1. PROTOCOL SUMMARY

1.1. Synopsis

Study title	A randomized, double-blind placebo-controlled, Phase 3 study of Debio 1143 in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck, suitable for definitive chemoradiotherapy (TrilynX).		
Study number	Debio 1143-SCCHN-301	**Study Phase**	3
Study design	This is a prospective, randomized, double-blind, placebo-controlled, multicenter, 2-arm, parallel-group Phase 3 study comparing the efficacy and safety of Debio 1143 versus matched placebo, when administered in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy (IMRT) in previously untreated patients with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN), suitable for definitive chemoradiotherapy (CRT) (stage III, IVA, IVB; hypopharynx, larynx and/or human papillomavirus [HPV]-negative oropharyngeal cancer [OPC]). Upon confirmation of eligibility, subjects will be enrolled and randomized using dynamic allocation in a 1:1 ratio to: **Arm A:** 3 cycles of Debio 1143 (200 mg/day from Day 1 to 14, per cycle) + IMRT (35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/7, up to 70 Gy to the gross tumor volume) + high-dose cisplatin (100mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of Debio 1143 (200 mg/day from Day 1 to 14, per cycle). or **Arm B:** 3 cycles of placebo (Day 1 to 14, per cycle) + IMRT (35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/7, up to 70 Gy to the gross tumor volume) + high-dose cisplatin (100mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of placebo (from Day 1 to 14, per cycle). One cycle is composed of 3 weeks. The following stratification factors will be considered for randomization: Region (North America vs Western Europe vs Rest of the world), Primary tumor site (larynx vs other), Lymph node involvement (N0-1 vs N2 vs N3), T size (T4 vs other). Study diagram and flow are provided in Section 1.2.		
Study objectives and endpoints	Primary, secondary and exploratory objectives with associated endpoints are presented in the table below. **Synopsis Table 1 - Objectives and endpoints**		

Objectives	**Endpoints**
Primary	
To demonstrate superior efficacy of Debio 1143 vs placebo when added to CRT in LA-SCCHN.	Event-Free Survival (EFS) as assessed by the Blinded Independent Review Committee (BIRC) defined as the time from randomization to the first occurrence of any of the following events: • Death from any cause. • Progression: o Radiological, assessed per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. or

	○ Clinical, with or without RECIST v1.1-radiologically documented progression, assessed endoscopically. • Primary treatment failure before achieving a complete response (CR): requirement for radical salvage surgery that includes the primary tumor site, with documented viable tumor presenting anatomopathological findings even in the absence of formal RECIST v1.1 radiological progression. • Any radiological or clinical relapse after achieving a CR (loco-regionally), including any event defined as locoregional treatment failure, even in the absence of formal radiological progressive disease confirmation: ○ Requirement for radical salvage surgery that includes the primary tumor site, regardless of anatomopathological findings. or ○ Elective neck dissection or biopsy, with positive viable tumor cells on anatomopathological findings at 22 weeks or later after randomization. • Second cancers unless anatomopathological findings exclude squamous histology. Note: Investigator-assessed EFS will be used for supportive analysis.
Secondary	
To assess the efficacy of Debio 1143 compared to placebo when added to CRT according to additional efficacy endpoints.	Progression-Free Survival (PFS) defined as the time from randomization to the first occurrence of progression (radiological or clinical, as assessed by the BIRC) or death from any cause. Note: Investigator-assessed PFS will be used for supportive analysis.
	Locoregional control defined as the time from randomization to the first occurrence of progression at the site of the primary tumor or the locoregional lymph nodes, either according to RECIST v1.1 or based on clinical assessment (radiological or clinical, as assessed by the BIRC). Note: Investigator-assessed locoregional control will be used for supportive analysis.
	Objective response rate, defined as the proportion of subjects with CR or partial response by RECIST v1.1, as assessed by the BIRC. Note: Investigator-assessed response will be used for supportive analysis.
	CR rate, defined as the proportion of subjects with CR by RECIST v1.1, as assessed by the BIRC.

	Note: Investigator-assessed response will be used for supportive analysis.
	Duration of response defined as the time from the first evidence of response (partial or complete, as assessed by the BIRC according to RECIST v1.1) to the first occurrence of progression (radiological or clinical, as assessed by the BIRC) or death from any cause. Note: Investigator-assessed duration of response will be used for supportive analysis.
	Overall survival defined as the time from randomization to death due to any cause.
	Proportion of subjects with radical salvage surgery (excluding elective neck dissection, without anatomopathological evidence of residual malignant cells).
	Time to subsequent systemic cancer treatments.
To compare safety, tolerability and treatment compliance of Debio 1143 vs placebo, when added to CRT.	Incidence and severity of adverse events, serious adverse events and adverse events of special interest, changes in laboratory values, vital signs, and electrocardiograms according to NCI-CTCAE v 5.0.
	Extent of exposure of the different treatment agents (i.e., Debio1143 or matched placebo, radiotherapy [RT], chemotherapy) including: • Treatment duration • Number of cycles • Actual dose • Dose intensity • Relative dose intensity • Incidence of treatment interruption • Incidence of treatment reduction • Incidence of treatment discontinuation
To compare the health-related quality of life of Debio 1143 vs placebo when added to CRT using patient-reported outcome questionnaires.	Changes from baseline in: • Global Health Scale/Quality of Life and Fatigue using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. • Swallowing and Pain using EORTC QLQ-HN35 questionnaire.
Exploratory	

In a subgroup of subjects: To assess the exposure/response (E/R) To evaluate the pharmacokinetic (PK) disposition and E/R in subjects with different renal functions To evaluate the PK disposition and E/R in subjects with different hepatic functions To identify potential drug metabolism enzymes and transporter genetic variations associated with variations in PK disposition and response.	Included but not limited to: • For "Exposure"; C_{trough} at Day 2 and area under the concentration vs time curve (AUC) (if appropriate), adjusted with relative dose intensity. • For "Response": safety laboratory measurement (e.g., aspartate aminotransferase / alanine aminotransferase) or other safety data as appropriate, tumor metrics supporting clinical response assessment, objective response rate, EFS, PFS (as appropriate). • C_{trough} at Day 2 and AUC (if appropriate) evaluation grouped by renal function and hepatic function. • For genetic variations: drug metabolism enzymes and transporter chip data associated with variations in C_{trough} at Day 2 and AUC (if appropriate).
To assess the efficacy of Debio 1143 compared to placebo when added to CRT according to exploratory efficacy endpoints.	Proportion of subjects with definitive tracheostomy.
	Proportion of subjects with enteral and parenteral feeding.
To compare on an exploratory basis the health-related quality of life of Debio 1143 vs placebo when added to CRT using patient-reported outcome questionnaires.	Changes from baseline in: • Domains from the EORTC QLQ-C30 questionnaire other than Global Health Scale/Quality of Life and Fatigue. • Domains from the EORTC QLQ-HN35 questionnaire other than Swallowing and Pain. • Domains from the EQ-5D-5L questionnaire.
To evaluate the health resource utilization patterns to inform economic analyses.	The focus will be on health resource utilization as part of routine clinical care including but not limited to: • Number of hospitalizations by cause. • Length of hospital stay. • Number of emergency department visits. • Number of stays in intensive care units. • Length of hospital stay in intensive care units. • Number of elective neck dissections. • Number of salvage surgeries. • Number of surgical reconstructions. • Number of subsequent systemic cancer treatments. • Number of subjects using a feeding tube. • Duration of feeding tube use. • Number of speech/language therapy visits. • Number of swallowing therapy visits. • Number of dental care visits.
To evaluate associations between clinical endpoints and potential predictive biomarkers such as, but not restricted to, cellular Inhibitor of Apoptosis Protein 1 (cIAP1), cIAP2 or X-linked Inhibitor of Apoptosis Protein (XIAP).	Predictive biomarkers such as, but not restricted to, cIAP1, cIAP2 or XIAP.

Study population and sample size	The study population includes adult subjects with LA-SCCHN (stage III, IVA or IVB) with histologically confirmed diagnosis in at least one of the following sites: oropharynx (HPV-negative), hypopharynx and larynx. Subjects should be previously untreated and suitable for definitive CRT as determined by a multidisciplinary oncology team, as is currently standard clinical practice. This study population will be defined by the inclusion and exclusion criteria below. No protocol waivers will be granted. Upon confirmation of eligibility, subjects will be enrolled and randomized. Assuming a 20% screening failure rate, approximately 875 subjects will be screened worldwide at approximately 200 sites and will undergo study related screening assessments to randomize ~700 subjects.
Inclusion criteria	The following inclusion criteria must be met during screening: 1. Willing and able to sign written informed consent prior to study screening. 2. Male or female ≥ 18 years of age (or based on the country legal age limit for adults) on day of signing the Informed Consent Form (ICF). 3. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. 4. Histologically confirmed diagnosis in previously untreated LA-SCCHN patient (stage III, IVA or IVB according to the American Joint Committee on Cancer [AJCC]/TNM Staging System, 8th Ed.) suitable for definitive CRT, of at least one of the following sites: oropharynx, hypopharynx and larynx. Note: Archival tumor sample to be provided, if available. 5. Evaluable tumor burden (measurable and/or non-measurable tumor lesions) assessed by computed tomography scan or magnetic resonance imaging, based on RECIST v 1.1. 6. For OPC patients, primary tumors must be HPV-negative as determined by p16 expression using immunohistochemistry (pathological report should be available). Note: If the site is not able to perform HPV testing by p16 IHC, it will be evaluated by a central laboratory. 7. Able to swallow liquids or has an adequately functioning feeding tube, gastrostomy or jejunostomy placed. 8. No hearing loss by clinical assessment and audiogram. 9. Peripheral neuropathy < grade 2. 10. Adequate hematologic, renal and hepatic function as indicated by: • Estimated glomerular filtration rate ≥ 60 mL/min/1.73m² (using the Chronic Kidney Disease - Epidemiology Collaboration [CKD -EPI] creatinine formula). • Absolute neutrophil count ≥ 1 500 cells/µL. • Platelets ≥ 100 000 cells/µL. • Hemoglobin ≥ 9.0 g/dL (transfusions during screening are permitted). • AST and ALT ≤ 3.0 × upper limit of normal (ULN). • Total bilirubin ≤ 1.5 × ULN (up to 2.0 × ULN is allowed if the direct bilirubin level is normal and the elevation is limited to indirect bilirubin). 11. Women of childbearing potential (according to recommendations of the Clinical Trial Facilitation Group) must have a negative serum pregnancy test at screening and must not be breastfeeding. Women of childbearing potential must agree to use highly effective contraceptive method(s) (see Section 8.1.3) from ICF signature to 6 months after the last administration of chemotherapy or 3 months after last dose of Debio 1143/matched placebo, whichever is the latest. Non-sterilized males who are sexually active with a female partner of childbearing potential must agree to use condom and spermicide from ICF signature to 6 months after the last administration of chemotherapy or 3 months after the last dose of Debio 1143/matched placebo, whichever is the latest. Because male condom and spermicide is not a highly effective contraception method, it is strongly recommended that

	female partners of a male study subject use highly effective contraceptive method(s) (see Section 8.1.3) throughout this period. Male subjects must refrain from donating sperm during the clinical study and for 6 months after the last administration of chemotherapy or 3 months after the last dose of Debio 1143/matched placebo, whichever is the latest. If not done previously, cryopreservation of sperm prior to receiving chemotherapy or Debio 1143/matched placebo is advised to male patients with a desire to have children.
Exclusion criteria	Meeting any of the following criteria at screening will render a subject ineligible for participation in the study: 1. Primary tumor of nasopharyngeal, paranasal sinuses, nasal or oral cavity, salivary, thyroid or parathyroid gland pathologies, skin or unknown primary site. 2. Metastatic disease (stage IVC as per AJCC/TNM, 8th Ed.). 3. Prior definitive or adjuvant RT and/or radical surgery to the head and neck region which may jeopardize the primary tumor irradiation plan, or any other prior SCCHN systemic treatment, including investigational agents (please refer to Section 6.1.1). 4. Use within 14 days prior to randomization or requirement for ongoing treatment with any drug(s) on the prohibited medication list (provided in Sections 6.5.3 and 6.5.4). 5. Treatment with an investigational agent or use of an investigational device within 4 weeks of the first dose of study treatment. 6. Known history of infection with human immunodeficiency virus (HIV). If unknown history of HIV, an HIV screening test is to be performed and subjects with positive serology for HIV-1/2 must be excluded. 7 Known chronically active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. If unknown status, the following tests are to be performed and subjects with positive serology must be excluded: • HBV screening tests: both HBV sAg and Anti-HepB core IgG. • HCV screening tests: both HCV-antibody and positive viral load HCV-RNA by PCR. 8. Other infections (viral and/or bacterial and/or mycotic) requiring systemic treatment. 9. Live-attenuated vaccinations within 30 days prior to first investigational treatment administration. 10. Ongoing uncontrolled infection requiring intravenous antibiotic therapy within 1 week prior to randomization. 11. Known gastrointestinal disorder with clinically established malabsorption syndrome and major gastrointestinal surgery that may limit oral absorption. 12. Documented weight loss of >10% during the last 4 weeks prior to randomization (unless adequate measures are undertaken for nutritional support), OR plasmatic albumin < 3.0 g/dL. 13. Active gastrointestinal bleeding, or any other uncontrolled bleeding requiring more than 2 red blood cell transfusions or 4 units of packed red blood cells within 4 weeks prior to randomization. 14. Active uncontrolled inflammatory disease (including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, severe extensive psoriasis) requiring ongoing treatment with anti-TNF medication. 15. Any concomitant medication known to prolong the QT interval that cannot be discontinued or replaced by safe alternative medication within 7 days prior to start of treatment. 16. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following: • Ongoing or history of uncontrolled or symptomatic ischemic myocardiopathy within 6 months prior to randomization. • Known left ventricular ejection fraction < 50%, left ventricular hypertrophy, ventricular arrhythmias, bradycardia (heart rate < 50 bpm). • History of myocardial infarction, or severe/unstable angina, within 6 months prior to randomization. • New York Heart Association grade ≥ 3 congestive heart failure. • Congenital long QT syndrome. • Family history of long QT syndrome.

- Symptomatic pulmonary embolism within 6 months prior to randomization.
- Ongoing or known history of transient ischemic attacks or stroke within 6 months prior to randomization.
- QTc using Fridericia's formula (QTcF) interval > 450 ms for males and > 470 ms for females.

17. Symptomatic pulmonary disease requiring continuous or intermittent oxygen supply.
18. History of another malignancy within the last 3 years prior to randomization, with the exception of completely resected non-melanoma cell skin cancer outside the head and neck area or completely resected stage I breast cancer, or completely resected in-situ non-muscular invasive bladder, cervix and/or uterine carcinomas.
19. Known contraindication to undergoing positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG-PET) scans, contrast-enhanced MRI or contrast-enhanced CT scans.
20. Known allergy to Debio 1143, cisplatin, carboplatin, other platinum-based agent or any excipient known to be present in any of these products or in the placebo formulation.
21. Non-compensated or symptomatic liver cirrhosis (Child-Pugh score: B or C).
22. Any ongoing condition or disorder, before randomization, including drug(s) or alcohol abuse, which in the judgment of the Investigator would make the patient inappropriate for entry into the study or precluding his/her ability to comply with study procedures.

Study intervention and dosing scheme

The study intervention includes administration of both investigational treatments and background treatments. In the current protocol, Debio 1143 (International Nonproprietary Name: xevinapant), matched placebo, cisplatin and carboplatin are investigational treatments. IMRT is considered as background treatment.

The following investigational and background treatments will be administered during the study according to randomization:

Arm A: 3 cycles of Debio 1143 (200 mg/day from Day 1 to 14, per cycle) + IMRT (35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/7, up to 70 Gy to the gross tumor volume) + high-dose cisplatin (100 mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of Debio 1143 (200 mg/day from Day 1 to 14, per cycle).

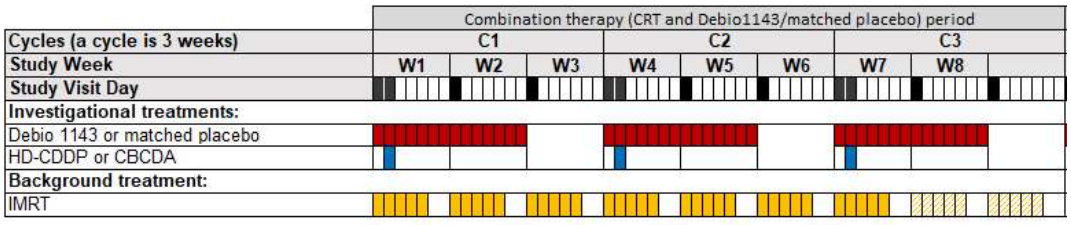
or

Arm B: 3 cycles of placebo (from Day 1 to 14, per cycle) + IMRT (35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/7, up to 70 Gy to the gross tumor volume) + high-dose cisplatin (100 mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of placebo (from Day 1 to 14, per cycle).

In case of toxicity after the first cisplatin dosing, subjects can be switched to carboplatin (AUC= 5 or 4 on Day 2 of each subsequent cycle depending on the toxicity observed, see Section 6.1.2.1.2).

Debio 1143, matched placebo and CRT will be administered as per Synopsis Figure 1 and Synopsis Figure 2.

Synopsis Figure 1 - Treatments administered during the combination therapy period



Abbreviations: C: cycle; **CBCDA:** carboplatin; **HD-CDDP:** high-dose cisplatin; **IMRT**: intensity-modulated radiotherapy; **W:** week.
One cycle is composed of 3 weeks.

Synopsis Figure 2 - Treatment administered during the monotherapy period

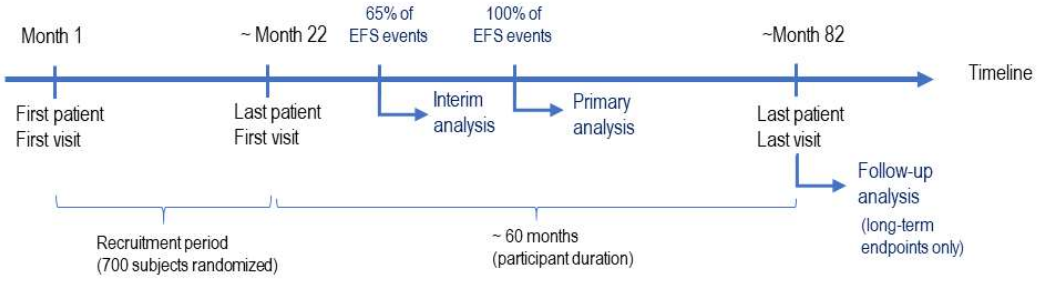
	Monotherapy (Debio 1143 or matched placebo) period										EOT
Cycles (a cycle is 3 weeks)	C4			C5			C6				
Study Week	W10	W11	W12	W13	W14	W15	W16	W17	W18	W19	W20
Study Visit Day											
Investigational treatments:											
Debio 1143 or matched placebo											
HD-CDDP or CBCDA											
Background treatment:											
IMRT											

Abbreviations: C: cycle; **CBCDA:** carboplatin; **EOT:** end of treatment; **HD-CDDP:** high-dose cisplatin; **IMRT**: intensity-modulated radiotherapy; **W:** week.
One cycle is composed of 3 weeks.

Study duration

It is expected that the total duration of the study will be around 82 months (6.8 years), excluding final follow-up analysis (Synopsis Figure 3).

Synopsis Figure 3 – Study duration and estimated milestones markers



Abbreviations: EFS: Event-Free Survival

Milestone markers are only estimates based on enrolment assumptions.

Participant duration

Subjects will be followed up until premature discontinuation from study or until the last on-study subject reaches his/her 60-months post-randomization visit, whichever occurs first.

Statistical methods

The following analysis sets will be used for planned analyses: Intent-to-treat, Safety, and Pharmacokinetic analysis set.

The primary hypothesis on EFS will be evaluated by comparing Debio 1143 with placebo in combination with CRT using a stratified log-rank test. The stratification factors are tumor size (T4 vs other) and lymph node involvement (N0-1 vs N2 vs N3). Hazard ratio will be estimated using a Cox-proportional hazard regression model adjusted for the randomization stratification factors. Treatment effect on other time-to-event endpoints will be estimated using Cox regression model adjusted for the randomization stratification factors.

Estimation of the treatment effect on binary endpoints will be done using a logistic model adjusted for the randomization stratification factors.

Descriptive statistics will be provided for safety endpoints.

Three comparative analyses are planned for the clinical trial (see also Synopsis Figure 3):

- One interim analysis once 279 EFS events (65% information rate) as assessed by the BIRC are observed. It will focus on primary and secondary endpoints analyses. The primary intent of this analysis is to demonstrate that Debio 1143 + CRT prolongs EFS as assessed by the BIRC versus placebo + CRT.
  Unblinded supporting personnel will produce the outputs for the interim analysis. Outputs related to the analyses of the exploratory endpoints will be produced only in the event of a positive recommendation from the Independent Data Monitoring Committee (IDMC), as needed.

	• One primary analysis once 429 EFS events, as assessed by the BIRC across both arms are observed. All endpoints will be analyzed. The primary intent of this analysis is to demonstrate that Debio 1143 + CRT prolongs EFS as assessed by the BIRC versus placebo + CRT. • One follow-up analysis once the last on-study subject has reached the 60 months post-randomization visit, or prematurely discontinued, whichever occurs first. Only endpoints affected by the follow-up assessments will be analyzed. The primary intent of this analysis is to provide OS evaluation. Hierarchical fixed sequence testing procedure is applied to control for the interim analysis and multiple hypotheses. The overall type I error is controlled at 0.025 one-sided (before or at primary analysis). An O'Brien & Fleming type α spending is used for the calculation of the significance levels and efficacy boundaries (Z-value scale). With 429 EFS events, the clinical trial has ~90% power to detect the expected hazard ratio benefit.
Safety and efficacy oversight	An IDMC will be established before the randomization of the first subject to provide safety and efficacy oversight during the study. The review of safety and efficacy data will be performed according to an IDMC Charter that will be prepared before data collection start. All relevant data available from this study will be provided for these reviews. The responsibilities of the IDMC include: • To minimize the exposure of subjects to an unsafe therapy or dose. • To make recommendations for changes in study processes where appropriate. • To advise on the need for dose adjustments because of safety issues. • To endorse continuation of the study. It will also be the responsibility of the IDMC to review the efficacy results at the interim analysis. At any time during the study when the IDMC recommends major changes, these recommendations will be presented to the Trial Steering Committee. Further details on the membership, responsibilities and working procedures of the IDMC are described in the IDMC Charter, provided as a separate document in the study file.