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Results of Phase II/III Study of ONO-2745/CNS 7056, a Short-acting General Anesthetic

Ono Pharmaceutical Co., Ltd. (Osaka, Japan, President and Representative Director: Gyo

Sagara; "Ono") announced today that it has completed a phase II/III clinical study of ONO-

2745/CNS 7056 (development code), which has been developed by PAION (formerly CeNeS,

Germany) and now its development in Japan is promoted by ONO for general anesthesia. The

outline of the study results are shown below.

This study was conducted in Japan as a multi-centre randomized parallel-group study with

propofol as a control in surgery patients undergoing general anesthesia in combination with

analgesics. ONO-2745/CNS 7056 and propofol were intravenously administered to 375 patients

(2 groups with induction speed at 6 mg/kg/h and 12 mg/kg/h, 150 subjects per group (ONO-

2745/CNS 7056) and 75 patients (propofol), respectively), with the purpose of induction and

maintenance of general anesthesia.

All 375 patients analyzed among the patients who received ONO-2745/CNS 7056 or propofol

achieved loss of consciousness and underwent successful intubation. The effectiveness rate of

function as a general anesthetic as a primary endpoint (it consisted of no intraoperative

awakening/memory, no rescue therapy for sedative effect and no body motion) were 100% in all

groups. Typically for an anesthesia study the study was designed as non-inferiority vs. propofol..

No adverse events of concern were observed. The incident rates of adverse events were 84.7%,

80.7% and 84.0% in 6 mg/kg/h and 12 mg/kg/h of ONO-2745/CNS 7056 and propofol groups,

respectively. Common adverse events include blood pressure decreased, primarily wound

complication, laboratory test abnormal, nausea/vomiting and injection site pain (observed only in

propofol group) ,etc. which correspond with relatively common events typically observed in

perioperative patients. The incident rates of blood pressure decreased were 35.3%, 34.7% and

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60.0% in 6 mg/kg/h and 12 mg/kg/h of ONO-2745/CNS 7056 and propofol groups, respectively, which suggests that the incident rate of blood pressure decreased was significantly lower in each ONO-2745/CNS 7056 groups than propofol group.

The evaluations of the pharmacokinetic parameters have not been completed. Whether these will have an influence on the future development plan can only be assessed when these evaluations have been completed.

ONO entered into a license agreement with PAION (formerly CeNeS) in August 2007, acquiring the exclusive right to develop and market ONO-2754/CNS 7056 in Japan.

## <References>

## About ONO-2745/CNS 7056

ONO-2745/CNS 7056 is an innovative short-acting benzodiazepine derivative, which binds to the benzodiazepine binding site of the GABA<sub>A</sub> receptors\*, enhancing binding of GABA to its binding site to increase function of GABA receptors, which leads to the onset of sedative effects. The results of preclinical studies showed that intravenous infusion of ONO-2745/CNS 7056 led to instant sedation, and its continuous infusion provided stable drug effects. Since it is rapidly metabolized by tissue esterase enzymes, resulting in rapid reversal of sedation after completion of treatment, ONO-2745/CNS 7056 is expected to have clinical applications for induction and maintenance of general anesthesia. It also has potential as a sedative during diagnostic procedures.

## \*GABA<sub>A</sub> receptor

GABA (gamma aminobutyric acid) is a kind of amino acid functioning as a neurotransmitter in the brain. GABA binds to GABA receptors in the cerebral cortex, cerebellum, hippocampus, and brainstem to exert sedative, hypnotic, anxiolytic, and anticonvulsant effects, inhibiting neural activity. There have been known 3 kinds of GABA receptors, GABA<sub>A</sub> GABA<sub>B</sub>, GABA<sub>C</sub> receptors. The GABA<sub>A</sub> receptor has GABA and benzodiazepine binding sites.

## About PAION (PAION AG)

PAION is headquartered in Aachen, Germany and has a second site in Cambridge, UK. The company is specialised in developing innovative drugs for the hospital-based treatment in indications for which there is a substantial unmet medical need. PAION is extending its "Search & Develop" business model, by transforming into a "Specialty Pharma Company", with a focus on anesthesia products.

For more information, please visit the website of PAION (<a href="http://www.paion.com/">http://www.paion.com/</a>).