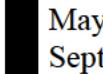


2. SYNOPSIS

Sponsor: Shionogi Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Not applicable	Volume:	
Name of Active Ingredient: S-297995 [Naldemedine]	Page:	
Study Title: A Randomized, Double-blind, Placebo- and Positive-controlled, 4-Period, Cross-over Study to Assess the Effect of S-297995 on ECG Parameters in Healthy Volunteers		
Investigator and Study Center: 		
Publication (reference): None		
Studied Period:  May 2013 (first subject enrolled) to September 2013 (last subject completed)		
Study Phase: Phase 1		
Objectives: The primary objective of the study was to demonstrate that single doses of 0.2 mg and 1 mg of S-297995 do not have an effect on the QTcF interval that exceeds 10 ms in healthy volunteers. The secondary objectives of the study were: <ul style="list-style-type: none">• To study the effect of single doses of 0.2 mg and 1 mg of S-297995 on other ECG parameters (heart rate [HR], PR, QRS, and QT) in healthy volunteers• To confirm sensitivity of study population by the assessment of the effect of moxifloxacin on the QTcF interval in healthy volunteers• To assess the safety of 0.2 mg and 1 mg of S-297995 in healthy volunteers• To assess the pharmacokinetic (PK) profile of 0.2 mg and 1 mg of S-297995 in healthy volunteers• To assess the relationship between S-297995 plasma concentration and the QTcF effect in healthy volunteers		

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<p>Methodology: This was a double-blind, randomized, placebo- and active-controlled 4-period cross-over study in healthy male and female volunteers using single doses of a therapeutic (0.2 mg) and a supratherapeutic (1 mg) dose of S-297995, placebo, and moxifloxacin in separate treatment periods. Each treatment period consisted of 2 days, during which the subjects were confined to the clinical pharmacology unit (CPU), with a 14-day washout period between treatments. An end-of-study (EOS) visit was on Day 45 and a final follow-up visit was performed 14 days after EOS on Day 59. Subjects were confined to the CPU from the day before dosing (Day 1) until the morning of Day 3 and were not discharged earlier than 26 hours after dosing (this process was followed for each treatment period). Study drug was administered with 240 mL of room temperature, non-carbonated water (eg, tap water) in the morning (at approximately 8 AM) of Days 2, 16, 30, and 44 after a minimum of an 8-hour fast.</p> <p>Electrocardiograms were obtained digitally using a 12-lead continuous ECG recorder. A 25-hour recording started approximately 1 hour before dosing in the morning of Days 2, 16, 30, and 44. The ECGs were extracted from recordings at the following time points: predose at 3 time points (1 hour, 30 minutes, and immediate predose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 hours postdose. Subjects rested in a supine position for 10 minutes before and 5 minutes after each time point at which an ECG was to be extracted. Vital signs and blood draws were performed after time windows from which ECG were extracted.</p>		
<p>Number of Subjects (Planned and Analyzed):</p> <p>Number of subjects planned: Forty-eight subjects were planned; with an estimated drop-out rate of 15%, 40 subjects were expected to complete the study. However, the study had a slightly higher than expected dropout rate in the first cohort of subjects. In order to ensure 40 evaluable subjects for analysis, recruitment continued as needed to support the primary goal of 40 evaluable subjects for the study as documented in an administrative letter dated 21 June 2013 (Appendix 16.1.1).</p> <p>Number of subjects randomized: 56</p> <p>Number of subjects analyzed: All 56 (100%) subjects were included in the Safety Population, 53 (94.6%) subjects were included in the PK Population, 55 (98.2%) subjects were included in QT/QTc Population, and 53 (94.6%) subjects were included in the PK/QTc Population.</p> <p>Number of subjects who completed the study: 44</p>		

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Main Criteria for Inclusion: Male and female healthy subjects ≥ 18 to ≤ 50 years of age, body mass index (BMI) of ≥ 18.5 to $\leq 32 \text{ kg/m}^2$, body weight $\geq 50 \text{ kg}$, and able to understand and willing to sign an informed consent form for the study. The target was to enroll an even distribution between genders with no less than 40% of 1 gender.		
Test Product: S-297995 (0.2 mg tablet) Dose and Mode of Administration: 0.2 mg (therapeutic) and 1 mg (supratherapeutic), oral administration Lot Number: [REDACTED]		
Control Product: Placebo, tablet matching S-297995 Dose and Mode of Administration: 0 mg, oral administration Lot Number: [REDACTED]		
Control Product: Moxifloxacin (Avelox [®] , 400 mg tablet) Dose and Mode of Administration: 400 mg, oral administration Lot Number: [REDACTED]		
Duration of Treatment: Screening occurred during the 21-day period prior to Day 1. Subjects entered the CPU on the day before each dosing (Days 1, 15, 29, and 43). Subjects were discharged from the CPU after all procedures had been completed on Days 3, 17, 31, and 45 (EOS). Subjects returned to the clinic on Day 59 ± 2 (14 days after the last discharge) for a follow-up visit and final safety evaluation. The total duration of time necessary to complete the study was estimated to be approximately 3 months.		
Criteria for Evaluation: Pharmacokinetic Parameters: Plasma concentrations of S-297995 and its metabolites (Nor-S-297995 and S-297995 3-O- β -D-glucuronide) were analyzed to determine their respective maximum observed plasma concentration (C_{\max}), time to maximum observed plasma concentration (T_{\max}), area under the plasma concentration–time curve from time 0 to the time of the last measurable concentration ($AUC_{0-\text{last}}$), area under the plasma concentration–time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), and apparent terminal elimination half-life ($t_{1/2}$) using non-compartmental methods within WinNonlin Version 6.2.1.		

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Pharmacodynamics: Electrocardiograms were obtained digitally using a 12-lead continuous ECG recorder [REDACTED]. The following ECG parameters were measured and assessed: RR, HR, QT, QRS, PR, T wave, and U wave (if present).		
Bioanalytical: <ul style="list-style-type: none">• Measurement method: liquid chromatography/tandem mass spectrometry• Lower limit of quantification of S-297995 in plasma: 0.0100 ng/mL• Lower limit of quantification of Nor-S-297995 and S-297995 3-O-β-D-glucuronide in plasma: 0.0400 ng/mL		
Safety: Safety was assessed by monitoring of adverse events (AEs), clinical laboratory evaluations (including hematology, blood chemistry tests, and urinalysis), vital signs, safety 12-lead ECGs, and physical examinations. Treatment-emergent adverse events (TEAEs), treatment-related AEs, and serious adverse events (SAEs) were tabulated.		
Statistical Methods: Pharmacokinetics: To assess the PK profile of S-297995 0.2 mg and 1 mg doses, C_{max} , T_{max} , AUC (AUC _{0-last} and AUC _{0-inf}) and $t_{1/2}$ for S-297995, Nor-S-297995, and S-297995 3-O-β-D-glucuronide were derived from the concentration versus time data using non-compartmental analysis. For concentration data at individual time points as well as C_{max} , AUC, and $t_{1/2}$, descriptive statistics included the number of observations, arithmetic mean, geometric mean, minimum, median, maximum, standard deviation (SD), standard error (SE), coefficient of variation (CV%), CV% of the geometric mean, and 95% confidence intervals (CIs) of the means. The CI for a geometric mean was based on log-transformed data that was back-transformed to the original scale. For T_{max} , descriptive statistics included the number of observations, arithmetic mean, minimum, median, maximum, SD. The dose-response relationship of the PK parameters was explored using graphical analysis.		
Pharmacodynamics: The primary endpoint was the baseline-adjusted, placebo-corrected QTcF ($\Delta\Delta QTc$). Secondary endpoints were: 1) the baseline-adjusted, placebo-corrected HR, PR, QRS, QT, and QTcB; 2) categorical analyses for QTcF, PR, QRS, and HR; and 3) the frequency of T-wave morphology changes and U-wave presence. The ECG QT and RR value for each beat was used for HR correction. The ECG QTcF was calculated as $QT/RR^{1/3}$.		

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<p><u>Central Tendency Analysis</u></p> <p>The primary analysis for each of the doses of S-297995 was based on an analysis of covariance model with the change-from-baseline in the QTcF interval as dependent variable, time (categorical), treatment (0.2 mg and 1 mg of S-297995, moxifloxacin, and placebo), and time-by-treatment interaction as factors, and baseline as covariate. Since this was a cross-over design, period and sequence terms were also included in the model. Subject was included as a random effect for the intercept. For this analysis, a 2-sided 90% CI was calculated for the contrast “treatment – placebo.” A baseline-adjusted, placebo-corrected QTc effect exceeding 10 ms could have been excluded for the respective dose, if the upper bound (UB) of the CI was below this level for all time points.</p> <p>For other ECG parameters (ie, HR, PR, QRS, and QT), descriptive analysis for change-from-baseline and time-matched placebo-adjusted change-from-baseline values were listed in the tables and graphically displayed.</p> <p>The analysis to show assay sensitivity was based on the change-from-baseline postdose of moxifloxacin. The same model as described for the primary analysis was used. For the time points 2, 3, and 4 hours, the contrast in treatment $\Delta\Delta QTc = \text{“moxifloxacin - placebo”}$ was tested against the 1-sided null hypothesis $\Delta\Delta QTc \leq 5$ ms on the 5% level. Multiplicity was controlled by using a Hochberg procedure for the 3 P-values obtained. If after this procedure $\Delta\Delta QTc$ was significantly larger than 5 ms for at least 1 time point, assay sensitivity was considered shown. In addition, 2-sided 90% CIs were obtained for the contrast at all time points for descriptive purposes and were used in the figures.</p> <p><u>Categorical Analysis</u></p> <p>The analysis results for categorical outliers and T-wave morphology were summarized in frequency tables with counts and percentages for both number of subjects and number of time points. For categorical outliers, the number (percentage) of subjects as well as time points with increases in QTc from baseline of > 30 and > 60 ms, and absolute QTc values > 450, > 480, and > 500 ms were determined by treatment group, respectively. For T-wave morphology, the analysis was focused on change-from-baseline, ie, treatment-emergent changes. Categorical analysis for PR, QRS, and HR were performed in a similar fashion.</p> <p><u>Concentration-QTc Analysis</u></p> <p>The relationship between $\Delta\Delta QTcF$ and S-297995 and Nor-S-297995 plasma concentrations was investigated by linear mixed-effects modeling. The following 3 linear</p>		

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models were considered: 1) Model 1 was a linear model with an intercept; 2) Model 2 was a linear model with mean intercept fixed to 0 (with variability); and 3) Model 3 was a linear model with no intercept. Time-matched concentration was included in the model as covariate and subject as a random effect for both intercept and slope, when applicable. The model that fit the data best was used for predicting $\Delta\Delta QTcF$ at the geometric mean peak S-297995 and Nor-S-297995 concentration.		
Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities Dictionary (Version 16.0). All AEs were summarized (number and percentage of subjects affected) by treatment group, preferred term, and system organ class. Serious AEs and AEs leading to discontinuation were listed separately.		
Summary of Results: Subject Disposition: A total of 141 subjects signed the consent form and were screened for the study. Fifty-six subjects failed to meet the eligibility criteria during the screening process. Twenty-nine subjects were dropped prior to randomization and 56 subjects were randomized for the study. Of these 56 subjects, 44 (78.6%) subjects completed the study per protocol and 12 (21.4%) subjects discontinued from the study prematurely. All 56 (100%) subjects were included in the Safety Population, 53 (94.6%) subjects were included in the PK Population, 55 (98.2%) subjects were included in QT/QTc Population, and 53 (94.6%) subjects were included in the PK/QTc Population.		

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Pharmacokinetics:			
A summary of S-297995 plasma PK parameters is presented in Table 1.			
Table 1 Summary of S-297995 Plasma Pharmacokinetic Parameters by Treatment (PK Population)			
Parameter	Statistics	S-297995 Dose	
		0.2 mg	1 mg
C _{max} (ng/mL)	n Geometric Mean CV% Geometric Mean 95% CI	51 2.36 30.7 2.17, 2.56	48 11.9 30.9 10.9, 13.0
T _{max} (hr)	n Median Min, Max	51 1.08 0.33, 4.13	48 1.08 0.33, 4.08
AUC _{0-last} (ng•hr/mL)	n Geometric Mean CV% Geometric Mean 95% CI	51 17.81 20.3 16.83, 18.85	48 91.29 20.4 86.09, 96.82
AUC _{0-inf} (ng•hr/mL)	n Geometric Mean CV% Geometric Mean 95% CI	47 ^{a, b} 20.11 21.1 18.92, 21.38	43 ^{a, b} 103.1 21.1 96.65, 109.9
t _{1/2} (hr)	n Geometric Mean CV% Geometric Mean 95% CI	48 ^a 7.81 13.3 7.52, 8.12	43 ^a 7.52 10.8 7.28, 7.78
Abbreviations: CI = confidence interval; CV% = coefficient of variation; n = non-missing observations. a. t _{1/2} and AUC _{0-inf} were excluded if elimination phase could not be determined or was poorly estimated. b. AUC _{0-inf} was excluded if extrapolated portion was greater than 20%.			
Source: Table 14.2.2.4			
For all 3 parameters, C _{max} , AUC _{0-last} , and AUC _{0-inf} , the geometric mean values were approximately 5.0- to 5.1-fold higher at 1 mg dose compared with 0.2 mg dose, indicating a proportional increase in S-297995 exposure with increasing dose (0.2 mg to 1 mg). Median T _{max} of S-297995 was 1.08 hour for both the 0.2 mg (range: 0.33 to 4.13 hours) and 1 mg (range: 0.33 to 4.08 hours) doses with similar individual ranges. The geometric mean t _{1/2} of S-297995 was also similar at the 0.2 mg (7.81 hours) and 1 mg (7.52 hours) dose levels. The plasma PK parameters of S-297995 were, in general, similar between male and female subjects at both the 0.2 mg and 1 mg dose levels.			

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For Nor-S-297995, the geometric mean C_{max} and AUC_{0-last} were 5.2-fold and 5.6-fold higher, respectively, following administration of 1 mg compared with 0.2 mg S-297995, suggesting a proportional increase in Nor-S-297995 exposure with increasing S-297995 dose from 0.2 mg to 1 mg. Median T_{max} of Nor-S-297995 was 4.08 hours for both the 0.2 mg (range: 3.08 to 12.08 hours) and 1 mg (range: 3.08 to 6.88 hours) S-297995 doses with comparable individual range. The plasma PK parameters of Nor-S-297995 were, in general, similar between male and female subjects at both the 0.2 mg and 1 mg S-297995 dose levels.		
For S-297995 3-O-β-D-glucuronide, the geometric mean C_{max} and AUC_{0-last} were 3.8-fold and 7.4-fold higher, respectively, following administration of 1 mg compared with 0.2 mg S-297995. The T_{max} of S-297995 3-O-β-D-glucuronide was similar for the 0.2 mg (median: 2.60 hours; range: 1.08 to 4.13 hours) and 1 mg (median: 3.08 hours; range: 1.08 to 4.08 hours) S-297995 doses with similar individual range. The $t_{1/2}$ of S-297995 3-O-β-D-glucuronide was determined in approximately 50% of subjects receiving 1 mg S-297995 with a geometric mean value of 7.98 hours.		
Pharmacodynamics: The $\Delta QTcF$ observed after dosing with 0.2 mg and 1 mg S-297995 was essentially the same as on placebo, whereas a clear QTcF prolongation was observed after 400 mg moxifloxacin. The largest observed placebo-corrected $\Delta QTcF$ ($\Delta\Delta QTcF$) was 1.3 ms (UB of 2-sided 90% CI: 3.2 ms) 4 hours after dosing with 0.2 mg S-297995 and 0.6 ms (UB of CI: 2.5 ms) 2 hours after dosing with 1 mg S-297995. There were no subjects with a QTcF value exceeding 480 ms or $\Delta QTcF$ above 30 ms in the PD analysis data set. A repeated gender analysis was not required. Assay sensitivity was confirmed by the moxifloxacin $\Delta\Delta QTcF$ response with a largest mean effect of 12.6 ms 4 hours after dosing and the lower bound of the 2-sided 90% CI at 2 hours, 2-sided 95% CI at 3 hours and 2-sided 96.7% CI at 4 hours above 5 ms. S-297995 0.2 mg and 1 mg did not have an effect on cardiac conduction. The $\Delta\Delta PR$ was within ± 2 ms and $\Delta\Delta QRS$ within ± 1 ms at each postdose time point. The results of the study demonstrate that S-297995 at doses of 0.2 mg and 1 mg does not have a meaningful effect on any ECG parameter. The mean QTcF effect ($\Delta\Delta QTcF$) of S-297995 was below 5 ms with UB of the 2-sided 90% CI below 10 ms at each postdose time point. Thereby, these results represent a negative thorough QT (TQT) study as defined by the ICH E14 guidance. Concentration effect modeling demonstrated the lack of a statistical relationship between the plasma concentrations of S-297995 or its main metabolite, Nor-S-297995, and		

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placebo-corrected ΔQTcF by very shallow, not statistically significant slopes for both: 0.0256 ms per ng/mL (90% CI: -0.0789 to 0.130 ms per ng/mL) for S-297995 and 0.660 ms per ng/mL (90% CI: -2.06 to 3.38 ms per ng/mL) for Nor-S-297995. The predicted ΔΔQTcF in the upper decile of plasma concentrations of S-297995 (around 12 ng/mL to 15 ng/mL) and Nor-S-297995 (around 0.8 ng/mL) was around 0 ms with an UB of the 90% CI of below 5 ms. The concentration effect analysis thereby supports the conclusion from the primary analysis.		
Safety: <ul style="list-style-type: none">• There were no deaths, other SAEs, or AEs leading to study discontinuation.• Overall, 21 (37.5%) of 56 subjects had 44 TEAEs during the study:<ul style="list-style-type: none">▪ 0.2 mg S-297995 (N = 52 subjects): 9 (17.3%) subjects had 11 TEAEs▪ 1 mg S-297995 (N = 49 subjects): 8 (16.3%) subjects had 15 TEAEs▪ 400 mg moxifloxacin (N = 49 subjects): 5 (10.2%) subjects had 9 TEAEs▪ Placebo (N = 46 subjects): 7 (15.2%) subjects had 9 TEAEsThe frequency of TEAEs was similar between placebo and S-297995.• Overall (N = 56 subjects), the most frequent (≥ 2 subjects) TEAEs were:<ul style="list-style-type: none">▪ abdominal pain (5 [8.9%] subjects)▪ nausea (4 [7.1%] subjects)▪ increased CRP (4 [7.1%] subjects)▪ headache (4 [7.1%] subjects)▪ diarrhea (3 [5.4%] subjects)▪ vomiting (3 [5.4%] subjects)▪ vessel puncture site pain (2 [3.6%] subjects)• The most frequent TEAEs by treatment were:<ul style="list-style-type: none">▪ 0.2 mg S-297995 (N = 52 subjects):<ul style="list-style-type: none">- abdominal pain (2 [3.8%] subjects)- diarrhea (2 [3.8%] subjects)- increased C-reactive protein ([CRP]; 2 [3.8%] subjects)- headache (2 [3.8%] subjects)▪ 1 mg S-297995 (N = 49 subjects):<ul style="list-style-type: none">- abdominal pain (4 [8.2%] subjects),- nausea (2 [4.1%] subjects), and- increased CRP (2 [4.1%] subjects)▪ 400 mg moxifloxacin (N = 49 subjects):<ul style="list-style-type: none">- vomiting (2 [4.1%] subjects)▪ Placebo (N = 46 subjects):<ul style="list-style-type: none">- diarrhea (2 [4.3%] subjects)		

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<ul style="list-style-type: none">• All TEAEs were mild or moderate in severity. Six subjects had at least 1 TEAE that was considered moderate in severity:<ul style="list-style-type: none">▪ 0.2 mg S-297995 (N = 52 subjects):<ul style="list-style-type: none">- abdominal pain (1 [1.9%] subject)▪ 1 mg S-297995 (N = 49 subjects):<ul style="list-style-type: none">- abdominal pain (1 [2.0%] subject)- abdominal pain upper (1 [2.0%] subject)- increased CRP (1 [2.0%] subject)▪ 400 mg moxifloxacin (N = 49 subjects):<ul style="list-style-type: none">- lethargy (1 [2.0%] subject)▪ Placebo (N = 46 subjects):<ul style="list-style-type: none">- abdominal pain (1 [2.2%] subject)• Overall, 12 subjects had at least 1 TEAE that was considered related to S-297995, moxifloxacin, or placebo:<ul style="list-style-type: none">▪ 0.2 mg S-297995 (N = 52 subjects):<ul style="list-style-type: none">- abdominal pain (2 [3.8%] subjects)- diarrhea (2 [3.8%] subjects)▪ 1 mg S-297995 (N = 49 subjects):<ul style="list-style-type: none">- abdominal pain (4 [8.2%] subjects)- nausea (2 [4.1%] subjects)- diarrhea (1 [2.0%] subject)- headache (1 [2.0%] subject)- generalized pruritus (1 [2.0%] subject)▪ 400 mg moxifloxacin (N = 49 subjects):<ul style="list-style-type: none">- vomiting (2 [4.1%] subjects)- nausea (1 [2.0%] subject)- drug hypersensitivity (1 [2.0%] subject)- decreased appetite (1 [2.0%] subject)- lethargy (1 [2.0%] subject)▪ Placebo (N = 46 subjects):<ul style="list-style-type: none">- diarrhea (2 [4.3%] subjects)- abdominal pain (1 [2.2%] subject)- nausea (1 [2.2%] subject)- increased blood uric acid (1 [2.2%] subject)• The majority of laboratory values were normal or abnormal considered not clinically significant. The TEAEs associated with abnormal laboratory values included elevated serum CRP (0.2 mg S-297995 and 1 mg S-297995) and elevated serum urate (placebo); all resolved without clinical intervention.		

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	<ul style="list-style-type: none">There were no TEAEs associated with vital signs or physical examination findings.The majority of ECGs values were normal or abnormal considered not clinically significant. One TEAE (0.2 mg S-297995) was associated with prolonged QTcF that was mild, considered not related to study drug, and resolved without clinical intervention. <p>All TEAEs resolved by the end of the study.</p>	
Conclusions:		
Pharmacokinetics:		
<ul style="list-style-type: none">Following oral administration of 0.2 mg and 1 mg S-297995, C_{max} and AUC of S-297995 increased dose proportionally. The T_{max} of S-297995 was approximately 1 hour and $t_{1/2}$ was approximately 7.5 to 7.8 hours.Following oral administration of 0.2 mg and 1 mg S-297995, T_{max} was approximately 4 hours for Nor-S-297995 and approximately 2.6 to 3 hours for S-297995 3-O-β-D-glucuronide. For both metabolites, C_{max} and AUC increased with increasing dose of S-297995.		
Pharmacodynamics:		
<ul style="list-style-type: none">S-297995 at doses of 0.2 mg and 1 mg did not have a clinically meaningful effect on the QTcF interval, HR, and cardiac conduction (ie, the PR and QRS intervals). The largest observed placebo-corrected $\Delta QTcF$ ($\Delta\Delta QTcF$) was 1.3 ms (UB of 2-sided 90% CI: 3.2 ms) with 0.2 mg S-297995 and 0.6 ms (UB of 2-sided 90% CI: 2.5 ms) with 1 mg S-297995. The results thereby represent a negative TQT study as defined by the ICH E14 guidance.The concentration effect analysis supports the conclusion from the primary analysis.Assay sensitivity was confirmed by the moxifloxacin $\Delta\Delta QTcF$ response.		
Safety:		
<ul style="list-style-type: none">A single dose of 0.2 mg or 1 mg of S-297995 was well tolerated in healthy subjects.		
Final Report Date: 02 February 2015		
Prepared in: Microsoft Word 2010		