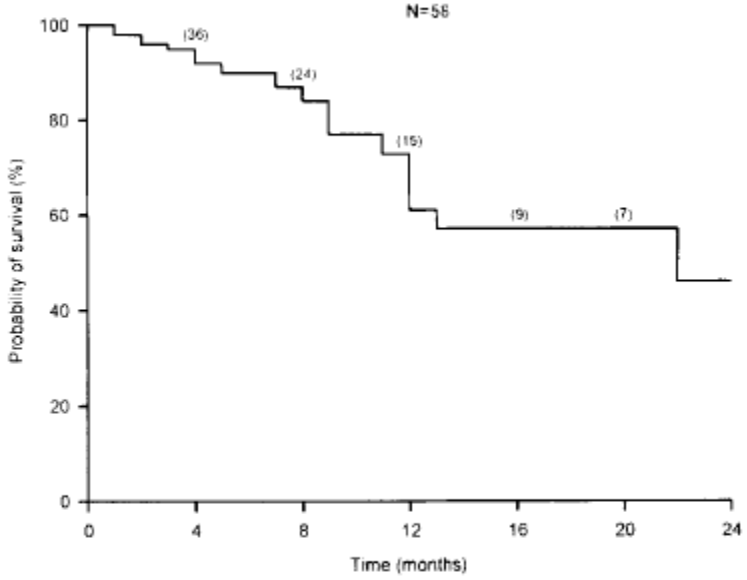



**FIGURE 2.** Overall survival from start of octreotide treatment in 58 patients. Patients who remain at risk of survival are shown in parenthesis.

**Figure 7. From paper by Di Bartolomeo *et al* 1996**

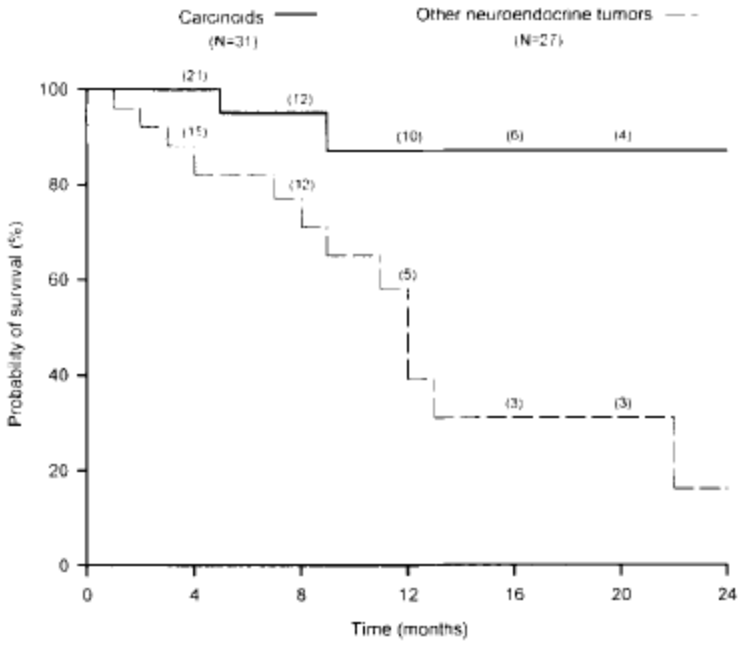



**FIGURE 3.** Survival according to histological subtypes. Patients who remain at risk of survival are shown in parenthesis. solid line: carcinoids; dotted line: other neuroendocrine tumors.

No correlation between disease status and survival could be made because of the heterogeneity of the studied population.

*Authors' conclusion*

Octreotide was disappointing in terms of tumour regression tested in a heterogeneous patient population but symptomatic and biochemical responses in carcinoid patients were satisfactory. Only two carcinoid patients obtained partial response of their hepatic metastases and no responders were observed in other histologic groups.

### *Study by Ricci et al 2000*

Title: "Octreotide acetate long-acting release in patients with metastatic neuroendocrine tumours pretreated with lanreotide." *Ann Oncol* 11(9):1127- 30.

An Italian, Phase II, single center, non blinded, prospective study investigating the efficacy and tolerability of octreotide LAR in patients (n = 15) with histologically confirmed metastatic GEP-NETs and disease progression after failure on lanreotide.

The enrolled subjects (8 females, 7 males) with a median age of 67 years (range: 28 - 81), included 7 patients with midgut carcinoid, and 8 endocrine pancreatic tumours.

All 15 patients had previous surgery and 7 patients had previously had other treatments, including 3 patients having SC octreotide, and SR lanreotide administered for a median of 8 months (range: 3 - 19). All patients were in progressive disease: objective (11), symptomatic (10) or biochemical (11), all 15 patients had liver metastases. Octreotide scintigraphy was positive in 13/15 patients.

At the study entry patients were required to have bi dimensionally measurable disease; CT of the evaluable lesion was done at study entry and imaging studies were repeated every 3 months. The duration of responses were calculated from the first documentation of response until disease progression. TTP was calculated from the first dose of octreotide LAR to the first evidence of disease progression (symptomatic, biochemical or objective).

*Intervention*

Octreotide LAR 20 mg IM every 4 weeks until PD. Median duration of octreotide LAR treatment was 7 months (range: 3 - 12).

*Results:*

There were no complete tumour responses. An objective PR was documented in one patient (7 %), no change was noted in 6 patients (40 %) and PD was reported in 8 patients (53 %).

The observed PR occurred in patient with non functional pancreatic tumour and progressive liver and lymph node metastasis, who had been pre treated with SC octreotide and IM lanreotide for a period of 5 and 16 months, respectively. The reduction in tumour size was documented at both metastatic sites after 6 months of octreotide LAR and was still lasting after 10 months of treatment.

The median duration of disease stabilisation was 7.5 months (range: 6 - 12+ months).

*Authors' conclusion*

Octreotide LAR is active in patients with progressive, metastatic GEP-NETs who had failed treatment with lanreotide. The activity of octreotide LAR was documented in terms of objective responses, biochemical and symptomatic control. There was no cross resistance between the two drugs.

### *Study by Tomassetti et al 2000*

Title: "Treatment of gastroentropancreatic neuroendocrine tumours with octreotide LAR."

*Aliment Pharmacol Ther 14:557-560*

An Italian, single center, prospective, non blinded study assessing efficacy, tolerability and safety of octreotide LAR in patients (n = 16) with GEP-NETs and liver metastases (n = 14).

The study included 10 carcinoid patients; 9 in ileum, 1 pancreas, 3 with non functioning pancreatic tumours, 2 patients with Zollinger-Ellison syndrome (ZES) and one patient with glucagonoma.

In all cases the diagnosis of GEP-NET was histologically confirmed. All were positive for somatostatin receptors (sstr) at Octreoscan scintigraphy. All except the two patients with ZES had multiple liver metastases.

The participants (8 males, 8 females) had mean age of 57 years (range: 39 - 82 years); 11 patients had prior surgery on the primary tumour and 11 patients had received prior treatment with octreotide SC or lanreotide IM for a mean of 2.8 years.

*Intervention*

Octreotide LAR 20 mg IM every 28 days (30 mg in 1 patient) for a mean of 10.7 months (range: 6 - 15).

All patients had CT scans before the start of treatment and every 6 months thereafter. Changes in the tumour size were assessed according to the WHO criteria by measuring the sum of the products of 2 greatest perpendicular diameters of the 2 - 3 main measurable lesions.

A major response was defined as ≥ 50 % decrease, a minor response as 25 - 50 % decrease, no response as any variation ≤ 25 % and progression as ≥ 25 % increase.

The Wilcoxon matched-pairs signed rank test was used for statistical analysis.

*Results*

Tumour size remained stable in 14/16 patients and increased in the remaining 2 patients (carcinoid and non functional tumour).

*Authors' conclusion*

Although it is difficult to determine whether the stability of the tumour size in the majority of patients could have been related to octreotide LAR administration, this cannot be totally excluded.

***Study by Aparicio et al 2001***

Title: "Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours." *Eur J Cancer* 37:1014-1019.

Single center, prospective study from the Cancer Institute in Villejuif, Paris, evaluating the antitumour efficacy of somatostatin analogues in patients (n = 35) with documented progressive NETs according to the WHO criteria, "who were sub classified according to their slope of tumour growth."

The primary tumour sites were the small intestine (n = 12), pancreas (n = 13), lungs (n=5), and other sites (n = 5); 18 patients (51 %) had the carcinoid syndrome.

Among these 35 patients, 29 had documented progression of the tumour surface area of >25 % over 6 months preceding their inclusion and in 6 other patients new metastases had emerged during that period. The slope of the tumour growth rate was determined in these 29 patients during the 3 months preceding treatment.

Patients were classified into 2 groups:

*Group 1.* Rapidly progressing tumours (an increase of ≥ 50 % in the lesion surface area in 3 months), and

*Group 2.* Tumours progressing more slowly (an increase of < 50 % but > 25 % in 6 months).

Tumour responses were evaluated every 3 months by CT and ultrasound according to the WHO criteria. The duration of response, or stabilisation and OS was calculated from the first day of treatment with somatostatin analogues (SSAs). The duration of PFS was

calculated from the first day of documented stabilisation or response until the day of documented progression.

*Intervention*

Consecutive patients were given SC octreotide 100 µg TDS in 17 patients (49 %), IM lanreotide 11 patients (31 %), and 7 patients (20 %) in whom "both somatostatin analogues were used successively during the follow up." Doses were increased in 4 patients to control carcinoid symptoms. The median duration of treatment was 7 months.

*Statistical analysis*

The Chi square test was used to compare qualitative variables. The Student's t test was used to compare quantitative variables. Survival analyses were performed using the Kaplan-Meier method. A p value of 0.05 was considered statistically significant.

*Results*

SSA treatment resulted in one partial response (3 %) and 20 cases of stabilisation (57 %) for a median duration of 11 months (6 - 48 months).

Stabilisation of patients in Group 1 (rapidly progressive tumour) was significantly less frequent at 6 months than that of patients in Group 2; 33 % (4/12) and 76 % (13/17), respectively; $p < 0.02$.

PFS for all 35 patients was 26 % at 1 Year and 11 % at 2 Years (Figure 8).

**Figure 8. From paper by Aparicio *et al* 2001.**

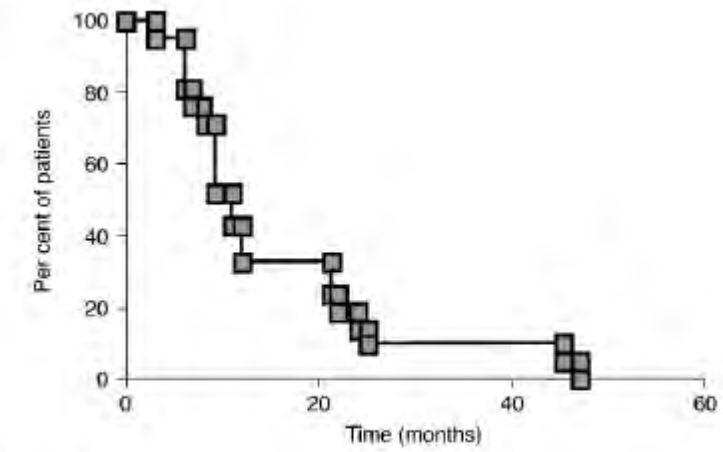



Fig. 1. Progression-free survival (PFS) of the 21 patients stabilised with somatostatin analogue.

A similar percentage of tumour stabilisation was observed in patients treated with octreotide (58.8 %) or lanreotide (54.5 %); 10/17 for a median duration of 9 months and 6/11 for a median duration of 10.5 months, respectively. Among the 7 other patients treated successively with both SSAs, 5/7 stabilizations were observed for a median duration of 22 months.

*Conclusions*

SSAs arrested the growth of progressive NETs in 60 % (21/35) of cases for a median duration of 11 months. However, only one objective response was observed, which is consistent with the weak anti tumour effect of SSAs.

A slow tumour growth rate before treatment is predictive of a good response to SSAs, which could be considered an option for first line treatment.

### *Study by Shojamanesh et al 2002*

Title: "Prospective study of the antitumor efficacy of long term octreotide treatment in patients with progressive metastatic gastrinoma." *Cancer* 94:331-343.

Single centre, prospective, non blinded USA study reporting the outcome of octreotide treatment in patients (n = 15) with Zollinger-Ellison syndrome with liver metastasis and evidence of disease progression.

The study population clearly represented foregut tumours involving pancreas and duodenum, and it is not relevant to the proposed indications. The evaluator included the main outcome of the study in the report for completeness as it is presented as supportive evidence and included in the table of supportive studies presented by the sponsor (Table 7).

In 14 patients (93 %) a pancreatic gastrinoma was present. Two patients also had duodenal gastrinoma; tumour site was unknown in one case. Patients were categorised as having either rapid, or slow tumour growth prior to treatment.

*Intervention*

All patients were treated initially with octreotide, 200 µg 12 hourly SC, and at last follow up were being maintained on octreotide LAR, 30 mg every month until uncontrollable side effects occurred or there was a significant disease progression.

*Results*

Fifty-three % of patients demonstrated tumour response with octreotide at 3 months; the predominant anti tumour effect was SD in 47 % of patients and one patient (6 %) had a decrease in tumour size. The mean duration of response was 25 ± 6.1 months (range: 5.5 - 54.1). There were no reported cases of complete disease remission with complete disappearance of the metastases.

Slow growing tumours prior to treatment were more likely to respond; 0 of responders and 86 % of non responders had rapid tumour growth prior to treatment; $p < 00014$. Although there was a trend ($p = 0.10$) toward longer survival in responders, this trend did not reach statistical significance.

*Authors' conclusion*

Octreotide was an effective treatment for patients with malignant gastrinoma and hepatic metastases; it was able to stabilise tumour growth, especially in patients with slow growing tumours. The number of patients in the current study was not sufficient to demonstrate that a response to octreotide is associated with increased survival.

### *Study by Arnold et al 2005*

Title: "Octreotide versus octreotide plus interferon-alpha in endocrine gastroentropancreatic tumours: a randomised trial." *Clin Gastroenterol Hepatol* 3:761-771.

A German, multicentre, randomised, non blinded comparative trial assessing the effect of octreotide + interferon-α (INF-α) versus octreotide monotherapy on the primary study endpoints of TTF and on long-term survival in patients (n = 109) with well differentiated, progressive, metastatic NETs.

The study enrolled adult patients with functional and non functional GEP-NETs with metastatic or locally advanced disease without curative therapeutic option. The study sample consisted primary of foregut (mainly pancreatic) and midgut tumours.

Overall, the majority of patients had either non functional or carcinoid tumours (n = 28 and 20 in the octreotide arm). In the octreotide arm, there were 25 midgut tumours (9 non functioning, 16 with carcinoid syndrome) and 9 tumours of unknown origin (6 and 3, respectively).

Localisation of the primary tumour in the midgut occurred more often in the monotherapy group (non significant). Tumours of unknown origin were believed to belong to the midgut as a result of the presence of carcinoid syndrome, or in 'non functioning tumours' as a result of histological criteria.

*Intervention*

Octreotide 200 µg SC TDS, either alone (n = 54), or in combination with $4.5x10^6$ IU of IFN-α x3/week (n = 55). Treatment continued until CT or MRI documented tumour progression. Additional antiproliferative therapy was not allowed.

The primary endpoint was TTF (tumour progression, tumour related death or discontinuation due to AEs), hierarchically followed by survival time.

Only patients with CT/MRI documented tumour progression according to WHO criteria were randomised; CT/MRI scans were evaluated in blinded manner but the rest of the study was not blinded. Randomisation was stratified: carcinoid versus other tumours, age (≤ 65 versus > 65 years), and luminal tumours (midgut + duodenal) versus non luminal (pancreatic), prior chemotherapy, prior octreotide.

A total of 9 patients were not randomised due to SD but were included in follow up and some of the analyses; 7 of those patients had metastatic midgut tumours and 2 had metastatic pancreatic gastrinomas. Final analysis was based on 105 patients: 51 on monotherapy and 54 on combination treatment. Analysis of TTF was performed in March 2000 and of long term survival in April 2004 (all analysed patients + 9 non randomised).

Tumour growth was assessed at 3 monthly intervals by CT or MRI.

*Statistical analysis*

A group sequential design of study was later implemented with two sided testing, two planned IAs; at 66 and 132 treatment failures, and an adjusted number of 198 treatment failures to be observed at the final analysis. To evaluate the influence of treatment response on survival, patients in both treatment arms were combined for exploratory survival analysis.

Treatment groups were compared descriptively with the Student test. Analysis of TTF and confirmatory as well as exploratory survival analyses were performed using the Kaplan-Meier method and the log-rank test. For the confirmatory analysis, the Type I error level was at α = 5 %.

Because of low recruitment frequency, after the first planned IA based on 66 treatment failures (49 progressions, 7 deaths and 10 discontinuations due to AEs), the recruitment for the study was stopped. The HR was 1.18, 95 % CI: 0.73 - 1.92; p = 0.498.

*Results*

The combination of octreotide + IFN-α was not superior to monotherapy with octreotide with respect to progression free and long term survival.

Primary endpoint of TTF: Overall tumour progression was the most frequent reason for treatment failure (82.4 % in octreotide arm), tumour related death occurred in 6 patients total (2 patients; 3.9 % in octreotide arm).

Overall partial tumour regression was reported in 2.9 %, 1.9 %, and 5.7 % and stabilisation of tumour growth in 44.8 %, 27.6 %, and 15.2 % at 3, 6, and 12 months, respectively, with no significant differences between the treatment arms (Table 15).

**Table 15. From paper by Arnold *et al* 2005.**

**Table 5.** Response to Treatment at 3, 6, and 12 Months After Randomization; Number (Percentage) of Patients

| | 3 Months | | | 6 Months | | | 12 Months | | |
|---|---|---|---|---|---|---|---|---|---|
| | Octreotide | Octreotide plus Interferon-alpha | Total | Octreotide | Octreotide plus Interferon-alpha | Total | Octreotide | Octreotide plus Interferon-alpha | Total |
| Death | 2 (3.9) | 3 (5.5) | 5 (4.8) | 6 (11.8) | 9 (16.7) | 15 (14.3) | 12 (23.5) | 16 (29.6) | 28 (26.7) |
| Treatment stopped | 3 (5.9) | 6 (11.1) | 9 (8.6) | 3 (5.9) | 8 (14.8) | 11 (10.5) | 2 (3.9) | 9 (16.7) | 11 (10.5) |
| Progressive disease | 20 (39.2) | 17 (31.5) | 37 (35.2) | 26 (51.0) | 18 (33.3) | 44 (41.9) | 25 (49.0) | 14 (25.9) | 39 (37.1) |
| Stable disease | 22 (43.1) | 25 (46.3) | 47 (44.8) | 13 (25.5) | 16 (29.6) | 29 (27.6) | 8 (15.7) | 8 (14.8) | 16 (15.2) |
| Partial regression | 1 (2.0) | 2 (3.7) | 3 (2.9) | 1 (2.0) | 1 (1.9) | 2 (1.9) | 1 (2.0) | 5 (9.3) | 6 (5.7) |
| Assessment not possible | 3 (5.9) | 1 (1.8) | 4 (3.8) | 2 (3.9) | 2 (3.7) | 4 (3.8) | 3 (5.9) | 2 (3.7) | 5 (4.8) |
| Total | 51 (100) | 54 (100) | 105 (100) | 51 (100) | 54 (100) | 105 (100) | 51 (100) | 54 (100) | 105 (100) |

The respective figures for partial tumour regression and SD for the octreotide arm at 3, 6 and 12 months were somewhat lower: 2.0 %, 2.0 %, 2.0 % and 43.1 %, 25.5 %, 15.7 %, respectively.

SD and partial tumour regression were observed at 3, 6 and 12 months, with a decreasing frequency and a tendency for more partial regressions in the combination arm at 12 months. The data indicated that tumour related death and tumour progression were the most frequent events at 12 months (26.7 % and 37.1 %, respectively).

Only 20 patients (9.5 %) were on study at final analysis (March 2000); 12 in the octreotide arm and 18 in the combination arm.

Thus, TTF and long-term survival did not differ significantly between the 2 groups; with a median survival of 32 and 54 months for the octreotide and the combination arms, respectively. *(These figures reported by the sponsor reflect in fact the data from the follow up analysis conducted in April 2004, not the final analysis in March 2000; see below).*

Median survival from randomisation until final study evaluation (March 2000) was 35 months for patients receiving monotherapy and 51 months for those receiving combination therapy; HR 1.19; 95 % CI: 0.67 - 2.13; p = 0.55.

Treatment failures occurred in 50 % of patients within 6 months in each treatment arm; tumour progression was the most frequent reason for treatment failure (69.5 %). Only 10 patients (9.5 %) were on study at final analysis (March 2000); median survival at that time was 35 and 51 months, respectively. *The study was not powered adequately to demonstrate long term survival benefit.*

The small advantage after 6 months and beyond for patients receiving combination therapy was not significant; (p = 0.59), HR 1.12; 95 % CI: 0.74 - 1.69.

Survival curves were crossing with a small negative trend during the first 2 years for patients receiving combination treatment, which was followed by a longer lasting positive trend during the subsequent 5 years. Survival was longest in patients not randomised, because of SD (median 68 months), and in those with low nuclear Ki-67.

The authors noted that a favourable response to treatment did not necessarily indicate longer survival. All patients responding to treatment with partial tumour regression and growth stabilisation failed to respond later on. Nevertheless, patient outcome was more favourable in spontaneously slowly growing tumours and in those responding to treatment.

Of note, 5/9 patients not randomised to either group due to SD at the end of randomisation (August 1998) were still alive at the end of follow up period (April 2004), despite PD in all, later on. Until April 2004, median survival of these patients was 68 months since the closure of randomisation. An exploratory analysis indicated a longer

survival for this group compared with patients treated according to the study protocol; p = 0.083.

On the basis of these 9 non randomised patients it was hypothesised that a longer period of SD in treatment naive patients could serve as a favourable prognostic marker for survival.

The types of treatment failure differed significantly between the groups (Fisher-Freeman-Halton; p = 0.0387); there were more progressions as reason for treatment failure in the octreotide and more AEs in the combination arm.

PFS was similar in patients with midgut or pancreatic tumours.

There was a gain in QoL score in the octreotide group while the group receiving the combination treatment recorded a reduced score after 3 months of therapy (information available on 45/105 patients at entry and 3 months).

To evaluate the influence of treatment response on survival, patients in both treatment arms were combined for exploratory survival analysis. At 6 months, 44 patients did not respond to treatment (PD) and 31 patients responded; 29 with SD and 2 with partial regression (Figure 9).

**Figure 9. From paper by Arnold *et al* 2005. Kaplan-Meier plots: exploratory survival analysis both treatment arms.**

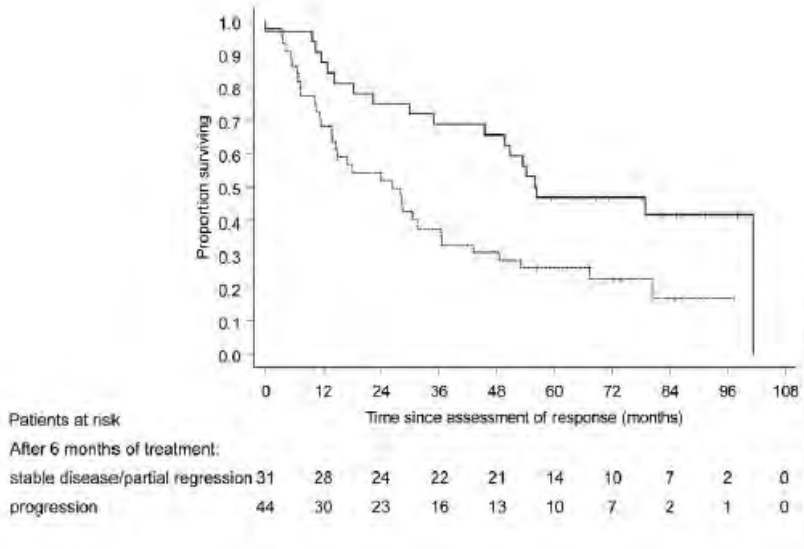



**Figure 5.** Survival of 31 patients with stable disease or partial regression at 6 months of treatment with monotherapy or combination treatment (*solid line*) versus survival in 44 patients with tumor progression (*dotted line*). (*P* = .0057). Vertical lines (|) indicate censoring, which means after a patient's last follow up, no further information on the patient was available.

Patients responding to either treatment at 6 months lived longer compared with those with tumour progression; HR 0.44; 95 % CI: 0.24 - 0.79; p = 0.0057.

Patients with slowly growing, well differentiated tumours before treatment and TTP > 6 months, and those with low pre-treatment values of Ki-67 had a survival advantage compared with patients with a more rapid progression of a well differentiated tumours and higher Ki-67 values.

The authors concluded that, the combination treatment was not superior to monotherapy concerning progression free and long term survival. Patients responding to treatment and those with slow spontaneous tumour growth had a survival advantage. A trend toward longer survival was shown for patients with slow spontaneous tumour growth before randomisation.

"This and all previous trials for endocrine gastroenteropancreatic tumours were not placebo controlled. One could, therefore, argue that the effects of octreotide and of the combination with IFN-α on tumour growth mirror spontaneous tumour growth with phases of partial regression, stable disease, and progression."

Treatment failed in 50 % of patients within 6 months in each treatment arm but a substantial proportion of patients with spontaneous tumour progression before treatment experienced tumour regression and stable disease. The findings of the trial are, however, in favour of the view that both octreotide monotherapy and the combination with IFN-α inhibit tumour growth.

The beneficial effects could occur late, as indicated by the number of partial regressions in the combination arm at 12 months (n = 5). "These figures are too high to suppose only spontaneous fluctuations of growth. To prove or to disapprove an antitumoural potency of biotherapy, a placebo-controlled trial with long-acting octreotide in patients with metastatic midgut tumours was started by the authors." *(Evaluator's comment: see RROMID study).*

Median PFS of 6 months in both treatment arms was rather short compared with other studies. The variation of data on growth stabilization reflects pitfalls in most but not all studies on NETs; tumours of different origin, if included in clinical trials, might differ in their spontaneous tumour growth and in their response to therapy, in a different tumour load, in different metastatic spread and in different histology.

### *Study by Öberg 1996* [15]

Title: "Interferon-α versus Somatostatin or the Combination of Both in Gastro-Enteropatic Tumors."

*Outcome*

"We combined IFN-α and octreotide treatment in 24 patients with malignant carcinoid tumours who did not respond biochemically to high-dose (300 µg/day) octreotide alone. Biochemical response occurred in 77 % but no significant anti tumour effect was noted besides disease stabilisation in 4 cases."

### *Study by Butturini et al 2006*

Title: "Predictive factors of efficacy of the somatostatin analogue octreotide as first line therapy for advanced pancreatic carcinoma." *Endocr Rel Cancer* 13:1213-1221.

An Italian, prospective, single center, Phase IV study restricted to Octreoscan positive patients (n = 21), with well differentiated non functioning pancreatic endocrine carcinomas aimed to access efficacy of octreotide (as first-line therapy) and indentify factors predictive of response to therapy.

*Intervention*

Treatment with SC octreotide (100 µg TDS 2 weeks) followed by 20 mg of octreotide LAR given at diagnosis, until disease progression.

The population studied in this trial (foregut NETs) does not include the group targeted by the proposed indication. The main conclusions are recorded for completeness:

*Results*

A total of 8 patients (38 %) had SD after a median follow up of 49.5 months and the disease progressed in 13 patients (62 %) after a median of 18 months.

The authors concluded that treatment with long acting octreotide was associated with stabilisation of disease and a good quality of life in 38 % of patients.

[15] Öberg K. (1996) lnterferon-α versus Somatostatin or the Combination of Both in Gastro-Enteropancreatic Tumours. *Digestion* 1996;57 (Suppl. 1):81-83

### *Study by Panzuto et al 2006*

Title: "Long-term clinical outcome of somatostatin analogues for treatment of progressive, metastatic, well-differentiated entero-pancreatic endocrine carcinoma." Ann Oncol 17(3):461-6.

An Italian, single center, prospective, non blinded study of patients (n = 31) with well differentiated, progressive, metastatic GEP-NETs treated with octreotide LAR or lanreotide SR aiming to identify predictors for efficacy of SSAs at inhibiting tumour growth and modifying patients' survival during long term follow up.

The set of patients was selected on the basis of the evidence of PD before treatment, histological diagnosis of well differentiated carcinoma according to WHO classification, presence of metastasis and positive somatostatin receptor scintigraphy (SRS).

Tumour response was assessed by helical CT and SRS 3 to 6 months after the beginning of treatment (early follow up) and then every 6 months during the subsequent period (late follow up).

The primary tumour site was pancreas in 58 % cases, small intestine in 35.5 % (n = 11), and unknown in 6.5 % (n = 2). There were 20 non functional tumours (64.5 %).

SSAs were the first line of treatment for all but 4 patients. The rate of growth was assessed in 25 patients; of these, 22 (88 %) had a slowly PD.

*Intervention*

Either octreotide LAR 30 mg IM (n = 21) or lanreotide SR 60 mg IM (n = 10) administered every 28 and 21 days, respectively. Median duration of treatment was 18 months (range: 6 to 60).

*Statistical analysis*

Univariate and multivariate analyses were performed to evaluate the effects of variables on response to treatment using a logistic regression model. Survival probabilities were calculated using the Kaplan-Meier method and comparisons were made using the log rank test. Unpaired Wilcoxon test was used to compare variables in the subgroups of patients. Fisher exact test was used to compare percentages.

*Results*

Response rate after 6 months was 45.2 % (all disease stabilisation: 27.8 % pancreatic versus 81.8 % intestinal tumours; p = 0.007).

The median duration of SD in patients (n = 14) was 26 months (range: 6 - 60). No patient had achieved tumour regression at the time of the early follow up (3 - 6 months).

Predictors for treatment efficacy: A lower proportion of pancreatic endocrine tumours (PETs) responded in comparison with intestinal carcinoids; SD being observed in 27.8 % (5/18) and in 81.8 % (9/11) of patients, respectively; p = 0.007.

There was no difference in outcome between functional and non functional tumours; SD being observed in 45.4 % (5/11) and 45% (9/20) of patients, respectively; p = not significant (N.S).

The two analogues showed similar efficacy, response being observed in 47.6 % (10/21) and 40 % (4/10) of patients treated with octreotide LAR and lanreotide SR, respectively. *The primary aim of the study was not to compare the efficacy of the two analogues.*

The predictors for non response were: pancreatic tumour (OR 5.8), no previous surgery (OR 6.7), and the presence of distant extra hepatic metastasis, the later being also confirmed by multivariate analysis (OR 10.0). The study, however, included 88 % of

patients with slowly progressive tumours and 93.6 % of patients with KPS score ≥ 80. Thus, these variables could not be analysed as predictors.

Response during long-term follow up: The 14 patients responding at the early follow up maintained SD for a median of 26.5 months after the initial documented response (range: 6 - 60).

Overall, the 3 year survival rate was 75 %. None of the patients that were responders at the early follow up died of the disease.

Thus, a statistically significant difference was observed in survival curves for patients, responders or not, to treatment; the 3 year survival rate being 100 % and 52.3 %, respectively; p = 0.004 (Figure 10).

**Figure 10. From paper by Panzuto *et al* 2006.**

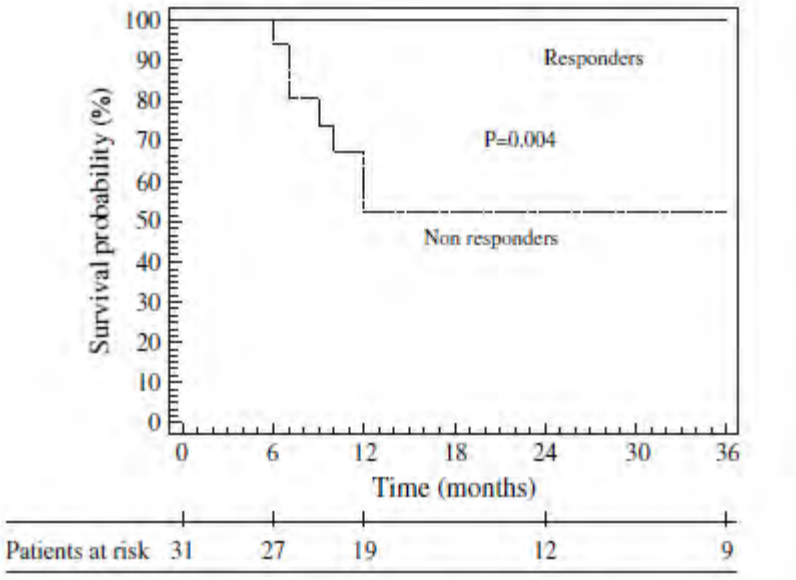



**Figure 1.** Survival probability according to the response to treatment at early follow-up.

*Authors' conclusion*

The presence of distant extra hepatic metastases was the major predictor of poor efficacy in progressive, metastatic well differentiated GEP-NETs. Patients responding after 6 months of treatment maintained their response throughout the long term follow up. Non responders after 6 months of treatment should be considered for alternative treatments.

***Study by Welin et al 2004***

Title: "High-dose treatment with long-acting somatostatin analogue in patients with advanced midgut carcinoids." *Eur J Endocrinol* 151:107-112.

The study included 12 heavily pretreated patients with midgut carcinoids and progressive disease treated with "high-dose" octreotide pamoate (160 mg IM 2 weekly for 2 months, then monthly).

"Unfortunately the treatment with octreotide pamoate had to stop since the drug became unavailable."

*This study involved different formulation of octreotide and hence is not relevant to current submission.*

***Paper by Strosberg et al 2009.***

Title: "Survival and Prognostic Factor Analysis of 146 Metastatic Neuroendocrine Tumors of the Midgut." *Neuroendocrinol* 89:471-476.

The study represents a retrospective analysis of survival data from a single center Cancer Research Institute in USA[16] providing background data on survival in midgut well differentiated tumours.

The analysis focused on metastatic NETs originating in the small intestine (jejunum and ileum) and proximal colon (cecum and appendix). This relatively homogeneous group of tumours categorised as 'midgut' in the Williams-Sandler classification, represents a majority of patients with metastatic gastrointestinal NETs and is strongly associated with the typical carcinoid syndrome.

The authors evaluated all cases of metastatic NETs of the midgut seen in their institution over 5-year period (1999 to 2003); 146 cases of metastatic midgut NETs were identified. Poorly differentiated (anaplastic) tumours were excluded. Metastatic NETs of unknown origin were included if suspicion for a small bowel primary tumour was high (due to involvement of mesenteric lymph nodes or presence of the carcinoid syndrome).

Absolute survival time was measured from time of diagnosis of distant metastases until death from any cause or latest follow up. Kaplan-Meier estimates were obtained of median, 5 year and 10 year survival. Relative survival at 5 years was measured by calculating the ratio of observed survival to expected survival (age and gender matched life expectancy in the USA).

The majority of tumours (52 %) were identified as originating in the ileum or ileocaecal region, including: 22 % in the small intestine (without specific anatomic localisation), 21% unidentified (clinically suspected to arise in the small intestine), 3% in the jejunum, and <1% in the ascending colon. There were no appendiceal primary tumours identified (presumably due to the rarity of metastatic carcinoid tumours of the appendix).

Liver metastases were observed in the large majority (92%) of cases. Nearly all patients (91%) received long term depot octreotide treatment *(no doses specified)*, either for palliation of the carcinoid syndrome or for its putative antiproliferative affect.

*Results*

The median survival from time of diagnosis of distant metastases was 103 months (8.6 years; 95 % CI: 88 - 118 months; range: 8 - 250 + months). Absolute 5 year survival was 75% (95 % CI: 67 - 81 %) and relative 5 year survival was 82 %. The 10 year survival was 38 % (95 % CI: 28 - 47 %).

This prolonged survival compares favourably with historical data.

For patients with an identifiable (as opposed to a suspected) midgut primary tumour, the median survival was 110 months (9.2 years). This figure represents the longest life expectancy documented in published reports of metastatic NETs and further validates a temporal trend of declining mortality among patients with this disease.

The population consisted predominantly of patients who were not the candidates for surgical cytoreduction because of wide dissemination of metastases. Among these medically managed patients, the observed median survival was 95 months (7.9 years; range: 1 - 22 + years) and an absolute 5 year survival rate of 71%, demonstrating that prolonged life expectancy is attainable even without surgical debulking of metastases.

The impact of SSAs on declining mortality rates has not been established thus far. In addition to alleviating the carcinoid syndrome, SSAs may also stabilise tumour growth. It

[16] H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA.

is possible that increasing utilisation of SSAs (as observed in the study), may play an important role in improving prognosis. Randomized, prospective trials are necessary to validate this hypothesis.

Confounding variables need to be considered when comparing contemporary outcomes with historical controls; including significant time and referral bias.

*Conclusions*

The study is the first to demonstrate an extended median survival (7.9 years) among patients who are not candidates for surgical cytoreduction of metastases, possibly reflecting the impact of SSAs and other medical treatment advances.

Resection of the primary tumour does not appear to be associated with a survival benefit in the metastatic setting. *(Of note, this is quite different observations from the PROMID study.)*

***Paper by Yao et al 2008.***

Title: "One Hundred Years after 'Carcinoid': Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States." *J Clin Oncol* 26:3063-3072.

The authors retrospectively analysed the epidemiology and prognostic factors for NETs in patients identified in the SEER[17] database from 1973 to 2004.

NETs are more common than generally believed. The results indicated a significant increase in the reported incidence of NETs over time.

A significant increase in the reported annual age adjusted incidence of NETs from 1973 (1.09/-100,000) to 2004 (5.25/100,000) was observed.

This increase was likely caused in part by improvements in classification of these tumours. Also, widespread use of endoscopy for cancer screening likely contributed to the increase in reported incidence of rectal carcinoid NETs.

One of the questions in the study was, whether the survival duration has improved in patients with NETs over time. Because the somatostatin analog octreotide was the only drug introduced for use against NETs during this period (in 1987), the study compared survival duration in patients who received diagnoses from 1973 to 1987 with those diagnosed between 1988 and 2004.

There was no observed statistically significant difference in survival duration among patients with local and regional NETs over time. However, a "dramatic improvement" was observed in survival duration among patients with metastatic NETs diagnosed in the later period (1998 to 2004).

Although the survival did not improve significantly among patients with localised NETs (HR = 0.96; 95 % CI: 0.87 - 1.06; p = 0.43) or regional NETs (HR = 0.91; 95 % CI: 0.82 - 1.01; p = 0.08), it did improve among patients with metastatic disease (HR = 0.67; 95 % CI: 0.62 - 0.73; p < 0.001).

One possible explanation is that the introduction of octreotide improved the control of carcinoid syndrome and changed the natural history of NETs. For example carcinoid crisis, which was a major cause of morbidity and mortality in the past, now occurs rarely. Organ failure, which tends to occur later in the course of illness, is now a major cause of mortality.

Whereas many researchers have speculated that octreotide has a disease stabilising effect in patients with NETs, conclusive data from randomised human studies are lacking.

[17] Surveillance, Epidemiology, and End Results Database.

**Consensus statements/guidelines/review articles**

***ENETS[18] guidelines . Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors - Well-Differentiated Jejunal-Ileal Tumor/Carcinoma. Eriksson et al 2006. Neuroendocrinol 87:8-19.***

The second ENETS Frascati Consensus Conference on Gastrointestinal Neuroendocrine Tumours was held in Frascati (Rome, Italy, November 2006).

Background: The conference focused on NETs of midgut and hindgut origin and the liver as a metabolic site of gut NETs. Based on the current WHO classification of tumours, 56 experts and practicing clinicians confronted their experience with published evidence-based data. (The First conference in November 2005 was designated to foregut NETs; stomach, duodenum and pancreas.)

*Key points in relation to therapy:*

Surgery: Curative surgery is always recommended whenever feasible after careful symptomatic control of the clinical syndrome. Cholecystectomy is always recommended. After curative surgery, there is no indication for medical therapy other than pre and perioperative SSA treatment to avoid carcinoid crisis. Palliative surgery should mainly be done for symptomatic reasons.

*Minimal consensus statement on somatostatin analogues:*

SSA therapy is recommended as first line medical treatment in functioning tumours. It provides symptomatic improvement in 70 - 80 % of patients and stabilisation of tumour growth in up to 50 % of patients with varying duration.

Whether SSAs should be used in non functioning tumours is not established but ongoing studies should clarify this issue. SRS positive tumours tend to respond better than SRS negative tumours.

Steatorrhea may lead to malabsorption of Vitamin D with reduced calcium absorption. Patients on SSAs should also have Vitamin $B_{12}$ levels monitored since these levels may be reduced, possibly due to inhibition of intrinsic factor.

*Evaluator's comment: Sponsor stated that a report from the PROMID Study Group published by Rinke et al in 2009 was "endorsed by the European Neuroendocrine Tumor Society". No relevant reference supporting the ENETS endorsement was included in the current Australian submission.*

***NCCN[19] Clinical Practice Guidelines in Oncology - Neuroendocrine Tumors. Clark et al July 2009. J Natl Compr Canc Netw 7:712-747.***

*Carcinoid tumours*

Background: 60 % of carcinoid tumours arise in the midgut, with the small bowel being the most common site, followed by the appendix. The carcinoid syndrome is usually associated with tumours of the midgut because they are the most common and frequently metastasize.

Primary treatment of carcinoid tumours: For patients presenting with tumours in the small bowel and colon, surgical resection is recommended. If octreotide therapy may be needed in the future, a prophylactic cholecystectomy should be considered in conjunction with surgical resection of a small bowel.

Management of recurrent or unresected carcinoid tumours:

[18] European Neuroendocrine Tumor Society
[19] National Comprehensive Cancer Network

If no symptoms of carcinoid syndrome are present and the tumour is unresectable, the panel recommends either observation with imaging studies as indicated every 3 - 6 months until the disease becomes symptomatic or progressive, clinical trial, or consideration of octreotide therapy.

The interim results of a placebo controlled phase III trial (PROMID) presented at the 2009 ASCO Gastrointestinal Cancers Symposium showed a 67 % reduction in risk for disease progression with octreotide therapy versus placebo in patients' with metastatic small bowel carcinoid tumours.

For symptomatic patients with carcinoid syndrome, clinically significant tumour burden, progression (positive Octreoscan or increased biomarkers) or local effects, the panel recommends octreotide SC and octreotide LAR for chronic management.

Octreotide LAR is also an accepted therapy for patients with progressive, metastatic, non functioning carcinoid tumours, especially if the Octreoscan is positive and/or a trial course of LAR results in a decrease or normalisation of the blood CgA level. *(With reference to chromogranin A level see comments above (U. Plöckinger and B. Wiedenmann)).*

*Neuroendocrine unknown primary tumours*

Background: The endpoint of evaluation is the pathological categorisation of NETs of unknown primary into two categories:

- Poorly differentiated, and
- Well and moderately differentiated.

Well and moderately differentiated tumours should be treated similarly to typical carcinoid tumours.

***Editorial by Öberg 2009***

Title: "Is it time to widen the use of somatostatin analogues in Neuroendocrine Tumors?" *J Clin Oncol* 27(28):4635-6.

Background: Most NETs (80 %) express a high density of somatostatin receptors (sstr). To date, 5 subtypes of sstr have been identified (sstr1 - 5). Each receptor subtype activates multiple intracellular transduction pathways, and the anti secretory effects of somatostatin on various hormones involve particularly sstr 2 and sstr 5. Native somatostatin binds to all 5 somatostatin receptors.

Octreotide binds with high affinity to sstr 2 and sstr 5, and is therefore effective inhibiting the secretion of peptides and amines from neuroendocrine cells. Other octapeptides with similar affinity to sstr 2 and sstr 5 were developed later, such as lanreotide and vapreotide. Both octreotide and lanreotide have long acting formulations that can be given once per month. These two analogues have been the" gold standard" in the treatment of acromegaly and different functioning NETs.

Octreotide has been available in clinical practice for more than two decades and has been the most effective drug to inhibit clinical symptoms related to hypersecretion of amines and peptides in NETs.

Possible antitumor effects of somatostatin analogues (SSAs) have always been in question but octreotide has not been registered in any country as an antitumor agent.

The antitumor effects of SSAs can be divided into direct and indirect effects. Direct effects are mediated through binding directly to receptors on the tumour cells, whereas indirect effects are via inhibition of growth factors, stimulation of the immune system or inhibition of angiogenesis.

Octreotide therapy results in remission or stabilisation of tumour markers, such as serotonin and CgA in ≈ 60 - 70 % of patients.

A more controversial area has been the treatment of non functioning NETs with SSAs. Non randomised studies have so far given disappointing results with regard to significant tumour regression according to criteria from WHO or RECIST. Tumor shrinkage is demonstrated in < 5% of patients. However, stabilisation of tumour growth after CT documented progression before SSA treatment occurs in up to 50 % of patients with NETs.

The recently published *PROMID study* is the first randomised prospective trial demonstrating a possible antitumor effect for octreotide LAR compared with a placebo in patients with well differentiated NETs of midgut origin, limited tumour mass and resected primary tumour.

*PROMID study* was not designed to demonstrate superior survival since patients progressing in the placebo group received treatment with octreotide LAR. The authors concluded that octreotide LAR significantly lengthens median TTP compared with placebo in patients with functionally active and inactive metastatic NETs of the midgut.

The long accrual time (8 years) indicates the problems involved in conducting a placebo controlled study of NETs. Over the years, it has been debated whether octreotide LAR has any significant antiproliferative effect. This study supports an antiproliferative effect in well differentiated midgut carcinoid tumours, with stabilisation being the most frequent tumour response.

However, only a limited group of patients, those with < 10 % tumour mass in the liver along with resected primary tumours, responded to treatment. There was no significant difference in TTP between octreotide LAR and placebo in patients with larger tumour burden.

Patients with limited clinical symptomatology could be included in the placebo controlled study.

The authors concluded that newly diagnosed patients with a low hepatic tumour burden and resected primary tumour were candidates for treatment with octreotide LAR.

New studies are needed to determine whether patients with a higher hepatic tumour load might be candidates for this treatment. Survival data are not available in the study and therefore it is not possible to tell whether this initial increased TTP translates into a survival benefit in the long run.

It has also been suggested that this study might support the use of octreotide LAR in an adjuvant setting after surgery with a curative intent in patients with well differentiated, low proliferating NETs. However, *PROMID* was not designed to answer this question. A randomised study is needed that compares no treatment with treatment using octreotide LAR to be able to show significance in an adjuvant setting.

This randomised, placebo controlled study showed that 30 mg octreotide LAR in low volume, well differentiated NETs of the midgut had an antiproliferative effect in patients with both functioning and non functioning tumours.

That will of course widen the indication for the use of octreotide in both functioning and non functioning small intestinal NETs of well differentiated origin. The role of SSAs in high proliferating tumours needs to be defined in forthcoming studies.

During the 45th Annual Meeting of the ASCO (29 May 29 - 3 June 2009), the NCCN presented an updated version of their guidelines for treatment of carcinoids; octreotide was included for treatment of asymptomatic unresectable carcinoids as well as for symptomatic tumours with significant tumour burden or significant progression.

“The ENETS has not yet upgraded their guidelines, but I assume that octreotide will be suggested as a therapeutic option for non functioning carcinoid tumours.”

There is another placebo controlled, randomised trial ongoing with lanreotide (Somatuline Autogel, Ipsen Pharma Biotech, Signes, France) in non functioning NETs of different types, and we are awaiting the results from this study. If this study confirms the *PROMID* data, it will further strengthen the role of SSAs as antitumor agents in non functioning NETs.

"The answer to the question in the title of this editorial will be "yes" for well differentiated, low proliferating small intestinal neuroendocrine tumours, but "maybe" for other subtypes of neuroendocrine tumours."

***Review paper by Öberg 2010***

Title: "Antitumor effects of octreotide LAR, a somatostatin analog." Nature Reviews Endocrinology. 6(4):188-189.

Similarly to the editorial above, the paper comments on the study published by Rinke *et al* 2009. The author summarizes the results from the PROMID study:

The investigators report a median TTP in the octreotide LAR group of 14.3 months compared with 6.0 months in the placebo group (HR 0.34, 95 % CI: 0.20 - 0.59, $p < 0.001$). After 6 months of treatment, 66.7 % of patients in the octreotide LAR group had SD compared with 37.2 % of patients in the placebo group. Functionally active and inactive tumours responded similarly to treatment with octreotide LAR. The most favourable effect was observed in patients with low hepatic tumour load (≤ 10 %) and resected primary tumours.

A limitation of the study by Rinke and colleagues is that tumour growth was not documented at the start of treatment with octreotide LAR. Furthermore, only those patients with ≤ 10% liver metastases and a resected primary tumour responded well to the treatment.

Given that the antitumor effect of SSAs has been questioned, octreotide has not been registered in any country as an antitumour agent. In some countries, such as Sweden, the US, Canada and Germany, octreotide has been used at the doctor's discretion in non functional tumours and some studies have indicated a clear antitumor effect.

On the basis of results from Rinke *et al* 2009 the NCCN in the US have presented an updated version of their guidelines for the treatment of carcinoid tumours.

The Canadian Neuroendocrine Tumor Network and the Nordic Neuroendocrine Tumor Network have also upgraded their guidelines to include octreotide treatment for both functioning and non functioning NETs.

"In conclusion, I believe that somatostatin analogues have potential antitumor effects, particularly when used at high doses, and agree with the revision of guidelines for the treatment of metastatic intestinal neuroendocrine tumours."

**Conclusions regarding efficacy**

Background: "Data presented in this submission demonstrate that Sandostatin LAR in addition to controlling symptoms associated with NETs is also effective in delaying disease progression."

There is only one study supporting this application. The results of the pivotal, double blind, placebo controlled *PROMID* study are suggestive that Sandostatin LAR has an effect in delaying the disease progression.

No firm conclusions could be drawn from the rest of the submitted data due to the deficiency of the search strategy and the methodological flaws in majority of the submitted papers (open label, uncontrolled studies conducted in a heterogeneous population), and hence these studies are regarded as a reference material only.

### *Summary of the planned IA of PROMID study*

The *PROMID study* was conducted in treatment naïve patients (n = 85) with advanced (locally inoperable or metastatic), well differentiated NETs of midgut origin. Patients with tumours of unknown origin were accepted, if after excluding other origins of the primary, tumours were believed to originate in midgut.

The primary efficacy endpoint was TTP, which reached statistical significance at planned, interim analysis. The resulting doubling of TTP in the octreotide arm was also clinically significant. Additionally, nearly 2/3 of patients achieved stable disease at 6 months. No conclusions could be drawn from current study regarding important secondary endpoint; overall survival.

The key results at the IA are as follows:

Median TTP *(cITT)* was 14.3 months in the octreotide LAR group and 6.0 months in placebo groups, respectively (HR = 0.34; 95 % CI: 0.20 - 0.59; p = 0.000072).

After 6 months of treatment, SD was observed in 66.7 % and 37.2 % of patients in the octreotide LAR and placebo groups, respectively.

Because of the low number of observed deaths, survival analysis was not confirmatory. In total, 7 and 9 deaths were observed in the octreotide LAR and the placebo groups, respectively. The HR for OS was 0.81 (95 % CI: 0.30 - 2.18; p = 0.7).

There was no gain in QoL in the octreotide arm; "global QoL comparable at both arms at 6 months".

The analyses conducted in 3 studied populations (cITT, ITT, PP) gave similar results.

Exploratory analyses suggested that:

- Functionally active and inactive tumours responded similarly.
- The most favourable effect was observed in patients with low hepatic tumour load and resected primary tumour. *(These analyses conducted in PP population were of small sample size.)*
- An additional analysis of data performed by Novartis further supported the validity of the original analysis by Rinke *et al* (2009).

The median TTP in the ITT analysis was 11.3 months (95 % CI: 6.7 - 14.3) in patients receiving Sandostatin LAR versus 5.6 months (95 % CI: 3.5 - 6.2) in placebo patients, the difference being statistically significant (HR 0.41; 95 % CI: 0.24 - 0.70; p = 0.0008).

Of note to the proposed indication are the following comments by the authors of the *PROMID study*:

"We believe that biotherapy with octreotide LAR is the treatment of choice in patients with newly diagnosed, functionally active or inactive, well differentiated metastatic midgut NETs and with a low hepatic burden." *(An additional comment was made in support of octreotide use in an adjuvant setting after surgery. This population was, however, not investigated in the study, also being not relevant to the proposed indication.)*

"We propose that impact of biotherapy on time to tumour progression and overall survival should be investigated further in clinical trials, in addition to studies including NETs of other origins."

In summary, the current placebo controlled *PROMID study* contributes positively to the clinical material relating to possible anti tumour effect of octreotide.

It is the evaluator's opinion, that *PROMID trial* does not support the proposed wide indications for octreotide LAR use for:

*"Advanced NETs of the midgut and unknown primary tumour location".*

This is because, based on the study inclusion criteria, practically only tumours of midgut origin were included in the trial; this needs to be clearly reflected in the indications.

The *PROMID trial* is considered adequate to support modified indications for octreotide LAR, as follows:

> *"The treatment of patients with well differentiated, advanced NETs of the midgut. Tumours of unknown primary origin which following exclusion of other primary sides are believed to originate from midgut, also belong to this category."*

Further specification of the population most likely to benefit from the drug (as proposed by the authors of the *PROMID trial*), is difficult to justify on the basis of the exploratory, subgroup analyses.

## Safety

The safety population in the pivotal *PROMID study* consisted of 42 patients who received Sandostatin LAR. In addition, the safety of 43 patients who received placebo served as a reference.

### Patient exposure

Octreotide has been used as treatment for carcinoid syndrome in patients with GEP-NETs for over 20 years and has a well established safety profile. Sandostatin LAR was first registered in 1995.

### Adverse events

#### *Pivotal studies*

There were no new safety findings in PROMID. All the findings were consistent with the well established safety profile of Sandostatin LAR.

#### *Other studies*

A review of the published studies of Sandostatin and Sandostatin LAR in the specific target population showed AEs to be consistent with the known safety profile of octreotide. The most frequently reported AEs were injection site reactions, abdominal pain, nausea, vomiting, diarrhoea, steatorrhoea and cholelithiasis, which is consistent with the Sandostatin LAR Novartis CDS. No SAEs were reported.

#### *Adverse reactions (drug related adverse events)*

No data provided from PROMID study.

### Withdrawals due to adverse events (PROMID study)

In *PROMID study*, before the disease progression, one patient switched from placebo to octreotide, 7 patients (5 in the Sandostatin LAR group and 2 in the placebo group) withdrew consent, and 5 (all in the Sandostatin LAR group) stopped study treatment due to AEs.

One of the patients in the Sandostatin LAR group who withdrew consent for therapy was lost to follow up at the date of withdrawal.

### Deaths and other serious adverse events (PROMID study)

There were no treatment related deaths in PROMID study.

In total, 7 and 9 deaths were observed in the Sandostatin LAR and placebo groups, respectively. The cause of death was unrelated to the tumour disease in 2 Sandostatin LAR recipients (CVA) and 1 placebo recipient (MI). In one placebo recipient the cause of death was unknown (Table 16).

**Table 16. PROMID study. Number of patients who died, had other serious AEs or discontinued prematurely because AEs.**

| | Sandostatin LAR n=42 | Placebo n=43 |
|---|---|---|
| No. (%) of patients with significant events | 11 | 10 |
| **Event type** | n (%) | |
| Death | 0 | 0 |
| Non-fatal serious AE(s) | 11 | 10 |
| AE-related treatment changes | | |
| treatment interruption | 5 | 0 |
| dose reduced | 0 | 0 |

Source: Rinke et al. 2009[5]

SAEs were observed in 11 octreotide LAR treated patients and 10 placebo recipients. The most frequently observed SAEs affected the gastrointestinal (GI) tract (octreotide LAR n = 6, placebo n = 8), the hematopoietic system (5 and 1, respectively), and general health (fatigue and fever; 8 and 2, respectively).

WHO Grade 2 - 4 AEs, were observed more often in the octreotide LAR arm, and included diarrhea and flatulence. Bile stones were recorded 6 times, with 5 instances in the octreotide arm.

### Laboratory abnormalities (PROMID study)

#### *Biochemistry*

Chromogranin A levels (see above), no further laboratory data discussed.

#### *Haematology*

Not discussed.

#### *ECG*

Not discussed.

### Postmarketing experience

The Periodic Safety Update Report (PSUR) No. 13 for Sandostatin and Sandostatin LAR (1 July 2005 - 30 June 2008), was included in the current Australian submission.

PSUR Addendum Report (1 July 2008 - 30 June 2009) has been added.

#### *PSUR No. 13*

*Conclusions from evaluator's report:*

The safety data remain in accord with the previous cumulative experience and the safety information presented in the CDS.

The AE section of Australian PI reflects the Company Core Data Sheet (CDS).

The evaluator recommended that the Australian PI Overdose section be updated in accordance with the CDS (and in line with in the US label of Sandostatin.)

This included adding the following terms recorded in the CDS: arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly and lactic acidosis.

The evaluator recommended that the incidence of AEs reflecting biliary tract abnormalities and gallstones be updated in the Australian PI, taking into account the data widely quoted in literature (50 - 60 %), and information already included in the US label of Sandostatin.

*The Australian PI states that the "development of gallstones has been reported in 15 - 30 % of long term recipients of Sandostatin."*

*The US label of Sandostatin contains the following warning: "In clinical trials (primarily patients with acromegaly or psoriasis), the incidence of biliary tract abnormalities was 63 % (27 % gallstones, 24 % sludge without stones, 12 % biliary duct dilatation. The incidence of stones or sludge in patients who received Sandostatin for 12 months or longer was 52 %. Less that 2 % of patients treated with Sandostatin for a1 month or less developed gallstones."*

Of note, international guidelines even provide advice that consideration be given to prophylactic cholecystectomy, at the time of surgical exploration for GEP-NETs, in patients in whom long term SSAs use is anticipated. This clearly reflects both; the significance and indicates the extent of the problem.

***PSUR Addendum Report (1 July 2008 - 30 June 2009)***

The significance of the data collected during the current review period was analysed, including the perspective of cumulative experience. Attention was given to reports with a fatal outcome and to the relevant safety findings from previous PSUR's, namely: hyperkalemia, thrombocytopenia, hepatobiliary and cardiovascular diseases.

A total of 2460 reactions were reported in the 854 cases during the reporting period.

In total, there were 91 reports with a fatal outcome. In many cases fatal outcome was associated with PD (39), in 14 cases other alternative causes for the fatal outcome were identified. In the remaining cases the information provided was too limited in order to be able to evaluate a potential causal relationship to the drug.

One fatal case of neonatal necrotising enterocolitis in a newborn from a mother treated with Sandostatin LAR during pregnancy was described.

Taking into account the patient population receiving Sandostatin/Sandostatin LAR (predominantly advanced cancer patients), no pattern with respect to the occurrence of fatal cases was identified in relation to Sandostatin/Sandostatin LAR administration.

Concerning the thrombocytopenia (6) and hyperkalemia (3) cases, no pattern concerning the occurrence of these AEs could be identified in relation to the use of Sandostatin/Sandostatin LAR. Novartis will continue to monitor closely the topics of thrombocytopenia and hyperkalemia.

The review of the reports of increased hepatic enzymes did not change the known safety profile of the drug.

No new pattern concerning cardiovascular events could be identified in relation to Sandostatin/-Sandostatin LAR administration.

The most recent Sandostatin LAR Core Data Sheet was dated 09 April 2009.

*Conclusions*

No new relevant safety findings were identified during the review period. The safety data of Sandostatin/Sandostatin LAR remains consistent with the information provided in the CDS of the products and confirms the favourable benefit/risk profile.

### Conclusions regarding safety

The AEs reported in *PROMID study* were those expected with the use of Sandostatin LAR in patients with NETs based on previous cumulative experience. These AEs are already properly reflected in the Sandostatin LAR Novartis CDS.

No new safety issue has been identified in PSUR No. 13. The two new potentially relevant safety findings identified for the first time in PSUR 12 (thrombocytopenia and hyperkalemia) continue to be monitored closely.

## Clinical summary and conclusions

The submitted LBS application contained one pivotal study terminated early due to the efficacy claim, and a number of reference material from earlier, open label, mostly uncontrolled studies conducted in a heterogeneous NETs population.

With regard to the current submission, the comments[20] written below, nearly two decades ago, still hold true:

"Although scattered reports of tumour regression to octreotide have been published, the anti-neoplastic activity of this drug has not been widely studied, either in terms of its effect on tumour growth or in terms of its effect on patient survival. Endpoint analysis, i.e. TTP or OS, was reported only in a minority of trials.

Furthermore, the drug has not been studied previously in substantial numbers of patients with non functional NETs."

Based on the results of pre planned IA of the multicentre, pivotal PROMID study the sponsor concluded that Sandostatin LAR in addition to controlling symptoms associated with NETs is also effective in the delaying the disease progression.

The PROMID study was the first large, prospective, double blind, placebo controlled, clinical trial to assess the antiproliferative effect of Sandostatin LAR in patients with well differentiated, metastatic, functioning and non functioning NETs of the midgut origin.

The PROMID trial was conducted in treatment naïve patients (n = 85) with advanced (locally inoperable or metastatic), well differentiated NETs originating from midgut. Patients with tumours of unknown origin were accepted, if after excluding other origins of the primary, tumours were believed to originate in midgut. Midgut NETs are strongly associated with carcinoid syndrome.

The primary efficacy endpoint was TTP, which reached statistical significance at the planned, interim analysis. The resulting doubling of TTP in the octreotide arm (14.3 versus 6 months; p = 0.000072) was also clinically significant.

This equated to a 66 % reduction in the risk of tumour progression during treatment with Sandostatin LAR.

The results in the cITT analysis population (Rinke *et al* 2009) were consistent in demonstrating that Sandostatin LAR treatment significantly prolonged TTP as compared to placebo; HR = 0.34; (95 % CI: 0.20 - 0.59; p = 0.000072).

Additionally, nearly 2/3 of patients achieved SD at 6 months (66.7 % versus 37.2 %).

The analyses conducted in three populations studied (cITT, ITT, PP) yielded similar results.

[20] Saltz *et al* 1993. Octreotide as an antineoplastic agent in the treatment of functional and non functional neuroendocrine tumours. *Cancer* 72(1):244–248

No conclusions could be drawn from the pivotal study regarding important secondary endpoint; overall survival.

Exploratory analyses suggested that functionally active and inactive tumours responded similarly.

An additional analysis of data for the primary efficacy endpoint (ITT) performed by Novartis further supported the validity of the original analysis by Rinke *et al* (2009).

Based on the exploratory subgroup analyses, the most favourable effect was observed in patients with low hepatic tumour load and resected primary tumour. These analyses conducted in PP population were of small sample size and needed to be interpreted with caution.

There was no gain in overall QoL in the octreotide group (one might say that octreotide was not worse than placebo).

The safety of Sandostatin LAR in this trial was consistent with its established safety profile.

In addition, the presented safety data (PSUR and Addendum report) remain in accord with the previous cumulative experience, and the safety information presented in the CDS.

The rest of the published papers submitted with the current application represented an interesting background reading material but cannot be taken as supporting data for this evaluation.

This is because some of the submitted papers were not relevant to the indications sought, many were clearly not evaluable or raised methodological concerns but overwhelmingly this is due to the flaws in the search strategy.

It is possible, however, to make some general observations from the submitted data.

Although the previously conducted open label studies brought conflicting outcomes regarding the anti proliferative effect of octreotide and octreotide repeatedly "was disappointing in terms of tumour regression", achieving stabilisation of the disease for some time, for well-differentiated GEP-NETs seems to be a frequent finding reported in published papers submitted with this application.

Taken together, the evaluator was inclined to agree with the sponsor, that the results of the placebo controlled, randomised PROMID study support the long standing hypothesis that octreotide has an effect at inhibiting the tumour growth in patients with metastatic GEP-NETs.

The results of PROMID trial are based on interim analysis; there are many shortcomings with the approach of terminating the trial based on efficacy claim.

The long time needed to register 90 patients in the study indicates the difficulties involved in conducting studies in rare populations, especially when conducted by relatively small independent groups.

Importantly, it is uncertain from PROMID study if the improvements in TTP demonstrated at IA will translate into survival benefit in long term. Responses to treatment do not necessarily indicate longer survival.

Given the rarity of the disease and crossover of placebo patients to active treatment which is allowed in such trials, the answer might not be available for long time. Of note, the impact of SSAs on declining mortality has not been established so far.

In the PROMID study, upon disease progression the protocol allowed crossover of placebo patients to Sandostatin and the use of other treatments for patients in both arms. The influence of these treatments on survival cannot be ruled out; the survival analysis may be confounded by subsequent therapies administered after a study drug is discontinued.

It has been raised by the critique[21] that the population studied in the PROMID trial did not include patients with progressive disease documented before the study entry.

This could be considered a major drawback of the study, particularly as we are dealing with tumours of predominantly indolent nature. The need of targeting NET patients with "clearly documented" progressive disease has been stressed by multiple authors in the past, including authors[22] involved in the PROMID trial.

There are only few prospective, randomised, multicenter studies in therapy naïve patients with documented progress before initiation of biotherapy.

As progressive disease was no prerequisite for inclusion in some studies, the rate of stabilisation as well as the intervals for progression free survival or overall survival may be overestimated.

In slow growing, well differentiated tumours, tumour growth is unpredictable, and slow tumour progression may alternate with long intervals of stable disease. As the quality of life is good in most patients with metastasized well differentiated neuroendocrine tumours, antiproliferative therapy should only be initiated whenever progressive disease has been demonstrated according to standard criteria. Chemotherapeutic options for tumours of the small bowel are poor.

The issue of demonstrating PD before initiating SSA therapy has not been discussed by the authors of the pivotal study or by the sponsor. The study enrolled newly diagnosed patients with advanced disease and it is uncertain how many of them would have progressive disease at the study entry.

Of note are also the following comments: Recent studies have demonstrated that up to 60 % of patients may have tumours that demonstrate either no growth, or slow disease progression with time. This group has been reported to have excellent survival and the results of treatment in these patients may not be applicable to the subset of patients with progressive disease. [23]

One can only base the conclusions from the pivotal study on the presumption, that due to the randomisation, equal numbers of patients with PD were distributed between the arms. There is no indication to suspect that the octreotide and placebo arms were not well balanced. The clear advantage of octreotide over placebo in such situation is very reassuring.

(The baseline characteristics of the two treatment arms appear to be well balanced except for the time since diagnosis. The median time since diagnosis was longer in the Sandostatin LAR arm than in the placebo arm; 7.5 versus 3.3 months; p = 0.0096).

The sponsor provided following comments which are important for this application:

Overall, the *PROMID study* was robustly designed to evaluate the anti proliferative effects of Sandostatin LAR in midgut NET patients without relying on historical controls, an important aspect that was not addressed by previous studies (whether the assumed anti proliferative effects of the therapeutic intervention were not in reality a spontaneous remission of the disease).

The inclusion of a placebo arm in *PROMID study* was essential to provide such evidence, that is, a clear estimate of the efficacy and safety of Sandostatin LAR in patients with this disease.

[21] Öberg K.E. (2010) Antitumor effects of octreotide LAR, a somatostatin analog. *Nature* 188 (6): 188-189.
[22] Arnold *et al* 1996. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut* 38:430-438.
[23] Shojamanesh *et al* 2002. Prospective study of the antitumor efficacy of long term octreotide treatment in patients with progressive metastatic gastrinoma. *Cancer* 94:331-343.

The eligibility criteria of the *PROMID study* aimed to ensure assessment of efficacy and safety in a homogeneous midgut NET patient population, an important aspect not addressed in previously conducted studies. At the same time, those criteria were kept to a minimum to still allow for the inclusion of a midgut NET patient population that closely reflects the population expected to be treated in clinical practice.

The *PROMID study* provides a clear evidence of efficacy, previously suggested by a number of prospective, uncontrolled studies and retrospective series in which ≈ 50% of patients experience SD during treatment with Sandostatin/Sandostatin LAR.

The *PROMID study* is the first randomised, double blind, placebo controlled study to demonstrate the antiproliferative efficacy of Sandostatin LAR in patients with NETs, based on a homogeneous patient population by histology and tumour type (midgut tumours or unknown primary tumour location).

The most important result of the *PROMID study* is a highly significant result for the primary endpoint of TTP.

Importantly, Sandostatin LAR provided an anti tumour benefit to patients with either functioning or non functioning tumours. The results were consistent across all three efficacy analyses populations and a trend favoring Sandostatin LAR was observed across all sub groups.

Regarding hepatic tumour load, although patient numbers in subgroups were small, significant benefit was seen in patients with liver involvement ≤ 10 % and there was a trend toward lengthened TTP in patients with higher hepatic tumour load receiving Sandostatin LAR. This suggests that treatment with Sandostatin LAR should be initiated as soon as the disease is diagnosed.

In the *PROMID study* TPP and PFS would yield identical results.

Medical therapy for NETs is indicated after non curative surgical intervention or when surgery is not an option. The aims if medical treatments are broadly defined as the amelioration of symptoms and suppression of tumour growth and spread. While effective drugs for controlling symptoms exist, there is a high unmet medical need for therapies able to interfere with the progression of the disease.

Patients in *PROMID study* had no curative therapeutic options available to them, highlighting the unmet medical need in this patient population.

The recommended dose of Sandostatin LAR in this population is 30 mg Sandostatin LAR administered every 4 weeks. Treatment with Sandostatin LAR for tumour control should be continued in the absence of tumour progression.

This recommendation is aligned with the updated NCCN treatment guidelines (NCCN 2009/2010[24]), that recommends Sandostatin LAR as treatment for metastatic, well or moderately differentiated, asymptomatic, unresectable carcinoid tumours (NETs of the small bowel, colon, rectum, appendix, lung, thymus, stomach, bronchi).

This is in addition to the previous recommendation of Sandostatin LAR use for treatment of symptoms of carcinoid syndrome and tumours with significant tumour burden, progression, or local effects.

The safety and efficacy of Sandostatin LAR, up to 30mg every 28 days is well established for the treatment of symptoms associated with NETs and other indications. As expected, no new safety findings have been identified in *PROMID study*. The safety profile of Sandostatin in the target indication is considered acceptable, and in fact, compares very favourably to other cancer therapies, such as chemotherapy.

[24] Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors. See <http://www.nccn.org/professionals/physician_gls/f_guidelines.asp>

The evaluator understands that at this stage, there has not been an overwhelming response from the major scientific NET societies involved; the results of Rinke *et al* 2009 study have been adopted by US NCCN, the Canadian counterpart and the Nordic Neuroendocrine Network.

*In summary*, the evaluator considers that the results of *PROMID study* are highly significant at IA in favour of Sandostatin LAR for the primary efficacy endpoint; TTP.

This outcome is considered satisfactory to support the modified version of the widening of indications for Sandostatin LAR, in NETs of midgut origin.

The data presented in the Australian PI needs to reflect clearly and prominently the preliminary nature of the findings from *PROMID study*; the uncertainty relating to the survival benefit, no clearly proven advantage in QoL and the exploratory nature of subgroup analysis (functional versus non functional status).

The known safety status of octreotide, together with the rarity of the disease together with no proven alternative therapies available, heavily weighted on the evaluator's decision.

Additional points considered by the evaluator:

This is a LBS (the pivotal study was submitted as a published paper) and therefore presented data varied in quality.

The current submission relates to rare tumours and there is a significant overlap between the various sub groups of NETs.

The anti tumour effect of Sandostatin has been controversial for decades and various pieces of information contributed to the evidence. They may not all be strictly related to the proposed indications (midgut NETs/Sandostatin LAR/dosing regimen).

**Recommendations**

The evaluator recommended approval of the submission by Novartis Australia seeking to extend the indications for Sandostatin LAR octreotide modified release injection vials to include the treatment of patients with advanced NETs of midgut origin.

The evaluator recommended the modified version of indications, as follows:

> *"The treatment of patients with well-differentiated, advanced neuroendocrine tumours of the midgut. Tumours of unknown primary origin which following exclusion of other primary sites are believed to originate from midgut, also belong to this category."*

# V. Pharmacovigilance findings

There was no requirement for a Risk management Plan evaluation in a submission of this type.

# VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

There was no requirement for a quality evaluation in a submission of this type.

## Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

## Clinical

### Efficacy

The pivotal evidence of efficacy is from a single published study, PROMID (Rinke *et al* 2009).

PROMID was a randomised, double blind, placebo controlled trial of octreotide (Sandostatin LAR) in previously untreated patients with metastatic, well differentiated midgut NETs. A quarter of subjects had NET of unknown origin but believed to be midgut. Stratification was by whether subjects had functioning or non functioning tumours. The dose of octreotide was 30 mg every 4 weeks by intramuscular injection. The primary endpoint was time to tumour progression. This endpoint was accepted as more appropriate than progression free survival because midgut NETs are slow growing and deaths not related to the tumour would confound progression free survival (Clinical Evaluation (CE)). Tumour response was assessed from CT or MRI scans using WHO criteria by blinded central readers. The median age of subjects was 62 years (range 38 to 82). Half the subjects were male.

The trial was stopped after a planned interim analysis showed a significantly greater time to progression in the octreotide group. Stabilisation of disease also favoured octreotide. There were no significant differences in tumour response, quality of life or survival. Table 17 lists the ITT analysis. "Conservative" ITT and per-protocol analyses gave similar results.

**Table 17. Efficacy in Metastatic Well-Differentiated Midgut NET (PROMID). ITT.**

| | **Octreotide** ***n=42*** | **Placebo** ***n=43*** | **Hazard Ratio[3] [95% CI] or P value of diff[4]** |
|---|---|---|---|
| Time to Progression median *months* | not stated[1] | not stated[1] | 0.32 [0.19, 0.55] |
| Survival median *months* | not reached | not reached | 0.81 [0.30, 2.18] |
| Tumour Response[2] | 2.4% | 2.3% | not stated |
| Stable Disease[2] | 67% | 37% | p=0.008 |

[1] In a "conservative" ITT analysis (2 octreotide subjects and one placebo subject censored at randomisation), median time to progression was 14.3 months for octreotide and 6.0 months for placebo. Hazard ratio was 0.34, 95% CI [0.20, 0.59]. [2] WHO criteria, central blinded assessment of CT or MRI. [3] Cox model. [4] Wilcoxon-Mann-Whitney test.

Based on post hoc PP analysis, octreotide significantly increased time to progression regardless of whether the tumour was functioning or non functioning; there was no ITT analysis of these subgroups.

Baseline characteristics were well balanced except for time since diagnosis; median 7.5 months in the octreotide group and 3.3 months in the placebo group (p=0.01). This imbalance may have favoured the octreotide group since longer duration between diagnosis and treatment suggests indolent disease[25]. Post hoc analysis based on the per protocol population showed that the shorter the time since diagnosis, the less the benefit in time to progression (based on a cut off of 4.3 months since diagnosis)[26].

Documented progressive disease was not a requirement for study entry[27]. These tumours are slow growing with intervals of slow progression and stable disease. Patients without progressive disease do not require octreotide according to US National Comprehensive Cancer Network (NCCN) criteria[28]. If such patients were entered in the trial, the rate of disease stabilisation and time to progression may have been overestimated.

Other data from 16 published papers did not specifically relate to midgut NETs and was of limited value with respect to the proposed indication.

### Safety

The safety of octreotide in the efficacy trial PROMID was consistent with the established safety profile of the drug. There were no new safety findings in a review of published studies or in recent Periodic Safety Update Reports.

The evaluator supported registration of a more restricted indication based on the population in the PROMID study:

> *"Treatment of patients with well-differentiated, advanced neuroendocrine tumours of the midgut. Tumours of unknown primary origin which following exclusion of other primary sites are believed to originate from midgut also belong to this category".*

The sponsor subsequently agreed to this in their response to the CE.

## Risk management plan

Not required.

## Risk-benefit analysis

### Delegate considerations

In the PROMID trial, octreotide significantly increased time to progression in patients with advanced, well differentiated midgut NETs. The median time to progression was not determined in the ITT analysis. In the conservative ITT analysis, it was 6 months with placebo and 14 months with octreotide. Time to progression was an acceptable primary endpoint in this setting of slow growing tumours. Post hoc analysis suggested that the increase in time to progression is similar for functioning and non functioning tumours.

Of the secondary endpoints, octreotide significantly increased disease stabilisation but not overall tumour response or survival. Increased overall survival would be difficult to demonstrate given the rarity of the disease and its prolonged course.

[25] Chua YJ *et al* (2010). Correspondence (on PROMID study report). *J Clin Oncol* 28(3): e41-44.
[26] Rinke A *et al* (2009). (PROMID Study Report). *J Clin Oncol* 28: 4660 (Table 2).
[27] Öberg K. Antitumor effects of octreotide LAR, a somatostatin analog (PROMID Study Report Editorial). *Nature Reviews/Endocrinology* 2010, 6:188-9.
[28] Neuroendocrine Tumours. (2009). J National Comprehensive Cancer Network.

There were two issues with the trial which may have led to overestimation of the octreotide benefit in time to progression and disease stabilisation. Firstly, documented progressive disease was not a requirement for study entry. NETs are slow growing with intervals of progression and stable disease. Secondly, there was a significant imbalance between the groups in time since diagnosis which was a median 7.5 months in the octreotide group and 3.3 months in the placebo group (p=0.01). Longer duration between diagnosis and treatment suggests non progressive disease. The imbalance has occurred in spite of randomisation because of the small number of subjects. The imbalance may have been overcome with a larger number of subjects. Hence, the trial has been stopped too soon. In any case, the treatment effect was relatively large; therefore, any overestimation of effect is not likely to affect the significance of the result.

The safety of octreotide in the trial was consistent with the established profile.

In view of the heterogeneous nature of NETs, the indication should be limited to that in the trial. The Delegate proposed a simpler statement than that recommended by the clinical evaluator and also required documented progression in line with NCCN criteria which state that patients without progressive disease do not require octreotide.

### Delegate's draft decision

The Delegate proposed to approve octreotide (Sandostatin LAR) injection powder and vehicle solution for the indication:

*Treatment of patients with documented progression of well-differentiated, advanced neuroendocrine tumours of the midgut or suspected midgut origin.*

Submitted to ACPM for advice.

### Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

#### *Safety and efficacy*

The ACPM noted the concerns raised by the Delegate over the early termination of the trial and subsequent difficulties in analysis of small patient numbers. The Committee agreed with the Delegate that despite the small study size, sufficient evidence of a reduction in time to progression was demonstrated. The secondary endpoints of overall tumour response or increased survival were not demonstrated. No new safety signals were evident in studies submitted, and the safety profile was consistent with the known profile.

#### *Indication*

The ACPM considered this product to have a positive benefit risk profile for the indication of:

> *Treatment of patients with progression of well-differentiated, advanced neuroendocrine tumours of the midgut or suspected midgut origin.*

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Sandostatin would support the safe and effective use of this product.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Sandostatin LAR containing octreotide for IM administration, indicated for:

*Treatment of patients with progression of well-differentiated, advanced neuroendocrine tumours of the midgut or suspected midgut origin.*

# Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

**Therapeutic Goods Administration**

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Email: info@tga.gov.au  Phone: 1800 020 653  Fax: 02 6232 8605
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