

**Ipsen announces that results from CLARINET<sup>®</sup> Phase III clinical trial presented at the 2013 European Cancer Congress showed the antiproliferative effect of Somatuline<sup>®</sup> (lanreotide) 120 mg injection in the treatment of non-functioning gastroentero and pancreatic neuroendocrine tumors (“GEP-NETs”)**

- Data showed that Somatuline<sup>®</sup> statistically significantly prolonged time to disease progression or death in non-functioning GEP-NET patients (p=0.0002; hazard ratio 0.47; 95% CI: 0.30–0.73)
- After 2 years of treatment with Somatuline<sup>®</sup>, disease progression or death was reduced by 53%: 62% of GEP-NET patients treated with Somatuline<sup>®</sup> had not progressed or died versus 22% with placebo
- Pre-specified subgroup analyses showed that the antiproliferative effect of Somatuline<sup>®</sup> is statistically significant in midgut tumors, clinically relevant in pancreatic NETs and independent of the tumor grade and hepatic tumor load
- Safety data generated from the study are consistent with known safety profile of Somatuline<sup>®</sup>

**Paris (France), 28 September 2013** – Ipsen (Euronext: IPN; ADR: IPSEY) today announced that the results of the CLARINET<sup>®</sup> study were presented on Saturday 28 September at the 2013 European Cancer Congress in Amsterdam. The results were presented in the LBA3 abstract: “A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET)”.

***Primary endpoint***

CLARINET<sup>®</sup> met its primary endpoint by demonstrating that treatment with Somatuline<sup>®</sup> Autogel<sup>®</sup> / Somatuline<sup>®</sup> Depot<sup>®</sup> (lanreotide) Injection 120 mg (referred to as Somatuline<sup>®</sup>) was associated with a statistically significant reduction of the risk of disease progression or death by 53% vs. placebo (hazard ratio 0.47, 95% CI: 0.30–0.73; p=0.0002). This result is based on the observation that 62% of GEP-NET patients treated with Somatuline<sup>®</sup> had not progressed or died versus 22% with placebo over the follow-up period (Kaplan-Meier estimates). The median progression free survival was not reached (beyond 2 years) in the Somatuline<sup>®</sup> group versus 18 months in the placebo group.

**Pr Martyn Caplin, Professor of Gastroenterology & Gastrointestinal Neuroendocrinology, Royal Free Hospital (London, UK) and Principal Investigator of CLARINET<sup>®</sup>**, commented: *“The CLARINET<sup>®</sup> study presents compelling data regarding the antiproliferative effect of Somatuline<sup>®</sup> in gastroentero and pancreatic neuroendocrine tumors. This is the first report from a prospective, double-blind trial showing increased PFS with a SSA in the treatment of non-functioning GEP-NETs. Importantly, the subgroup analysis showed statistically significant benefit in patients with midgut tumors, with well to moderately differentiated tumors and with tumors with high hepatic load”.*

**Claude Bertrand, Executive Vice-President Research & Development and Chief Scientific Officer of Ipsen** commented: *“CLARINET<sup>®</sup> is the first large-scale, multinational, phase III trial to demonstrate the antiproliferative effect of Somatuline<sup>®</sup>, Ipsen’s long-acting somatostatin analog, in patients with non-functioning GEP-NETs. We are pleased with the robust results demonstrated in the study, which adds to the available data regarding treatment of gastroentero and pancreatic neuroendocrine tumors”.*

**Subgroup analysis**

The effect of Somatuline<sup>®</sup> on disease progression was observed across certain pre-specified subgroups of patients. Statistically significant results were obtained in patients with midgut tumors, in patients with G1 and G2 (proliferation index Ki67 <10%) tumors, and in patients with moderate (≤ 25%) and high (>25%) hepatic tumor load.

The data on Somatuline<sup>®</sup> with respect to progression free survival showed a clinically relevant difference vs placebo in patients with pancreatic NETs, although the subgroup analysis did not reach statistical significance.

The results per subgroup are disclosed in the table below:

<b>Subgroups</b>	<b>Progression free survival (PFS)</b>	<b>Statistical results</b>
Midgut NETs (n=73)	Median PFS: • Somatuline <sup>®</sup> : > 2 years • Placebo: 21.1 months	<ul style="list-style-type: none"> <li>• hazard ratio 0.35</li> <li>• 95% CI: 0.16 -0.80</li> <li>• p=0.0091</li> </ul>
Pancreatic NETs (n=91)	Median PFS: • Somatuline <sup>®</sup> : > 2 years • Placebo: 12.1 months	<ul style="list-style-type: none"> <li>• hazard ratio 0.58</li> <li>• 95% CI: 0.32 -1.04</li> <li>• p=0.0637</li> </ul>
WHO grade tumors: G1 (n=141)	Median PFS: • Somatuline <sup>®</sup> : > 2 years • Placebo: 18.3 months	<ul style="list-style-type: none"> <li>• hazard ratio 0.43</li> <li>• 95% CI: 0.25 -0.74</li> <li>• p=0.0016</li> </ul>
WHO grade tumors: G2 (n=61)	Median PFS: • Somatuline <sup>®</sup> : > 2 years • Placebo: 12.1 months	<ul style="list-style-type: none"> <li>• hazard ratio 0.45</li> <li>• 95% CI: 0.22 -0.91</li> <li>• p=0.0235</li> </ul>
Hepatic tumor load (≤ 25%) (n=133)	Median PFS: • Somatuline <sup>®</sup> : > 2 years • Placebo: 21.1 months	<ul style="list-style-type: none"> <li>• hazard ratio 0.34</li> <li>• 95% CI: 0.18 -0.62</li> <li>• p=0.0002</li> </ul>
Hepatic tumor load (> 25%) (n=67)	Median PFS: • Somatuline <sup>®</sup> : 24.1 months • Placebo: 9.4 months	<ul style="list-style-type: none"> <li>• hazard ratio 0.45</li> <li>• 95% CI: 0.23 - 0.88</li> <li>• p=0.0170</li> </ul>

### **Safety profile**

Safety data generated from the CLARINET<sup>®</sup> study were consistent with the known safety profile of Somatuline<sup>®</sup>. Treatment-related adverse events occurred in 50% of patients treated with Somatuline<sup>®</sup> versus 28% in the placebo arm, and very few of these were serious (3% with Somatuline<sup>®</sup> versus 1% with placebo). The most frequent treatment-related adverse events included diarrhea (26% with Somatuline<sup>®</sup> versus 9% with placebo), abdominal pain (14% with Somatuline<sup>®</sup> vs 2% with placebo) and gallstone formation (10% with Somatuline<sup>®</sup> vs 3 % with placebo).

The data from CLARINET<sup>®</sup> is considered investigational, as Somatuline<sup>®</sup> is not approved specifically to treat non-functioning GEP-NETs in any market. Somatuline<sup>®</sup> is approved for treatment of symptoms associated with neuroendocrine tumors, which can include the treatment of GEP-NETs patients experiencing symptoms from carcinoid syndrome, in many markets where it is marketed as Somatuline<sup>®</sup> Autogel<sup>®</sup>. Somatuline<sup>®</sup> is not approved in the US to treat neuroendocrine tumors or symptoms thereof, where it is marketed as Somatuline<sup>®</sup> Depot<sup>®</sup>.

### **About CLARINET<sup>®</sup>**

CLARINET<sup>®</sup> is a randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with non-functioning gastroenteropancreatic NeuroEndocrine Tumours (ClinicalTrials.gov NCT00353496). This 96-week multinational study was conducted in collaboration with UK & Ireland Neuroendocrine Tumour Society (UKI NETS) as well as the European Neuroendocrine Tumour Society (ENETS).

A total of 265 patients from 44 centres across 14 countries were enrolled, with 204 patients with well or moderately differentiated non-functioning GEP-NETs and a proliferation index (Ki67) of <10%, subsequently randomly allocated to treatment (n=101 in Somatuline<sup>®</sup> Autogel<sup>®</sup> 120 mg group and n=103 in placebo group). At enrollment, primary tumor locations were pancreas (44%), midgut (36%), hindgut (7%) and unknown (13%). Most patients had stable tumors (96%) and were treatment-naïve (84%). 30% of patients had Ki67 3%–10% (WHO grade 2), 33% had hepatic tumor load >25%.

The primary endpoint of efficacy was time to either disease progression (using Response Evaluation Criteria In Solid Tumors, RECIST) or death. Two baseline computed tomography scans (≥12 weeks apart) were performed, followed by additional scans at 12 weeks intervals during the first year and 24 weeks intervals during the second year up to 96 weeks.

### **About gastroenteropancreatic neuroendocrine tumors**

Gastroentero and pancreatic neuroendocrine tumors (GEP-NETs) are rare but their incidence is increasing. They constitute a heterogeneous group of tumors with location of the primary tumor in the gastric mucosa, pancreas, small and large intestine. GEP-NETs when they are functioning secrete hormones and neuroamines that cause distinct clinical symptoms, such as the carcinoid syndrome associating diarrhea and flushing. However, non-functioning GEP-NETs do not secrete hormones and can remain clinically silent, delaying the diagnosis until late presentation with symptoms like weight loss or related to mass effects such as abdominal pain.

### **About Somatuline<sup>®</sup>**

The active substance in Somatuline<sup>®</sup> is lanreotide acetate, a somatostatin analogue that inhibits the secretion of several endocrine, exocrine and paracrine functions. It has been shown to be effective in inhibiting the secretion of GH and certain hormones secreted by the digestive system. Somatuline<sup>®</sup> is marketed as Somatuline<sup>®</sup> Depot<sup>®</sup> within the United States and as Somatuline<sup>®</sup> Autogel<sup>®</sup> in other countries where it has marketing authorization.



Somatuline<sup>®</sup> was initially developed and continues to be used for the treatment of acromegaly in many countries, including the United States, where it is indicated for the long-term treatment of patients with acromegaly who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy. Somatuline<sup>®</sup> is not indicated for its antiproliferative effect on GEP-NETs. Somatuline<sup>®</sup> is approved for the treatment of symptoms associated with neuroendocrine tumors in many markets, but is not approved within the United States for this indication.

### **About Ipsen**

Ipsen is a global specialty-driven pharmaceutical company with total sales exceeding €1.2 billion in 2012. Ipsen's ambition is to become a leader in specialty healthcare solutions for targeted debilitating diseases. Its development strategy is supported by 3 franchises: neurology, endocrinology and uro-oncology. Moreover, the Group has an active policy of partnerships. Ipsen's R&D is focused on its innovative and differentiated technological platforms, peptides and toxins. In 2012, R&D expenditure totalled close to €250 million, representing more than 20% of Group sales. The Group has close to 4,900 employees worldwide. Ipsen's shares are traded on segment A of Euronext Paris (stock code: IPN, ISIN code: FR0010259150) and eligible to the "Service de Règlement Différé" ("SRD"). The Group is part of the SBF 120 index. Ipsen has implemented a Sponsored Level I American Depositary Receipt (ADR) program, which trade on the over-the-counter market in the United States under the symbol IPSEY. For more information on Ipsen, visit [www.ipsen.com](http://www.ipsen.com).

### **Forward Looking Statements**

The forward-looking statements, objectives and targets contained herein are based on the Group's management strategy, current views and assumptions. Such statements involve known and unknown risks and uncertainties that may cause actual results, performance or events to differ materially from those anticipated herein. All of the above risks could affect the Group's future ability to achieve its financial targets, which were set assuming reasonable macroeconomic conditions based on the information available today. Use of the words "believes," "anticipates" and "expects" and similar expressions are intended to identify forward-looking statements, including the Group's expectations regarding future events, including regulatory filings and determinations. Moreover, the targets described in this document were prepared without taking into account external growth assumptions and potential future acquisitions, which may alter these parameters. These objectives are based on data and assumptions regarded as reasonable by the Group. These targets depend on conditions or facts likely to happen in the future, and not exclusively on historical data. Actual results may depart significantly from these targets given the occurrence of certain risks and uncertainties, notably the fact that a promising product in early development phase or clinical trial may end up never being launched on the market or reaching its commercial targets, notably for regulatory or competition reasons. The Group must face or might face competition from generic products that might translate into a loss of market share. Furthermore, the Research and Development process involves several stages each of which involves the substantial risk that the Group may fail to achieve its objectives and be forced to abandon its efforts with regards to a product in which it has invested significant sums. Therefore, the Group cannot be certain that favourable results obtained during pre-clinical trials will be confirmed subsequently during clinical trials, or that the results of clinical trials will be sufficient to demonstrate the safe and effective nature of the product concerned. There can be no guarantees a product will receive the necessary regulatory approvals or that the product will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements. Other risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the Group's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the Group's patents and other protections for innovative products; and the exposure to



litigation, including patent litigation, and/or regulatory actions. The Group also depends on third parties to develop and market some of its products which could potentially generate substantial royalties; these partners could behave in such ways which could cause damage to the Group's activities and financial results. The Group cannot be certain that its partners will fulfil their obligations. It might be unable to obtain any benefit from those agreements. A default by any of the Group's partners could generate lower revenues than expected. Such situations could have a negative impact on the Group's business, financial position or performance. The Group expressly disclaims any obligation or undertaking to update or revise any forward looking statements, targets or estimates contained in this press release to reflect any change in events, conditions, assumptions or circumstances on which any such statements are based, unless so required by applicable law. The Group's business is subject to the risk factors outlined in its registration documents filed with the French Autorité des Marchés Financiers.

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