Press release

Ipsen establishes optimal biological dose for BN83495 steroid sulphatase (STS) inhibitor in ER-positive metastatic breast cancer

Preliminary results of on-going Ipsen-sponsored phase I in ER-positive metastatic breast cancer trial presented at the 32nd San Antonio Breast Cancer Symposium (SABCS)

Paris (France), 14 December 2009 - Ipsen (Euronext: FR0010259150; IPN) today announced the preliminary results of a phase I trial in metastatic breast cancer with BN83495, Ipsen's lead and first-in-class orally available irreversible steroid sulfatase (STS) inhibitor. In the course of the study, the optimal biological dose was determined as 40 mg once daily oral administration for future phase II trials in this indication.

Preliminary results were the subject of a poster (#4097) entitled "A Phase I Dose Escalation Study of Steroid Sulfastase Inhibitor BN83495 (STX64) in Postmenopausal Women with ER-Positive Breast Cancer" presented at the 32nd San Antonio Breast Cancer Symposium held from December 9 to December 13, 2009, in San Antonio (Texas, USA).

The compound is currently in further clinical development for advanced endometrial cancer (phase II) as well as in Phase I clinical evaluation for castrate resistant prostate cancer in North America.

Professor R. Charles Coombes, Imperial College, Clinical Professor, Division of Surgery, Oncology, Reproductive Biology and Anaesthetics London, UK, lead author of the poster said: *"To date, four of the patients who received BN83495 had tumours that remained stable for at least 6 months. One of these had cutaneous metastases that improved after one month of treatment. This is very encouraging, as these women are patients who are reaching the end of their hormonal treatment options. Importantly, BN83495 was well tolerated at the selected dose."* He added: *"I am confident that BN83495 will become a new hormonal option in the treatment of post-menopausal women with ER-positive metastatic breast cancer".*

Stéphane Thiroloix, Executive Vice-President, Corporate Development commented: "*Metastatic breast cancer clearly deserves R&D effort to identify new hormonal agents that can delay disease progression and prolong overall survival. Following this important clinical milestone, we look forward to progressing the global development of BN83495 in this indication and in other selected hormone-dependent cancer indications.* "

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About the study
Thirty-five post-menopausal women with estrogen receptor (ER) positive metastatic breast cancer, having already received one or two different types of hormonal therapy for their disease, were treated with increasing doses of BN83495 given orally once daily.

Key findings are:

- The primary endpoint of determining the optimal biological dose (OBD) was met. It was established as being once daily oral 40 mg. This dose will be used for future phase II trials in this indication.
- An almost complete (95%) inhibition of the target enzyme (STS) was achieved in peripheral blood mononuclear cells at the 40 mg dose level. Thus, it resulted in a decrease of circulating steroid hormones.
- BN83495 was well-tolerated with no Grade 3 or higher toxicity observed during the first 28 days of treatment.
- Four patients in the three higher dose groups had stable disease > 6 months (according to RECIST criteria)

The trial presented at SABCS is ongoing and is being conducted in five centres in France, Belgium and the UK. 15 additional patients are being enrolled to evaluate metabolic anti-tumour activity.

About BN83495
Ipsen's lead oncology development candidate, BN83495, is a first-in-class orally available irreversible steroid sulfatase (STS) inhibitor. The steroid sulfatase pathway gives rise to oestrone and dehydroepiandrosterone (DHEA) that in turn produce oestradiol and androstenediol (Adiol) that can both stimulate the growth of hormone-dependent tumours.

About Metastatic Breast Cancer
Breast cancer is the second most common form of cancer and the second leading cause of cancer death among American women. In 2009 in the USA, according to the American Cancer Society, an estimated 192,000 women will be diagnosed with breast cancer and approximately 40,000 will die from the disease. Approximately 75 percent of women with newly diagnosed metastatic breast cancer are ER+.

About SABCS
The SABCS is one of the largest annual symposium in the world devoted to breast cancer research and physician education. The symposium provides an important venue for cancer experts to review the latest information on the experimental biology, etiology, prevention, diagnosis and therapy of breast cancer and premalignant disease.

About Ipsen
Ipsen is an innovation-driven global specialty pharmaceutical group with over 20 products on the market and a total worldwide staff of nearly 4,200. Its development strategy is based on a combination of specialty medicine, which is Ipsen's growth driver, in targeted therapeutic areas (oncology, endocrinology, neurology and haematology), and primary care products which contribute significantly to its research financing. The location of its four Research & Development centres (Paris, Boston, Barcelona, London) and its peptide and protein engineering platform give the Group a competitive edge in gaining access to leading university research teams and highly qualified personnel. More than 800 people in R&D are dedicated to the discovery and development of innovative drugs for patient care. This strategy is also supported by an active policy of partnerships. In 2008, Research and Development expenditure was

about €183 million, close to 19% of consolidated sales, which amounted to €971 million while total revenues exceeded €1 billion. Ipsen's shares are traded on Segment A of Euronext Paris (stock code: IPN, ISIN code: FR0010259150). Ipsen's shares are eligible to the "Service de Règlement Différé" ("SRD") and the Group is part of the SBF 120 index. For more information on Ipsen, visit our website at www.ipsen.com.

Ipsen Forward Looking Statement

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. 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. Notably, future currency fluctuations may negatively impact the profitability of the Group and its ability to reach its objectives. Actual results may depart significantly from these targets given the occurrence of certain risks and uncertainties. The Group does not commit nor gives any guarantee that it will meet the targets mentioned above. Furthermore, the Research and Development process involves several stages each of which involve 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. 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 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.

For further information:

Ipsen
Media
Didier Véron
Director, Public Affairs and Corporate Communications
Tel.: +33 (0)1 58 33 51 16
Fax: +33 (0)1 58 33 50 58
E-mail: didier.veron@ipsen.com

Financial Community
David Schilansky
Investor Relations and Financial Officer
Tel.: +33 (0)1 58 33 51 30
Fax: +33 (0)1 58 33 50 63
E-mail: david.schilansky@ipsen.com

Pierre Kemula
Investor Relations Manager
Tel.: +33 (0)1 58 33 60 08
Fax: +33 (0)1 58 33 50 63
E-mail: pierre.kemula@ipsen.com

Press release

9th *Colloque Médecine et Recherche* of *la Fondation Ipsen* in the series Endocrinology: "Novel insights in adipose cell functions"

Discovery of a new type of fat cell in humans with potential impact in obesity, diabetes, stroke, kidney failure and cancer

Obesity is a problem with pressing medical, public health and social implications on a global scale

Paris (France), 14 December 2009 - The ninth *Colloque Médecine et Recherche* of *la Fondation Ipsen* devoted to Endocrinology, held in Paris on December 4, 2009, has reviewed the recent progress in understanding the regulation of fat storage in the body and the consequences of the breakdown of this regulation. Among these breakdowns of regulation are insulin resistance leading to type-2 diabetes; cardio-vascular disease and stroke, kidney failure and cancer. The meeting has been organised by Karine Clément (*Institut des Cordeliers, Paris, France*), Bruce Spiegelman (*Harvard Medical School, Boston, USA*) and Yves Christen (*la Fondation Ipsen, Paris, France*) and thirteen leading scientists have presented their latest research

The many forms of adipocyte regulation that were discussed at this meeting hold out promise for developing therapeutic interventions, some sooner than others. All the speakers discussed the potential applications of their work and the questions that need answering to make such interventions a reality.

Fatty tissue, distributed throughout the body, was for many years considered as a passive store for fat. This perception began to change with the discovery in 1994 that fat cells, or adipocytes, secrete a hormone, leptin, which is involved in the control of food intake and a variety of other regulatory functions throughout the body. Now the white adipose tissue (WAT), the main fat-storing tissue, is recognized as a complex organ making a crucial contribution to the control of food intake, energy balance, glucose and lipid metabolism, immunity and reproduction (Philipp Scherer, *University of Texas Southwestern Medical Center, Dallas, USA*). As well as mature adipocytes, the WAT contains adipocyte progenitor cells, macrophages, blood vessels, and other regulatory and protective components (Karine Clément, *Institut des Cordeliers, Paris, France*).

Fat is stored as triglycerides in the adipocytes when energy input to the body exceeds energy output. When energy demands are high, it is mobilized by lipolysis and details of the lipolysis pathways, which break the triglycerides down into fatty acids and glycerol, are now being elucidated (Dominique Langin, *Inserm U858, Université Paul Sabatier, CHU Toulouse, Toulouse, France*). More frequently, the imbalance between energy input and output persists, so that over many years the person becomes first over-weight and then obese. As this happens, the functions of the WAT become profoundly altered, with reduced capacity for fat storage; more macrophages and increased inflammation; oxidative stress; and hypoxia (Karine Clément, *Institut des Cordeliers, Paris, France*; Scherer, *University of Texas Southwestern Medical Center, Dallas, USA*). Consequences of this are the spread of inflammation to other organs and fat being stored in liver and muscles, as well as the

development of insulin resistance, leading to type-2 diabetes (Karine Clément, *Institut des Cordeliers, Paris, France*; David Savage, *University of Cambridge, Cambridge, UK*).

The inflammation in the WAT seems to result from the poor oxygenation of the expanded tissue, which stimulates the production of pro-inflammatory signalling molecules and switches the adipocytes to producing lactate (Paul Trayhurn, *University of Liverpool, Liverpool, and University of Buckingham, Buckingham, UK*). The adipocytes secrete a hypoxia-induced factor that promotes the production of collagen fibres, making the fat body more rigid and limiting its ability to store fat (Philipp Scherer, *University of Texas Southwestern Medical Center, Dallas, USA*). In the stressed adipocytes, the activity of genes associated with metabolic pathways decreases and gene activity associated with inflammatory pathways in the macrophages in the WAT increases (Dominique Langin, *Inserm U858, Université Paul Sabatier, CHU Toulouse, Toulouse, France*).

A further complication to the understanding of WAT functions is that the fat deposits in the different areas of the body do not all function in the same way. Furthermore embryological studies have now demonstrated that the adipocytes in different regions of the body have different embryonic origins (Christian Dani, *Université de Nice Sophia-Antipolis, Nice, France*). In adults, contrary to previous understanding, adipocytes do die and they are replaced at a rate of about 10% per year (Peter Arner, *Karolinska Institute, Huddinge, Sweden*). A pool of adipocyte progenitor cells in adults provides for replacement of outworn cells and allows the WAT to expand as the demand for fat storage increases (Christian Dani, *Université de Nice Sophia-Antipolis, Nice, France*). When weight is lost, fat is lost from the adipocytes but the number of cells remains steady. The turnover rate is set in adolescence, is higher in obese than in lean subjects and is linked to susceptibility to develop insulin resistance and type-2 diabetes (Peter Arner, *Karolinska Institute, Huddinge, Sweden*).

Macrophages resident in the WAT secrete factors that stimulate the adipocyte progenitors to produce activin A, a molecule that promotes their proliferation (Christian Dani, *Université de Nice Sophia-Antipolis, Nice, France*) – another example of the tight regulatory communication between adipocytes and macrophages that changes balance as stored fat increases. Key pathways in the switch between proliferation of adipocyte progenitors and their differentiation into adult adipocytes are being revealed using a whole genome approach (Evan Rosen, *Beth Israel Deaconess Medical Center, Boston, USA*).

One obvious way to restore the energy input – output balance, though one that is often difficult to implement, is to increase energy output. Consequently, there is much excitement about the recent discovery that some human adults have another type of fat, the brown adipose tissue (BAT), which is dedicated to the generation of heat (Sven Enerbäck, *University of Gothenburg, Göteborg, Sweden*). Previously known only in rodents, animals that hibernate and human infants, brown fat cells rapidly take up triglycerides and, through a unique mitochondrial mechanism, convert them to heat rather than the normal synthesis of the energy-rich molecule ATP. Studies on mice are revealing that BAT protects against obesity, insulin resistance and type-2 diabetes (Sven Enerbäck, *University of Gothenburg, Göteborg, Sweden*; Barbara Cannon, *Stockholm University, Stockholm, Sweden*).

A further discovery makes the presence of brown fat not just lucky for those adults who have it: under certain laboratory conditions, white fat cells can be converted to brown. As the therapeutic implications of this potential are clear, the molecular mechanisms and the requisite conditions that promote this conversion are now under intense investigation (Dominique Langin, *Inserm U858, Université Paul Sabatier, CHU Toulouse, Toulouse, France*; Christian Dani, *Université de Nice Sophia-Antipolis, Nice, France*; Bruce Spiegelman, *Harvard Medical School, Boston, USA*; Stephen Farmer, *Boston University School of Medicine, Boston, USA*).

Regulation of body weight concerns not only the WAT: the brain is also involved. This level of regulation turns out to be quite subtle, with the hypothalamic and higher brain circuits protecting more against weight loss than against weight gain (Rudolph Leibel, *Columbia University, New York, USA*). As well as making evolutionary sense, here is a mechanism that supports common experience that it is far easier to gain weight than to lose it! Understanding this complex neural and hormonal regulation may well point to ways to shift the balance towards weight loss. Genetics of course also plays a part and studies of single-gene mutations that affect the functioning of the WAT are helping to dissect the molecular pathways underlying insulin resistance (David Savage, *University of Cambridge, Cambridge, UK*).

La Fondation Ipsen

Established in 1983 under the aegis of the *Fondation de France*, the mission of *la Fondation Ipsen* is to contribute to the development and dissemination of scientific knowledge. The long-standing action of *la Fondation Ipsen* is aimed at furthering the interaction between researchers and clinical practitioners, which is indispensable due to the extreme specialisation of these professions. The ambition of *la Fondation Ipsen* is not to offer definitive knowledge, but to initiate a reflection about the major scientific issues of the forthcoming years. It has developed an important international network of scientific experts who meet regularly at meetings known as *Colloques Médecine et Recherche*, dedicated to six main themes: Alzheimer's disease, neurosciences, longevity, endocrinology, the vascular system and cancer science. In 2007, *la Fondation Ipsen* started three new series of meetings. The first is in partnership with the Salk Institute and *Nature* and is an annual meeting which focuses on aspects of Biological Complexity; the second is the "Emergence and Convergence" series with *Nature*, and the third is with *Cell* and the Massachusetts General Hospital entitled "Exciting Biologies". Since its beginning, *la Fondation Ipsen* has organised more than 100 international conferences, published 69 volumes with renowned publishers and more than 205 issues of a widely distributed newsletter *Alzheimer Actualités*. It has also awarded more than 100 prizes and grants.

For further information, please contact:
Brunswick Group
Robin Gilliland
Telephone: +1- 212 333 3810
Email: rgilliland@brunswickgroup.com

Justine McIlroy
Telephone: + 44 (0)207 396 3536
Fax: + 44 (0) 207 936 7836
Email: jmcilroy@brunswickgroup.com