PRESS RELEASE

Ipsen announces positive results from Phase IIIb/IV ENGAGE study of the combination of Dysport® (abobotulinumtoxinA) with Guided Self-rehabilitation Contracts in adult patients with upper and lower limb spastic hemiparesis[1,2,3,4]

Results presented at the International Congress of Parkinson's Disease and Movement Disorders (MDS) in Nice, France, 22-26 September 2019

Paris (France), 23 September 2019 – Ipsen (Euronext: IPN; ADR: IPSEY) today announced first results from the ENGAGE study which reports that simultaneous treatment with Dysport of both upper and lower limb spasticity in adult patients along with a Guided Self-rehabilitation Contract (GSC) – a personalized diary-based rehabilitation program – improved patients' voluntary movement as measured by a composite active range of motion (CX_A) outcome.[1] Results from the study will be presented at the MDS International Congress in Nice, France, September 22-26, 2019 as poster #1370[5] and poster #1371[1].

ENGAGE is the first study to investigate treatment with Dysport in patients with spastic hemiparesis in both upper and lower limbs in combination with GSC. The primary efficacy endpoint of this international, prospective, single-arm study was the percentage of patients classified as responders at week six after the second injection, according to the CX_A in the primary treatment target (PTT) limb.[1]

Professor Jean-Michel Gracies, Professor and Chair in the Department of Neurorehabilitation at Hospital Henri Mondor, in Créteil, France, and the primary investigator for ENGAGE said: "This study provides insight into treatment strategies that can improve the outcomes of patients living with spastic paresis, specifically the role of Guided Self-rehabilitation Contracts combined with Dysport for the improvement of voluntary movement, an area of limited data availability. Importantly, stronger active motion improvements and a longer time to reinjection was seen in ENGAGE versus previous Dysport studies, which suggests a synergistic effect of adding a GSC intervention to treatment with Dysport for patients with UL and LL spasticity."

Patients in the study received two open-label injection cycles of Dysport, together with personalized GSC. A total dose of 1,500 U Dysport was administered across the primary treatment target (PTT) and non-PTT limbs at each injection cycle. Dosing was determined by the investigators, providing ≥750 U was administered to the PTT limb. Results from the study show that 72.1% (98/136; 95% CI: 64.0, 78.9) of patients in the study were classified as responders, achieving the predefined CX_A improvement threshold in the PTT limb of ≥35° in upper limbs (UL) or ≥5° in the lower limbs (LL).[1] These favorable outcomes were corroborated by the time to reinjection. Investigators could re-inject Dysport per their clinical judgment.

Mean time to reinjection was 110.1 days (standard deviation: 25.2 days) and median time to reinjection was 106.5 days (range: 78–157 days).[1] The time to reinjection recorded in ENGAGE was longer compared with previous studies in UL and LL which did not include GSC.[1,2,3,4] Safety data were consistent with the known profile of abobotulinumtoxinA.[1]

Systemic standardized rehabilitation protocols are not commonly used in the majority of abobotulinumtoxinA spasticity studies. Similarly, pivotal studies of Dysport in these patients have focused on either UL or LL treatment strategies and outcomes;[2,3] however, in real-life clinical practice patients can present with spasticity simultaneously in both the UL and LL.

Importantly, and in contrast to previous pivotal studies of Dysport, ENGAGE also provided insight into healthcare professionals' real-world muscle selection for the administration of Dysport as it allowed investigators the flexibility of choosing varied muscle groups in the primary target limb. Prior pivotal/phase 3 adult UL and LL studies have all previously defined the target muscle group as elbow, wrist or finger flexors (UL) and gastrocnemius complex (LL) for primary endpoint.[2,3]

In ENGAGE, each patient received a personalized GSC tailored to their individual needs and focused on their PTT limb.[1] Patients were asked to carry out the exercises detailed in the GSC – with a minimum cumulative 10 minutes of submaximal self-stretch postures per muscle – on a daily basis throughout the study. Patients kept a diary of each of the exercises performed and were contacted via telephone every two weeks to check how the GSC therapy was being performed and to ensure the diary was being filled out every day.

Antony Fulford-Smith, Vice President Medical Affairs, Neurosciences, R&D, at Ipsen said: "Over the last two decades there has been a shift from patients being recipients of healthcare to active participants empowered in their own health journey. Through ENGAGE, we have been able to demonstrate for the first time the benefit of combining treatment with Dysport with a systematic rehabilitation protocol, validating the positive impact of encouraging patients to take an active role in their own treatment. At Ipsen, we are constantly searching for ways to improve disease management and comprehensive care with a patient-centred approach. By using active range of motion as its primary measure, ENGAGE offers important insights on the potential benefit of using Dysport with GSC combination therapy in the context of meaningful functional outcomes for patients."

About ENGAGE[1]

ENGAGE is a Phase IIIb/IV (depending on country) international, prospective, single-arm study designed to assess the influence of abobotulinumtoxinA (1500 U) administered with GSC on voluntary movements in the UL and LL in adults with spastic hemiparesis.

A total of 160 patients from the Czech Republic, France, the Russian Federation and the USA were enrolled in the study; the majority of patients in the study were male and stroke was the leading cause of acquired brain injury (ABI).

Patients received 2 open-label injection cycles of aboBoNT-A, together with personalized GSC. Cycles were 12–20 weeks apart (maximum study duration of 40 weeks). Recruitment was stratified by country to ensure a 50% (±10%) split of patients with UL or LL as PTT. A total dose of 1,500 U aboBoNT-A was administered across PTT and non-PTT limbs at each injection cycle. Dosing was determined by the investigators, providing ≥750 U was administered to the PTT limb.

The primary efficacy endpoint was the percentage of patients classified as responders at Week 6 after the second injection, according to the CX_A, measured by goniometer, in the PTT limb. Response was defined as an improvement in composite active range of motion (CX_A) of ≥35° or 5° in UL or LL, respectively. CX_A of the UL was

calculated as the sum of XA values for elbow flexors, wrist flexors and extrinsic finger flexors. CX_A of the LL was calculated as the sum of XA values for the soleus and gastrocnemius muscles.

In the intention-to-treat (ITT) population, overall median (95% CI) time to first response was 47.0 days (44.0, 62.0), with a median (95% CI) time to first response in the upper limb (UL) of 54.5 days (44.0, 89.0), and 46.0 days (43.0, 50.0) in the lower limb (LL). Overall responder rates were 62.0% (95% CI: 50.3, 72.4) in the UL and 83.1% (95% CI: 72.0, 90.5) in the LL in the modified ITT population. Responder rates were higher in patients who were naïve to BoNT for spasticity (78.4%; 95% CI: 62.6, 88.9; N=37) compared with those who were non-naïve (69.7%; 95% CI: 60.0, 77.9; N=99). Patients who were naïve to GSC had a lower response rate (68.7%; 95% CI: 59.0, 77.0; N=99) compared with those who were non-naïve to GSC (80.6%; 95% CI: 64.7, 90.6; N=36).

About spasticity
Spasticity affects more than an estimated 12 million people worldwide.[6] It is a condition in which certain muscles are continuously contracted causing stiffness or tightness of the muscles which can interfere with normal movement, speech and gait.[6] Spasticity is usually caused by damage to the portion of the brain or spinal cord that controls voluntary movement. The damage causes a change in the balance of signals between the nervous system and the muscles which leads to increased activity in the muscles.[6] There are many causes of spasticity including spinal cord injury, multiple sclerosis, cerebral palsy, stroke, brain or head trauma and metabolic diseases.[7] Spasticity, is experienced by 34% of stroke survivors within 18 months following a stroke.[8]

About Dysport®
Dysport® is an injectable form of a botulinum neurotoxin type A product, which is a substance derived from Clostridium bacteria producing BoNT-A that inhibits the effective transmission of nerve impulses and thereby reduces muscular contractions[9]. It is supplied as a lyophilized powder. As of 31 December 2018, Dysport® had marketing authorization in more than 85 countries and more than 30 years of clinical experience[10].
NOTE: Dysport® labels and approved indications may vary from country to country

INDICATIONS AND IMPORTANT SAFETY INFORMATION
Dysport® is approved for the treatment of adult upper and lower limb spasticity, paediatric lower limb spasticity and cervical dystonia (referred to spasmodic torticollis in some markets) in many international markets. Please refer to national labelling for details of the locally approved prescribing information in each of these indications.

Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been reported. Patients treated with therapeutic doses may present with excessive muscle weakness. The risk of occurrence of such undesirable effects may be reduced by using the lowest effective dose possible and by not exceeding the maximum recommended dose. Very rare cases of death, occasionally in the context of dysphagia, pneumopathy (including but not limited to dyspnoea, respiratory failure, respiratory arrest) and/or in patients with significant asthenia have been reported following treatment with botulinum toxin A or B. Patients with disorders resulting in defective neuromuscular transmission, difficulty in swallowing or breathing are more at risk of experiencing these effects. In these patients, treatment must be administered under the control of a specialist and only if the benefit of treatment outweighs the risk. Dysport® should be administered with caution to patients with pre-existing swallowing or breathing problems as these can worsen following the distribution of the effect of toxin into the relevant muscles. Aspiration has occurred in rare cases and is a risk when treating patients who have a chronic respiratory disorder. Dysport® should only be used with caution and under close medical supervision in patients with clinical or sub-clinical evidence of marked defective neuro-muscular transmission (e.g. myasthenia gravis). Such patients may have an increased sensitivity to agents such as Dysport®, which may result in excessive muscle weakness. Caution should be exercised when treating adult patients, especially the elderly, with focal spasticity affecting the lower limbs, who may be at increased risk of fall. In placebo controlled clinical studies where patients were treated for lower limb spasticity, 6.3% and 3.7% of patients experienced a fall in the Dysport® and placebo groups, respectively. The recommended posology and frequency of administration for Dysport® must not be exceeded. Patients and their care-givers must be warned of the necessity to seek immediate medical treatment in case of problems with swallowing, speech or respiratory problems. For the treatment of spasticity in children, Dysport® should only be used in children 2 years of age or over. As with any intramuscular injection, Dysport® should only be used where strictly necessary in patients with prolonged bleeding times, or infection/inflammation at the proposed site(s) of injection. Dysport® should only be used to treat a single patient, during a single session. Any unused product remaining should be disposed of in accordance with Special Precautions for Disposal and Handling. Specific precautions must be taken during the preparation and administration of the product and the inactivation and disposal of any unused reconstituted solution. This product contains a small amount of human albumin. The risk of transmission of viral infection cannot be excluded with absolute certainty following the use of human blood or blood products."

For full prescribing information, see SmPC for Dysport (300 units) Powder and Dysport (500 units) Powder.

About Ipsen

Ipsen is a global specialty-driven biopharmaceutical group focused on innovation and specialty care. The group develops and commercializes innovative medicines in three key therapeutic areas – Oncology, Neuroscience and Rare Diseases. Its commitment to Oncology is exemplified through its growing portfolio of key therapies for prostate cancer, neuroendocrine tumors, renal cell carcinoma and pancreatic cancer. Ipsen also has a well-established Consumer Healthcare business. With total sales over €2.2 billion in 2018, Ipsen sells more than 20 drugs in over 115 countries, with a direct commercial presence in more than 30 countries. Ipsen's R&D is focused on its innovative and differentiated technological platforms located in the heart of the leading biotechnological and life sciences hubs (Paris-Saclay, France; Oxford, UK; Cambridge, US). The Group has about 5,700 employees worldwide. Ipsen is listed in Paris (Euronext: IPN) and in the United States through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information on Ipsen, visit www.ipsen.com.

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. 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 favorable 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. The risks and uncertainties set out are not exhaustive and the reader is advised to refer to the Group's 2018 Registration Document available on its website (www.ipsen.com).

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