

## ***Positive Phase II preliminary results of Validive®***

### ***For the prevention of Severe Oral Mucositis in Head and Neck cancer patients***

- ***Significant reduction of incidence of severe mucositis***
- ***Improved oral mucositis related symptoms and decreased adverse events related to radiotherapy***
- ***Good Safety profile***
- ***Strong Compliance to treatment***

### ***Trial Advisory Board validated data as supportive to enter into Phase III trial***

**Paris (France), Copenhagen (Denmark), October 30, 2014** – Onxeo S.A. (Euronext Paris, NASDAQ OMX Copenhagen: ONXEO), an innovative biopharmaceutical company specializing in the development of orphan oncology drugs, today announced positive preliminary top-line results from its Phase II clinical trial of Validive® (mucoadhesive buccal tablet MBT clonidine Lauriad®) for prevention of severe oral mucositis (OM).

Oral mucositis is a radio/chemotherapy related condition occurring very frequently in patients undergoing head and neck cancer treatment. Based on the well-established WHO scale, OM is considered as “non severe” for grades 0 to 2, based on level of pain and burden for the patients. From grade 3 to 4, OM is rated severe, based on symptoms such as pain and mouth dryness which prevents patients from drinking and eating and induces increased hospitalization and treatment breaks. With no curative or preventive treatment currently, OM represents a serious unmet medical need for the patients.

Onxeo has performed a large international randomized, double-blind, placebo-controlled Phase II trial comparing the efficacy and safety of Validive® 50 µg and 100 µg applied once daily to those of placebo in the prevention and treatment of chemoradiation therapy-induced severe oral mucositis in 183 patients with head and neck cancer.

All patients received a postoperative radiochemotherapy with a mean cumulative dose of 61 Gray in combination with cisplatin-based chemotherapy in most of the cases. Endpoints were to compare the incidence, severity, time to onset and duration of severe OM as well as use of opioids and other adverse events related to cancer radiation treatment between the Validive® pooled groups and placebo. They were evaluated twice a week during the whole radiotherapy treatment.

The key results of the Phase II study showed:

- Significant decrease in the incidence of severe oral mucositis (grades 3 and 4) in the Validive® pooled arms versus placebo. Overall incidence of severe OM was 45% in the Validive® groups, with a maximum absolute decrease of 16% compared to placebo.
- Occurrence of severe OM has been delayed in the Validive® groups compared to placebo.

- . Higher doses of radiation have been received by the Validive® treated patients before severe OM occurred.
- . Improvement of critical conditions related to severe oral mucositis and radiation therapy, especially dysphagia, nausea and vomiting in both Validive® groups.
- . No significant difference in efficacy observed between Validive® 50 µg and 100 µg groups.
- . In terms of safety, Validive® showed a good safety profile with no major difference in the nature, incidence and severity of adverse events in the placebo and the Validive® groups.

At last, patient's compliance was very high, with more than 80% of patients applying Validive® or placebo tablets on the gum every day during radiation therapy as requested in the trial.

The trial Advisory Board gathering Pr Michael Henke (Freiburg Germany), Pr René-Jean Bensadoun (Poitiers, France) and Pr Jordi Giralt (Barcelona, Spain), trial's coordinators, and Pr Steve Sonis, all international experts in oral mucositis, met to analyze and validate the main preliminary results.

Based on these preliminary data the Board has recommended pursuing the development of Validive® with the initiation of a Phase III trial in the same patient population. The company plans to initiate this trial in 2015.

Validive® was granted a fast track designation by the FDA in January 2014, allowing facilitated interactions with the FDA and optimized development time and review period for drugs investigated as treatments for serious or life-threatening diseases with a high unmet medical need. Moreover, Validive® enjoys the orphan status in Europe, enabling optimization of the product's development plan in terms of cost and duration, as well as strengthening its protection (market exclusivity).

*"All investigators in the study were looking forward these positive preliminary results which confirm the interest of Validive® as a highly promising treatment to tackle a devastating inflammation in heavily stressed patients, with virtually no side effects ", comments Judith Greciet, CEO of Onxeo. "With these promising positive Phase II results for Validive® and the product ready to enter Phase III, Onxeo now has a second program reaching the last stage of development, ahead of registration. This is a crucial step that significantly reinforces Validive®'s value and makes of this strong asset a success for Onxeo. I take the opportunity of this great achievement to thank everybody, investigators, clinical and non-clinical experts as well as our internal teams for their help and strong support in the development of Validive®".*

#### **About Severe Oral Mucositis**

Severe oral mucositis is a particularly invalidating pathology occurring in more than 60% of patients treated with radio/chemotherapy for head and neck cancer and has currently no validated curative or preventive treatment. It may induce intense oral pain and eating disability requiring enteral or parenteral nutritional support. Thirty percent of patients need to be hospitalized as a result and symptoms can force patients to stop treatment for an undefined period thus reducing treatment efficacy.

Validive® is a therapeutic application of clonidine based on the mucoadhesive technology Lauriad®.

Clonidine stimulates the alpha-2 adrenergic receptors traditionally used to treat high blood pressure. It stimulates these receptors in the brain. This leads to a decrease in peripheral resistance and thus a lowering of blood pressure, as well as a reduction in heart rate and renal vascular resistance.

However, clonidine also acts as an agonist of the alpha-2 adrenergic receptors on leucocytes and macrophages, thereby decreasing the expression of the pro-inflammatory genes and the release of cytokines IL6, IL1β and TNFα. This effect leads to a reduction in the pro-inflammatory mechanisms. It also acts on the anti-inflammatory mechanisms by increasing the release of TGF β.

Clonidine therefore has the following properties:

- Painkilling properties due to changes in the inflammatory response and its direct action on nociceptors;
- Anti-inflammatory properties due to its action on the expression of the pro-inflammatory genes and the resulting release of cytokines IL6, IL1  $\beta$  and TNF $\alpha$  and due to the release of TGF  $\beta$ .

#### **About Onxeo**

Onxeo has the vision to become a global leader and pioneer in oncology, with a focus on orphan or rare cancers, through developing innovative therapeutic alternatives to “make the difference”. The Onxeo teams are determined to develop innovative medicines to provide patients with hope and significantly improve their lives.

#### **Key products at advanced development stage are:**

Livatag<sup>®</sup> (Doxorubicin Transdrug<sup>™</sup>): Phase III in hepatocellular carcinoma

Validive<sup>®</sup> (Clonidine Lauriad<sup>®</sup>): Phase II in severe oral mucositis

Beleodaq<sup>®</sup> (belinostat): Registered and available in the USA for peripheral T-cell lymphoma

For more information, visit the website [www.onxeo.com](http://www.onxeo.com)

#### **Disclaimer**

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