2. STUDY SYNOPSIS

Name of Company: Eisai Limited	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: E6201 Gel	Referring to Part IV of the Dossier	
Name of Active Ingredient: E6201	**Volume:** **Page:**	

Study Title:	A 12-Day Randomized, Blinded, Vehicle and Active Comparator-Controlled Study to Determine the Efficacy and Safety of Six Concentrations of Topical E6201 Gel in Subjects with Psoriasis Vulgaris
Investigator(s)/ Center(s):	W. Wigger-Alberti, MD; H. Siemetzki, MD Bioskin GmbH, Bergmannstrasse 5, 10961 Berlin, Germany
Publication (Reference):	None
Study Period:	16 Mar 2010 to 11 Dec 2010
Phase of Development:	Phase 2A
Objective(s):	**Primary study objective:** • To demonstrate that at least one concentration of topical E6201 gel has superior efficacy compared with vehicle on the reduction of psoriatic infiltrate thickness during 12 days of treatment in subjects with psoriasis vulgaris **Secondary study objectives:** • To evaluate the safety and tolerability of six topical concentrations of E6201 gel as measured by rates of adverse events (AEs), and relative to vehicle • To explore the concentration/response relationship
Methodology:	This was a single-center, randomized, blinded, intraindividual comparison in two sequential cohorts of 15 subjects each (30 subjects in total) in an outpatient setting, in which each subject simultaneously received five topical treatments (three active, one vehicle, and one positive control) within one or two psoriatic plaques.
Number of Subjects (planned and enrolled):	It was planned that 30 subjects (15 per cohort) would be randomized to treatment. Forty-one subjects (24 in Cohort 1 and 17 in Cohort 2) were enrolled and 30 were randomized into the study (15 in each cohort).
Diagnosis and Main Criteria for Inclusion:	Subjects included adult males and females 18 to 75 years old, who had chronic stable plaque psoriasis with one or two stable psoriatic plaque(s) suitable in size and location for five separate treatment fields to be assessed within it. Key exclusion criteria were any clinically significant skin diseases other than chronic stable plaque psoriasis; other types of psoriasis than chronic stable plaque variant; an unstable course of the disease defined as flare(s) in the previous month; subjects who used any concomitant topical treatment for the psoriatic plaque(s) to be studied (other than emollients or salicylic acid) within 8 weeks before the Baseline Visit.
Test Treatment, Dose, Mode of Administration, and Batch Number(s):	Topical E6201 Gel. Doses 0.005% (approx. 0.01 mg/day [Lot: L0610009]); 0.01% (approx. 0.02 mg/day [Lot: L0610010]); 0.03% (approx. 0.06 mg/day [Lot: L1009014]); 0.05% (approx. 0.1 mg/day [Lot: L0610012]); 0.1% (approx. 0.2 mg/day [Lot: L1009015]); 0.2% (approx. 0.4 mg/day [Lot: L1009016]).

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):	Topical Gel vehicle: 0% (Lots: N1009013, N0810015). Topical Daivonex®: 0.005% calcipotriene cream (approx 0.01 mg/day).
Treatment Schedule:	A total of six concentrations of topical E6201 gel were tested. Subjects in Cohort 1 received concentrations of E6201 gel of 0.03%, 0.1%, and 0.2%, and subjects in Cohort 2 received concentrations of E6201 gel of 0.005%, 0.01%, and 0.05%. Subjects in Cohort 2 were not dosed until all subjects in Cohort 1 completed treatment and safety data were collected and evaluated. The decision on continuing into Cohort 2 was made after reviewing the data from Cohort 1.
Duration of Treatment:	Duration of study treatment administration was 12 days.
Criteria for Evaluation:	**Primary Efficacy Variable:** Area under the time curve (AUC) of the baseline-corrected thickness of the psoriatic infiltrate (20 MHz sonographic measurement) at Days 0, 8, and 12. **Secondary Efficacy Variables:** • Change from baseline in thickness of the psoriatic infiltrate (20 MHz sonographic measurement) at Day 12. • Change from baseline in thickness of the psoriatic infiltrate (20 MHz sonographic measurement) at Day 8. • Clinical (global) assessment of efficacy was based on a 5-point scale on Days 8 and 12 (-1 = worsened, 0 = unchanged/no effect, 1 = slight improvement, 2 = clear improvement but not completely healed, 3 = completely healed). Comparisons were made with the untreated plaque(s) beneath the hydrocolloid dressing. **Safety Assessments:** Safety was assessed by physical examinations, by the monitoring of vital signs and laboratory measurements, and by recording all AEs and serious adverse events (SAEs). In addition, in Cohort 2 special attention was given to a close, daily monitoring of the local safety (i.e., signs of skin irritation at the application site). Any suspected ecchymoses or petechiae were to be followed up with a diascopy test that was to be documented with digital photographs. Any positive diascopy test was to be followed up by biopsy for skin ultrastructural analysis, if it was agreed that this was appropriate after discussion between the sponsor and the investigator and if consent was given by the subject. **Other Assessments:** Photo documentation of test sites were to be taken at baseline, Day 8, and at Day 12/End of Treatment.
Statistical Methods:	**Efficacy Analyses:** **Primary analysis:** The primary efficacy variable was the intraindividual AUC for baseline-corrected thickness of the psoriatic infiltrate at Days 0, 8, and 12 for each treatment field calculated by applying the linear trapezoidal rule. The primary analysis utilized an appropriate analysis of covariance (ANCOVA) model, including terms for subject, treatment, and baseline infiltrate thickness. Comparisons between topical E6201 concentrations and vehicle and an exploration of the concentration response relationship were made using least square means and contrasts, within the analysis of variance framework. All statistical analyses were carried out at the two-sided 5% significance level, unless otherwise stated. Point estimates for differences between treatments and associated 95% confidence intervals and *P* values were presented. The assumptions associated with analysis of variance were assessed by investigating the distribution of the residuals. Where there were concerns about departure from normality and homogeneity of variance, appropriate transformations of the data or the use of nonparametric tests were to be considered. As this was an exploratory study, no adjustments for multiplicity were applied. There were no substitutions for missing data.

	Secondary analyses: Secondary efficacy variables were the change from baseline in psoriatic infiltrate thickness at Days 8 and 12 and the clinical (global) assessment of efficacy measured on a 5-point scale at Days 8 and 12. A similar ANCOVA model, including subject, treatment and baseline thickness as a covariate, was used to compare the change from baseline in psoriatic infiltrate thicknesses recorded at Day 8 and at Day 12. An ordered categorical analysis using a Cochran-Mantel-Haenszel test was performed to test for differences in clinical (global) assessment of efficacy between treatments at Day 12 and Day 8. **Handling of dropouts and missing data:** Dropouts were included in the Full Analysis Population but excluded from Per Protocol Population.
Results:	**Subject Disposition:** Thirty subjects were randomized and received treatment (15 in each cohort). The first six subjects in Cohort 1 received all five treatments; however, following a review of the safety data the remaining nine subjects did not receive the E6201 0.1% or 0.2% concentrations. No subject withdrew from the study; however, Daivonex treatment was discontinued for one subject, and E6201 0.03% and vehicle were discontinued for one subject (both in Cohort 1) after 8 days due to skin-related AEs. All 30 randomized subjects were included in the Safety Analysis, Full Analysis, and Per Protocol Populations. However, partial exclusions from the Per Protocol Population were imposed as a result of study treatment being terminated in the above-mentioned subjects. **Efficacy:** In the Full Analysis Population, E6201 gel at the concentrations tested (0.005% to 0.2%) was superior to vehicle ($P = 0.0001$) in the AUC of the baseline-corrected thickness of the psoriatic infiltrates. E6201 gel at the concentrations tested was also statistically significantly better than vehicle in decreasing the psoriatic infiltrate thickness at the end of the treatment (Day 12) in the Full Analysis Population based on changes from baseline to Day 12 (end-of-treatment). The decreases in psoriatic infiltrate thickness on Day 8 were also significantly better than vehicle, but less evident than those on Day 12, suggesting further improvement between Day 8 and Day 12. In the Full Analysis Population, a greater percentage of subjects treated with E6201 gel or Daivonex achieved 'slight improvement', 'clear improvement but not completely healed', or 'completely healed' in target psoriatic lesions based on clinical (global) assessment compared with vehicle. Results from supportive analyses were generally similar to those observed in the Full Analysis Population. **Safety:** Skin reactions were observed in all (100%) subjects who received the E6201 0.1% and 0.2% concentrations, five (33.3%) subjects who received the E6201 0.05% concentration, four (26.7%) subjects who received the E6201 0.03% concentration, no (0%) subjects who received the E6201 0.01% and E6201 0.005% concentrations, three (10.0%) subjects who received Daivonex, and one (3.3%) subject who received vehicle. All AEs were considered to be mild in severity. In Cohort 1, three events of contact dermatitis resulted in discontinuation of study treatment at Day 8; one subject in the Daivonex treatment field and one subject in the vehicle- and E6201 0.03%-treated fields. There were no safety concerns highlighted in the laboratory and vital signs data.
Conclusions:	• E6201 gel at the concentrations tested (0.005% to 0.2%) was, overall, better than vehicle in decreasing the psoriatic infiltrate thickness during 12 days of once daily topical treatment. • A greater percentage of subjects treated with E6201 gel achieved 'slight improvement', 'clear improvement but not completely healed', or 'completely healed' in target psoriatic lesions based on clinical (global) assessment of efficacy compared with vehicle. • Results from both evaluations of psoriatic infiltrate thickness and clinical (global) assessment of efficacy provide evidence of potential clinical efficacy of the E6201 gel formulation.

	• In this study, there was no evidence of systemic adverse effect of once daily topical treatment of E6201 at 0.005% to 0.2% concentrations. E6201 at concentrations of 0.03% or higher resulted in increasing incidences of mild skin related TEAEs, suggesting a potential local skin effect of the E6201 active ingredient, which warrants further evaluation.
Date of Report:	09 Februayr 2012