3. Synopsis

Study title:	A Phase 2, Multi-center, Randomized, Double-blind, Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of ALD518 in the Reduction of Oral Mucositis in Subjects with Head and Neck Cancer Receiving Concomitant Chemotherapy and Radiotherapy
Clinical phase:	2
BACKGROUND and STUDY DESIGN	
Study objectives:	The primary objective of the clinical trial is to evaluate the safety and efficacy of ALD518 in modifying the course of oral mucositis in subjects with head and neck cancer receiving concurrent chemotherapy and radiotherapy. The secondary objectives of the clinical trial are to determine the pharmacokinetics and pharmacodynamics of ALD518 and to evaluate the impact of ALD518 on health and economic outcomes in subjects with head and neck cancer receiving concurrent chemotherapy and radiotherapy.
Test drug/agent:	ALD518
Name of active ingredient(s):	ALD518
Bulk batch number(s):	1-FIN-1245
Dose:	160 mg or 320 mg
Route of administration:	Intravenous
Duration of treatment:	Two intravenous infusions 3 weeks apart
Reference drug:	Placebo (0.9% Sodium Chloride)
Bulk batch number(s):	N/A
Dose:	Not applicable
Route of administration:	Intravenous
Duration of treatment:	Two intravenous infusions 3 weeks apart
Background treatment:	Subjects were newly diagnosed with head and neck cancer and had not received previous treatment for oral mucositis.
Indication:	Oral mucositis in patients with head and neck cancer

Diagnosis and main criteria for inclusion:	Study enrollment was to include adult subjects who were recently diagnosed with, pathologically confirmed, non-metastatic SCC of the oral cavity, oropharynx, hypopharynx or larynx and who had treatment plans for first-line CRT. The following are key inclusion criteria: 1. Have recently diagnosed (< than 6 months prior to screening visit date), pathologically confirmed, non-metastatic SCC of the oral cavity, oropharynx, hypopharynx or larynx that will be treated with CRT as first-line treatment; subjects with a history of surgical (approximately 4-6 weeks before RT with sufficient time for post-surgical healing) management are eligible 2. Have a plan to receive a continuous course of conventional external beam irradiation delivered by intensity-modulated radiotherapy (IMRT) as single daily fractions of 2.0 to 2.2 Gy, with a cumulative radiation dose between 55 and 72 Gy at each site. Planned radiation treatment fields must include at least 2 oral sites (retromolar trigone, buccal mucosa, floor of mouth, tongue, or soft palate), with each site receiving ≥ 55 Gy 3. Have a plan to receive a standard cisplatin or carboplatin CT regimen 4. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 5. CRP < 80 mg/L 6. Have adequate hematopoietic, hepatic, and renal function at the screening visit: Hematopoietic function • Hemoglobin ≥ 10 g/dL • Absolute neutrophil counts (ANC) ≥ 1,500 cells/mm^3 • Platelet count ≥ 100 × 10^9/L Hepatic function • Total bilirubin ≤ 1.25 times the upper-normal limit (ULN) • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 times the ULN Renal function: Serum creatinine concentration ≤ 2 mg/dL; if result is ≥ 1.4 mg/dL and ≤ 2.0 mg/dL, a 24-hour urinary creatinine clearance test must be performed by the site's local laboratory. To be eligible for the clinical trial, a subject must demonstrate a 24-hour urinary creatinine clearance ≥ 50 mL/min or via Cockcroft-Gault calculation
Study design:	Small open-label lead in portion followed by a double-blind placebo controlled portion.
Methodology:	The trial was designed to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of ALD518, and the health and economic outcomes in subjects who received CRT for the treatment of squamous cell carcinomas (SCCs) of the oral cavity, oropharynx, hypopharynx, or larynx.
Type of control:	Placebo
Publication(s) based on the study:	None as of August 2013

Study period:	**First subject, first visit:**	17 October 2011
	Last subject, last visit:	19 April 2013
Early termination:	The study was halted early due to lack of efficacy by the Steering Committee in consultation with the Data Monitoring Committee.	
Number of subjects:	**Planned: 96**	
	Analyzed: 76	
Criteria for evaluation	Planned efficacy measures included:	
Efficacy / clinical pharmacology:	• Clinically assessed ulcerative OM (WHO Grade ≥ 2) at a cumulative radiation dose of 55 Gy • OM assessments o Ulcerative (WHO Grade ≥ 2) and severe (WHO Grade ≥ 3) OM at cumulative doses of 35 Gy, 45 Gy, 55 Gy and 65 Gy o Duration of ulcerative and severe OM o Time to onset of ulcerative and severe OM • Pain assessments: Mouth and throat soreness associated with OM (as measured with OMDQ Question 2)	
Safety:	Safety: Planned Safety measures included incidence of AEs, SAEs, deaths, and clinically significant laboratory abnormalities.	
Other:	**Pharmacodynamics:** Blood samples for CRP and IL-6 biology (e.g., total IL-6, sIL-6r, soluble gp130, sIL-6 Complex) were collected at baseline (CRP only), Week 2, Week 4, Week 6 (CRP only), Week 18, and 4 weeks post-RT. On clinical visit days when the subject received treatment with ALD518 or placebo, the sample was collected prior to any dosing. **Pharmacokinetics:** Plasma samples for the analysis of ALD518 concentration were collected for all subjects pre-dose and 2 hours post-dose on each day of dosing. Plasma samples were additionally obtained for ALD518 concentration analysis on Week 2, Week 4, Week 6, Week 18, and 4 weeks post-RT.	
Statistical methods:	The clinical trial results were tabulated and descriptive statistics were produced. Confidence intervals were presented as 2-sided 95% intervals. Binary measures were reported as frequencies and percentages and continuous measures were summarized with n, mean, standard deviation, median, minimum, and maximum. The statistical decision rule for this trial was based on the Phase 2 screening methodology presented in Fleming and Richardson.[14] This methodology formally established a Phase 2 decision rule which was implemented for this study as a 15% one-sided alpha level. If the one-sided p-value was less than 15%, then the ALD518-based regimen was considered to be plausibly efficacious (≤15% chance the results seen would have been seen by chance alone) and should be evaluated definitively in a subsequent Phase 3 clinical trial. Decisions concerning the future development of ALD518 were not to be exclusively based upon statistical testing of the primary endpoint.	

RESULTS	
Study subjects	Overall 76 subjects were enrolled in the study and met the criteria for inclusion in the full analysis set; 7 subjects underwent open-label treatment at 160 mg and received 2 doses administered 4 weeks apart and 69 subjects underwent randomized double-blind treatment with ALD518 administered at either 160 mg or 320 mg or with placebo for 2 doses administered 3 weeks apart. This report presents data through June 5th 2013 and includes at a minimum all data through the Week 4 post RT visit. This report does not include all data from the long-term follow-up period (months 3, 6, 9 and 12). Those data will be summarized (when available) in an addendum to this report.
Efficacy / clinical pharmacology evaluation:	A total of 76 subjects were enrolled, randomized, and received at least one dose of study medication. These subjects were included in the analysis of efficacy for this study. Most baseline characteristics were balanced between the subjects randomized by treatment; however, the incidence of baseline ECOG scores of 1 occurred at approximately twice the rate among subjects who received placebo compared to subjects who received ALD518. This difference is a result of 4 additional placebo subjects with an ECOG score of 1. Overall, the mean radiation received by subjects was 66.3 Gy and was similar by treatment group, 67.4 Gy (placebo) and 65.8 Gy (ALD518). The primary efficacy endpoint for this study was clinically assessed ulcerative OM (WHO Grade ≥ 2) at a cumulative radiation dose of 55 Gy. At 55 Gy, ulcerative OM was experienced in 86.5% of subjects who received ALD518 versus 79.2% of subjects who received placebo; however, at 55 Gy, the incidence of ulcerative OM was found to be significantly higher among subjects who were randomized to receive 160 mg ALD518 compared to subjects who received placebo (p=0.0496) The difference in rates resulting in this p-value was 21% (79% placebo vs. 100% 160 mg randomized ALD518), which included the imputation of ulcerative OM for one 160 mg subject. A difference of this magnitude was not seen at other radiation levels and severe OM rates for these two populations were comparable. Secondary efficacy analyses included OM assessments by cumulative radiation level, duration, and time to onset; subjective pain assessments; analgesic consumption; and PROs as measured by OMDQ, FACT-HNC, and FACIT-fatigue scales. No notable differences in OM by cumulative radiation level, duration of OM, or time to onset of OM were observed by treatment group, nor were notable trends observed over time for any of the patient-reported outcomes. Analyses of analgesic use were not performed. Study enrollment was terminated early due to lack of efficacy, based upon both measures of OM.

Safety evaluation:	The safety analysis for this Phase 2 trial was conducted in all treated subjects, n=76; 65 subjects (85.5%) received both doses of study drug and 11 (14.5%) received the first dose only. Overall, 75 (98.7%) subjects experienced one or more adverse events and 45 (59.2%) subjects experienced at least one treatment-related AE. The overall frequency of AEs was similar by treatment group (95.7% placebo and 100% ALD518). The most frequently occurring AEs were: nausea (67.1%), constipation (57.9%), oral candidiasis (48.7%), vomiting (42.1%), weight decreased (38.2%), dysgeusia (36.8%), leukopenia (34.2%), and dry mouth (34.2%) and the most frequently occurring treatment-related AEs were: leukopenia (23.7%), platelet count decreased (19.7%), nausea (14.5%), weight decreased (13.2%), asthenia (13.2%), anemia (11.8%), and aspartate aminotransferase (AST) increased (10.5%). A total of 6 deaths were recorded. Two deaths were attributed to disease progression as the primary cause, and in a third subject the primary cause of death was unknown, but disease progression was recorded as the secondary cause. The remaining 3 deaths were attributed to AEs: cerebrovascular accident, pharyngeal hemorrhage, and acute myocardial infarction. A total of 30 (39.5%) subjects experienced SAEs. The majority of SAEs occurred as single events. Events that occurred in more than 1 subject were: dehydration, pneumonitis, nausea, and oral pain, pyrexia, pneumonia, and pharyngeal hemorrhage. Of these, only pneumonia and pharyngeal hemorrhage occurred more frequently in ALD518 treated subjects compared to those who received placebo. Clinical laboratory findings of decreases in neutrophils and platelets in ALD518 treated subjects were consistent with previous observations in subjects treated with IL-6 inhibitors. No important changes in mean vital sign values were observed, nor were any changes in the frequency of abnormal ECG findings s by treatment group. This study was halted for lack of efficacy; no safety signals were detected that would suggest the need to halt ALD518 treatment.
Other evaluations:	**Pharmacokinetics:** Plasma concentrations of ALD518 increased following each of the two IV administrations, Week 0 and Week 4 for the open-label treatment, and Week 0 and Week 3 for the randomized treatments. For the randomized subjects, the observed mean maximum plasma ALD518 concentrations increased in a less than dose-proportional manner from 160 to 320 mg ALD518. The mean trough ALD518 concentrations on Week 3 for subjects receiving 160 mg or 320 mg ALD518 were approximately equivalent too or above, respectively, the targeted threshold trough value of 15 ug/mL ALD518. As expected, accumulation of ALD518 was observed following the second dose on Week 3. **Pharmacodynamics:** Subjects who received treatment with ALD518 experienced a suppression of their CRP levels throughout treatment and at 4 weeks post-RT. No suppression was observed among placebo-treated subjects. At most time points, subjects who received placebo treatment experienced IL-6 values that were elevated above that measured at baseline. By contrast, subjects who received treatment with ALD518 experienced either suppression or no change in their IL-6 levels.

Overall conclusions:	This report presents data through June 5th 2013 and includes at a minimum all data through the Week 4 post RT visit. This report does not include all data from the long-term follow-up period (months 3, 6, 9 and 12). Those data will be summarized (when available) in an addendum to this report.

3 SYNOPSIS

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Clinical phase:	2
LONG TERM FOLLOW-UP (MONTHS 3-12)	
Report Objective:	The primary objective of this addendum to the ALD518-CLIN-009 clinical study report is to provide long-term follow-up information (Months 3-12).
Methodology:	The long term follow-up (LTFU) period includes long term follow-up visits, primarily for the assessment of tumor response and survival. These assessments took place at Months 3, 6, 9 and 12 following the last dose of RT. At Months 3, 6, 9, and 12 tumors were assessed clinically. At the Month 6 and Month 12 follow-up visits, tumor status was assessed using standard TNM criteria.
Study period:	**First subject, first visit:** 29 August 2011 **Last subject, last visit for long-term follow-up:** 27 March 2014
Number of subjects:	**Planned: 96** **Analyzed: 76 (72 entered LTFU)**
Criteria for Evaluation:	The LTFU period focused on the assessment of tumor response and survival. These assessments took place at Months 3, 6, 9 and 12 following the last dose of RT. At Months 3, 6, 9, and 12 tumors were assessed clinically. At the Month 6 and Month 12 follow-up visits, tumor status was assessed using standard TNM criteria. Additionally, AEs and SAEs were collected.
RESULTS	
Study subjects:	Overall 72/76 subjects were enrolled in the long term follow-up period. This addendum presents data following the Week 4 post RT visit (discussed in the main CSR) through Month 12.
Overall conclusions:	This report presents a data update through 27 March 2014 and includes data from the LTFU period (Months 3, 6, 9 and 12). Based on the review of data from the LTFU period, the safety analysis (AEs/SAEs) remains the same as that concluded in the main CSR, with the exception of the observation of decreased survival and progression free survival in ALD518 treated subjects.