**Indication** Head and Neck, carcinome épidermoïde, stade localisé avancé

**Title** A Phase I/II randomized study to determine the maximum tolerated dose, safety, pharmacokinetics and antitumor activity of Debio 1143 combined with concurrent Chemo-Radiation Therapy in patients with locally advanced squamous cell carcinoma of the head and neck.

**Protocol ID** Debio 1143-201

**Phase** Phase I/II

**Sponsor** Debiopharm SA

**Local PI** Prof. Jean Bourhis

**Primary Objective**

**Phase I study (dose escalation)**
To determine the maximum tolerated dose (MTD) of Debio 1143 in combination with concurrent CRT in patients with LA-SCCHN.

**Phase II study (randomized, double-blind, placebo-controlled at Recommended Dose)**
To evaluate the anti-tumour activity of Debio 1143 in comparison with placebo when added to standard concurrent CRT in patients with LA-SCCHN

**Inclusion/exclusion criteria**

<table>
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<th>Inclusion Criteria</th>
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<td>1. Willing and able to sign a written informed consent;</td>
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<td>2. Male or female ≥18 ≤75 years of age.</td>
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<td>3. Histologically confirmed diagnosis of previously untreated LA-SCCHN (Stage III, IVa and IVb according to the American Joint Committee on Cancer Staging System) of one or more of the following sites: oral cavity, oropharynx, hypopharynx and larynx;</td>
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<td>4. Tumour HPV negative status for oropharynx cancer patients, determined by p16 IHC;</td>
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<td>5. Positive smoking history (&gt; 10 packs/year);</td>
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<td>6. Availability of pre-treatment tumour sample (optional for Phase I; mandatory for Phase II [10-20 tumour slides]);</td>
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<td>7. Measurable disease by the RECIST 1.1 criteria;</td>
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<td>8. Negative medical history of Hepatitis B and Hepatitis C;</td>
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<td>9. Women of child-bearing potential:</td>
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<td>a. Negative serum pregnancy test at screening;</td>
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<td>b. Agreement to use appropriate contraception methods from study entry to 6 months after the last day of treatment. Agreement to use contraception methods from her male partner.</td>
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<td>10. Male patients agree to use contraception methods from study entry to 6 months after the last day of treatment;</td>
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<td>11. ECOG performance status 0 or 1</td>
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12. Subjects must have adequate haematological, renal and hepatic function;
   a. calculated creatinine clearance ≥ 60 mL/min as determined by the modified method of Cockcroft and Gault or by the EDTA method,
   b. absolute neutrophil count ≥ 1500/μL,
   c. platelets ≥ 100 000/μL,
   d. haemoglobin ≥ 10 g/dL,
   e. aspartate (AST) and alanine transaminase (ALT) less than 3 times the upper limit of the normal range (ULN),
   f. total bilirubin ≤ 2.0 mg/dL,
   g. serum albumin > 35 g/L.

13. QTcF interval ≤ 450 ms

14. Left ventricular ejection fraction (LVEF) within the institutional normal ranges as measured by echocardiogram (ECHO) or multigated acquisition (MUGA) scan;

15. No prior treatment with IAP inhibitors.

16. No use or requirement for use of aspirin or aspirin containing products with > 100 mg of aspirin per day;

17. No history of gastrointestinal bleeding within 1 year;

18. No active rheumatoid arthritis, active inflammatory bowel disease, chronic infections, or any other disease or condition associated with chronic inflammation.

**Exclusion Criteria**

1. Nasopharyngeal, paranasal sinuses, nasal cavity tumours or thyroid cancers;

2. Squamous cell cancer involving cervical neck nodes but from unknown primary site;

3. Metastatic disease;

4. Any prior or current treatment for invasive head and neck cancer of any kind. This will include but is not limited to: prior tyrosine kinase inhibitors, prior neoadjuvant therapy, prior surgical resection, or use of any investigational agent;

5. Weight loss of >10% during the last month;

6. Not compensated liver cirrhosis (Child-Pugh class C);

7. Gastro-intestinal disorders that could affect drug absorption (including, but not limited to, major abdominal surgery, significant bowel obstruction, ulcerative colitis, Crohn’s disease);

8. Impaired bone turnover (serum C-terminal telopeptide [CTX] <300 pg/mL);

9. Concurrent treatment with any other systemic anti-cancer therapy that is not specified as part of the protocol regimen;

10. Concomitant treatment with any drug on the prohibited medication list.
(provided separately);
11. Subjects with known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure;
12. History of another malignancy within the last 5 years, with the exception of completely resected basal or squamous cell skin cancer, or successfully treated in-situ carcinoma. History of non-invasive lesion or in-situ carcinoma, including in the head and neck region that was successfully treated with surgery, photodynamic or laser, will be permitted;
13. Peripheral neuropathy ≥ grade 2;
14. Clinical hearing loss (to be confirmed by audiogram in doubtful cases);
15. If female, pregnant or lactating;
16. History of allergic reactions to appropriate antiemetics (e.g. 5-HT3 antagonists) to be administered with chemotherapy;
17. The investigator considers the subject unfit for the study as a result of the medical interview, physical examinations, or screening investigations.