clinical adverse events, by body system and COSTART terminology. If a patient experienced more than 1 episode of an adverse event, the patient was counted only once for that event. If a patient had more than 1 adverse event in a body system category, the patient was counted only once in that body system total.

No. (%) of Patients with Clinical Adverse Events by Body System: ALA-018

Body System Category/ Adverse Event (COSTART)	LEVULAN® (N=88)	Vehicle (N=29)
With Any Adverse Events	31 (35%)	12 (41%)
Body as a Whole	17 (19%)	8 (28%)
Accidental Injury	2 (2%)	0 (0%)
Allergic Reaction	1 (1%)	1 (3%)
Back Pain	1 (1%)	2 (7%)
Chest Pain	0 (0%)	1 (3%)
Cyst	1 (1%)	0 (0%)
Flu Syndrome	0 (0%)	2 (7%)
Headache	6 (7%)	1 (3%)
Hernia	1 (1%)	0 (0%)
Infection	4 (5%)	3 (10%)
Neck Pain	1 (1%)	0 (0%)
Unevaluable Event*	1 (1%)	0 (0%)
Cardiovascular System	0 (0%)	1 (3%)
Syncope	0 (0%)	1 (3%)
Digestive System	4 (5%)	0 (0%)
Diarrhea	2 (2%)	0 (0%)
Gastrointestinal Disorder	1 (1%)	0 (0%)
Tooth Disorder	1 (1%)	0 (0%)
Hemic and Lymphatic System	1 (1%)	0 (0%)
Abnormal Platelets	1 (1%)	0 (0%)
Metabolic and Nutritional System	1 (1%)	0 (0%)
Gout	1 (1%)	0 (0%)
Musculoskeletal System	1 (1%)	0 (0%)
Arthrosis	1 (1%)	0 (0%)

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No. (%) of Patients with Clinical Adverse Events by Body System: ALA-018 (Continued)

Body System Category/ Adverse Event (COSTART)	LEVULAN® (N=88)	Vehicle (N=29)
Nervous System	3 (3%)	0 (0%)
Amnesia	1 (1%)	0 (0%)
Anxiety	1 (1%)	0 (0%)
Tremor	1 (1%)	0 (0%)
Respiratory System	4 (5%)	0 (0%)
Bronchitis	1 (1%)	0 (0%)
Laryngitis	1 (1%)	0 (0%)
Rhinitis	2 (2%)	0 (0%)
Skin and Appendages	6 (7%)	3 (10%)
Herpes Simplex	1 (1%)	0 (0%)
Lichenoid Dermatitis	1 (1%)	0 (0%)
Rash	1 (1%)	1 (3%)
Seborrhea	0 (0%)	1 (3%)
Skin Carcinoma	2 (2%)	1 (3%)
Skin Hypertrophy	1 (1%)	0 (0%)
Special Senses	2 (2%)	0 (0%)
Cataract NOS	1 (1%)	0 (0%)
Conjunctivitis	1 (1%)	0 (0%)

* Unevaluable event: This patient had 3 procedures associated with surgery (Pt.18219, Table 16.2.13)

The five patients in the LEVULAN® arm who experienced serious adverse events (patients 18102, 18219, 18221, 18402, and 18501) experienced broken left leg (from accident), implant of a thalamic stimulator (to treat a tremor), a pre-existing hyperkeratotic (Grade 3)actinic keratosis (at an untreated site), pre-existing squamous cell carcinoma on the left ear, and ruptured abdominal hernia. Investigators considered these episodes unrelated to exposure to LEVULAN®.

Conjunctivitis developed in one patient (no. 18711) 44 days after LEVULAN® application. The investigator concluded that it was not related to LEVULAN® treatment.
Reviewer's Comment:

Reviewer's Comment:
With most topical medications, there is only one relevant period during which adverse events need to be assessed: the period of drug administration. In contrast, with LEVULAN®, three distinct periods must be assessed for the incidence and severity of adverse events: (a) [pre-PDT] the period from LEVULAN® application until light administration; (b) [peri-PDT]the period during and shortly after light administration; and (c) [post-PDT]the period from shortly after administration of light therapy to end-of-follow-up. The reason why adverse events within each of these three time periods must be

assessed separately is that the type and quantity of the adverse events differ. A timepoint useful for separating short- from long-term adverse events would be 24 hours after treatment, because for most patients the peri-PDT adverse events have resolved or returned to baseline by this timepoint.
Another complication in assessment of adverse event incidence and severity is that untreated actinic keratoses manifest some of the signs (e.g. erythema, hyper- and hypopigmentation) that are considered adverse events.

Adverse Events: pre-PDT

The percentage of patients who develop signs and/or symptoms of a photodynamic response (e.g., burning/stinging and/or edema) during the time interval between application of LEVULAN® and administration of blue light may be an indirect measure of the prevalence of an (inappropriate) photodynamic response that results from inadvertent exposure to ambient light. Despite the presence of information in the protocol that warns patients to protect the lesions being treated from light exposure for a minimum of 14 to 18 hours after application (i.e., "to avoid direct exposure of target sites to sunlight or other high intensity light sources, including tanning light devices"), active-treated patients do manifest signs/symptoms of a photodynamic response **prior** to blue light administration: 47% of active treatment patients develop burning/stinging between Baseline A and B, while 14% of vehicle treatment patients develop burning/stinging; 17% of active treatment patients develop edema between Baseline A and B, while no vehicle treatment patients develop edema between Baseline A and B.

Reviewer's Comment: The incidence and/or increased prevalence of burning/stinging and edema that develops between Baseline A and B is attributable either to irritancy or to an inappropriate photodynamic response. Since no irritancy study has been performed with the to-be-marketed formulation, it is not possible to discern which of these two alternative explanations is correct.

Adverse Events: peri-PDT

The medical reviewer analyzed the incidence of signs and/or symptoms expected during a photodynamic response from the period including Baseline B until 24 hours after light treatment for patients undergoing active and control treatment, as is depicted below.

Incidence of erythema, edema, and burning/stinging during and/or 24 hours after photodynamic therapy*: ALA-018

	FACE				SCALP			
	ACTIVE		VEHICLE		ACTIVE		VEHICLE	
Fraction of patients with some or all target lesions involved:	SOME	ALL	SOME	ALL	SOME	ALL	SOME	ALL
Erythema♦	8/72 (11%)	64/72 (88%)	12/21 (57%)	7/21 (33%)	2/16 (19%)	14/16 (81%)	4/8 (50%)	4/8 (50%)
Edema♦	23/72 (32%)	12/72 (17%)	0/21	0/21	5/16 (31%)	3/16 (19%)	0/8	0/8
Burning/Stinging	3/72 (4%)	68/72 (94%)	7/21 (33%)	2/21 (10%)	0/16	16/16 (100%)	1/8 (13%)	2/8 (25%)

*defined as the prevalence of adverse events during the time points at baseline B, through light treatment, and at 24 hours after light treatment

♦Sponsor has not collected data that would permit the classification of these adverse events as mild, moderate, or severe.

From Data Listings 15, 16, and 18, Vol. 1.56

Sponsor's analysis of the data listings (not shown) largely corroborated the medical officer's analysis. The consequence of treatment with LEVULAN® and blue light was to increase the prevalence of patients who experienced erythema, edema, and stinging/burning associated with treated lesions in the period during and shortly after photodynamic therapy.

As depicted in the following table, approximately half of the patients in whom all the target lesions were erythematous during and/or shortly after photodynamic therapy did not have all their target lesions erythematous at one week after treatment. The adverse events of edema and burning/stinging resolved more quickly, usually within 24 hours after completion of light therapy.

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