16.1.9 Documentation of Statistical Methods

Allergan
Biostatistics
Statistical Analysis Plan

Study ID: CMO-MA-MED-0530

Study Title: Multicenter, Open-Label, Interventional Study on the Safety and Tolerability of Oxymetazoline and Energy-Based Therapy in Subjects with Rosacea

Study Phase: IV

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Contents

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses and reporting that are outlined in the study protocol, which is dated on Oct 12, 2017 and titled "Multicenter, Open-Label, Interventional Study on the Safety and Tolerability of Oxymetazoline and Energy-Based Therapy in Subjects with Rosacea". This SAP should be reviewed in conjunction with the study protocol. Information contained in the protocol will not be restated unless it is essential for the descriptions in this SAP. In case of any discrepancies (for example, the definition of the Safety Analysis Population) between the protocol and the SAP, the SAP will supersede the protocol, as the SAP is intended to be more specific and precise with respect to statistical analysis and reporting. Any amendments to the SAP will be made prior to database lock. Any additional analyses not described in the final SAP or deviations from the final SAP will be documented in the clinical study report.

This study is a Phase 4 study sponsored by Allergan Plc. This study is a multicenter, interventional, open-label safety and tolerability study to evaluate the safety and tolerability of oxymetazoline HCl cream 1.0% when used as an adjunctive treatment to energy-based therapy for subjects with moderate to severe persistent facial erythema associated with rosacea.

Approximately 45 subjects will be enrolled into this study at 4 clinical sites in the United States. The duration of the study for each subject is 10 weeks. This includes a screening period of up to 2 weeks, a treatment period of 8 weeks, comprising of daily dosing of study drug and 2 energy-based therapy sessions, followed by a final exit visit at Week 8 (Day 56).

There will be no interim analysis. One final analysis is planned for this study. The final analysis will be performed at the completion of the study. Database lock will be executed for the final analysis.

1.1 Primary Study Objectives and Design

1.1.1 Study Design

This is a multicenter, interventional, single-arm, open-label safety and tolerability study.

Sample size calculation and power consideration are discussed in Section 8.2 of the study protocol. A total of 45 subjects with rosacea-associated moderate to severe persistent facial erythema will be enrolled into this study. Subjects will be screened for eligibility, and will be consented for the study entry.

On Day 1, all subjects will receive one of the following energy-based therapies: Potassium Titanyl Phosphate (KTP), Pulsed Dye Laser (PDL) or Intense Pulsed Light (IPL). After a 2-day washout, oxymetazoline HCl cream 1.0% will be applied once-daily starting from Day 3 up through Day 27. On Day 29, all subjects will receive a second energy-based therapy, followed by a 2-day washout and then once daily application of oxymetazoline HC1 cream 1.0% up through Day 56.

1.1.2 Primary Objectives

The primary objective is to evaluate the safety and tolerability of oxymetazoline HCl cream 1.0% when used as an adjunctive treatment to energy-based therapy for subjects with moderate to severe persistent facial erythema associated with rosacea.

1.1.3 Secondary and Other Objectives

The secondary objective is to evaluate preliminary measures of efficacy of oxymetazoline HCl cream 1.0% when used as an adjunctive treatment to energy-based therapy for subjects with moderate to severe persistent facial erythema associated with rosacea.

2. Analysis Populations and Data Conventions

2.1 Analysis Populations

To adequately describe the appropriate statistical analyses, four analysis populations are defined as follows:

- Enrolled Population: consists of all subjects who signed an informed consent form (ICF), thus deemed as enrolled for the study.
- Safety Analysis Population: consists of all enrolled subjects who met the eligibility criteria and had an energy-based therapy and received at least one dose of study drug as treatment in this study.
- Evaluable Population: consists of all safety subjects who had at least one baseline efficacy assessments at Day 1 or prior to Day 1 and had at least one post-treatment efficacy assessments between Day 3 and Day 56, inclusive.
- Per Protocol Population: consists of all evaluable subjects who have not had any significant violations of the protocol, including but not limiting to significant deviations from the scheduled visit windows.

Unless specified otherwise, the enrolled population will be used for subject disposition, demographics, and baseline characteristics summaries; the safety analysis population will be used for safety analyses, and the evaluable population will be used for the efficacy analyses. Efficacy analyses may be repeated on the per protocol population if significant protocol violations are found prevalent in the evaluable population.

Note that in the context of this analysis plan (including the Table/Listing/Figure mockup shells), the terms safety analysis population and safety population are interchangeably used, and subjects in the safety population can be called safety subjects and subjects in the evaluable population can be called evaluable subjects.

2.2 Visit and Timepoint Windows

There is no plan to programmatically derive visit/timepoint windows. The scheduled visits/timepoints as recorded on the electronic Case Report Form (CRF) will be directly taken as the analysis visits/timepoints and will be used in reporting and analyses. The analysis visits include the Screening Visit, the Baseline (Day 1) Visit, the Day 3 Visit, the Day 29 Visit, the Day 31 Visit and the Day 56 (Exit Visit). The analysis timepoints corresponding to each visit on and after Day 1 include the Pre-Dose and the Post-Dose. Also refer to Table 1 Schedule of Assessments and Procedures (page 18) of the Protocol (Oct 12, 2017) for scheduled visits/timepoints.

If there are multiple observations of same assessment within the same scheduled visit/timepoint window, all values of multiple observations will be included for listing, but only the mean value of multiple observations will be used for the by-visit/timepoint summary or analysis. Assessment outside the scheduled visit/timepoint window will be marked as unscheduled assessment, and will be used for listing only.

2.3 Data Conventions

2.3.1 Study day

For each subject, the reference start date (also referred to as Day 1) is the date when the subject had an energy-based therapy. Study day will be calculated using visit date and the

reference start date as follows: (1) study day = visit date – reference start date + 1, for any visit date ≥ reference start date. (2) study day = visit date – reference start date, for any visit date < reference start date.

2.3.2 Imputation for missing measurement or assessment data

On some certain parameters, a subject has multiple assessments prior to the initiation of the energy-based therapy at Day 1. Specifically, those parameters include vital sign measurements, urine pregnancy tests, Clinician's Telangiectasia Assessments (CTA), Satisfaction assessments for Rosacea facial redness, FACE-Q satisfaction with skin scale. The baseline values for subjects on those parameters will be derived using the rule of Last Observation Carried Forward (LOCF) as follows: The value immediately prior to the initiation of energy-based therapy at Day 1 will be used as the baseline value; if that value is missing or does not exist, then the value at screening will be used. On other parameters, a subject has one single assessment or measurement during screening or prior to the initiation of the energy-based therapy at Day 1, then the single value will simply be used as the baseline value for the subject.

There is no imputation of missing values for any post-baseline measurements or assessments. All data summaries and analyses of post-baseline data will be conducted using observed cases.

2.3.3 Study end date for patient

Study end date for each individual patient is defined as the date of completion of last assessment on the Day 56 visit or the date of the early withdrawal visit in case of earlier discontinuation from treatment. Note that subjects who are discontinued earlier from treatment for whatever reasons will be invited to attend the early withdrawal visit for the end-of-study data collection.

2.3.4 Study completer

Study completers are defined as those evaluable subjects who have completed the last assessment on the Day 56 visit.

2.3.5 Other conventions

Summary statistics (used interchangeably with the term descriptive statistics) for continuous data include sample size (N), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using sample size (N), frequency and percentages of patients. In calculating the percentage, unless specified otherwise, the count of

subjects “at risk” will be used as denominator. Ordinal variables will be handled as categorical variables when presenting summary statistics using ordinal variables.

Change from baseline is calculated as follow-up minus baseline. Percentage change from baseline is calculated as change from baseline divided by baseline value, then multiplied by 100. If baseline value is zero, percentage change from baseline will be undefined. If baseline value is missing, percentage change from baseline will be missing.

Data will be pooled across clinical sites/centers for analyses with an exception of one patient enrollment table.

The International System of Units (Système international d'unités or SI) is the current international standard metric system. The SI units will be used for the reporting in all Tables/Figures/Listings for this study.

All statistical analysis and reporting will be performed using SAS® version 9.3 or higher.

3. Disposition and Exit Status

3.1 Screening Log Data

Subject eligibility criteria (including both inclusion and exclusion criteria) and date of informed consent will be listed for the enrolled population. Note that date of informed consent will be included in the subject disposition listing.

3.2 Disposition and Exit Status

Reasons for exclusion from safety population will summarized and will be listed for the enrolled population. Subject disposition will be listed for the enrolled population.

4. Demographics and Baseline Characteristics

4.1 Demographics

All patient demographic and baseline characteristic data will be summarized using descriptive statistics for the enrolled population and the safety population.

Age (years) captured at enrollment will be summarized as a continuous variable. Other continuous variables to be presented include weight, height and body mass index (BMI) and baseline vital signs (i.e., blood pressure, pulse rate, and oral body temperature). Categorical or ordinal variables to be presented include sex, race, ethnicity, the type of energy-based therapy on Day 1 and Fitzpatrick skin phototype.

Demographic tables will also be presented for the safety population stratified by the presence or absence of Treatment-Emergent Adverse Events (TEAE) during the study, and by whether having had at least 1-grade worsening from baseline in Clinician's Telangiectasia Assessments (CTA) at any timepoint in the study.

All demographic data will be listed.

4.2 Prior Medications

Prior medications are defined as any medication which is administered any time prior to the initiation of the energy-based therapy treatment at Day 1 regardless when the medication stops.

Prior medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization (WHO) Drug WHODDE March 2016 or later. Medications will be summarized by ATC class (level 2) and subclass preferred term (PT) for all patients in the safety analysis cohort.

The summary tables will show the frequency count and percentage of patients with at least 1 usage of medications on the subclass level within each ATC class, sorted alphabetically. Percentages will be calculated using the number of patients in the safety population as the denominator.

All prior medications will be listed.

4.3 Concomitant Medications

Concomitant medications encompass any medication that is administered any time after the initiation of the energy-based therapy, regardless of when the medication starts or stops. Note that concomitant medication includes on-going prior medications. i.e., medicinal products

that are administered prior to the initiation of the energy-based therapy at Day 1 and is still being used during the study.

Any concomitant medication will be recorded at each visit, including the medication name, dose, unit, frequency, route of administration, indication, and medication start and end dates.

Concomitant medications will be coded by the ATC classification system according to the WHO Drug WHODDE March 2016 or later. Medications will be summarized by ATC class (level 2) and subclass (PT) for all patients in the safety analysis cohort.

The summary tables will show the frequency count and percentage of patients with at least 1 usage of medication on the subclass level within each ATC class, sorted alphabetically. Percentages will be calculated using the number of patients in the safety population as the denominator.

All concomitant medications will be listed.

Prohibited Medications are listed in Section 5.6.10.1 of the Protocol. Prohibited concomitant medications that were inadvertently administered will be summarized similarly as that for concomitant medications. Listing will also be provided for prohibited medications that were inadvertently administered.

Per Section 5.6.10.2 of the Protocol, treatments by laser, light-source, or other energy based therapies to the face, other than those treatments performed as part of the study, are not permitted during the study. Dermatological treatments on the face (e.g., facial peels, microdermabrasion, exfoliating treatments) are prohibited for the duration of the study. The use of any of such treatments is considered as a deviation (violation) of protocol per this SAP. Listing of protocol deviation (violation) will be provided.

4.4 Medical History

Descriptions of medical history findings will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later. Medical history will be summarized for the safety population by the number and percentage of patients within each system organ class (SOC) and PT, sorted descending overall frequency.

Medical history will be listed for all patients in the safety population. Medical history data listings will be sorted by patient number, start date, SOC, PT and verbatim term.

5. Efficacy Analyses

For this study, efficacy analyses will be exploratory in nature. Certain efficacy analyses will be conducted to evaluate the effect of daily application of oxymetazoline 1.0% cream adjunctive to energy-based therapy on Clinician Erythema Assessment (CEA), rosacea facial redness and subject's satisfaction rating. These analyses as described below will be based on the evaluable population.

5.1 Collection of Efficacy Measurements and Derivation of Efficacy Variables

The following measurements and variables are of the primary interest.

- Measurement: CEA;
  Variable: Improvement on CEA from baseline. An improvement is defined by a negative change from baseline.

- Measurement: Satisfaction rating per the Satisfaction Assessment for Rosacea Facial Redness;
  Variable: Proportion of subjects who rate "Satisfied" or "Very Satisfied".

- Measurement: Satisfaction rating per the FACE-Q Satisfaction with Skin Scale;
  Variable: Proportion of subjects who rate "Somewhat Satisfied" or "Very Satisfied".

- Measurement: Rosacea facial redness using DIA of standardized facial photographs;
  Variable: Percentage change from baseline in rosacea facial redness.

5.2 Analyses of Efficacy Variable(s)

There is no statistical testing of hypotheses pertaining to efficacy variables. Statistical inference will be limited to the construction of distribution-free 95% CI for the median percentage change from baseline variables, since these percentage change variables are known for the deviation from normality in distribution. The distribution-free 95% CI for the

median will be calculated using SAS® procedure Proc Univariate. In this section, summary tables mainly in the forms of descriptive statistics will be presented for the above-specified efficacy and patient reported outcomes (PRO) variables.

- The number and percentage of subjects with at least a 1-grade improvement on the CEA from baseline, by visit/timepoint.
- Summary statistics of CEA by visit/timepoint.
- Proportion of subjects indicating Satisfied or Very Satisfied with treatment on the Items of Satisfaction Assessment for Rosacea Facial Redness, by visit. There are two items (questions). See Appendix 14.2 of the Protocol. Item 1 (Question 1) is: Right now, how satisfied are you with the appearance of your facial redness? Item 2 (Question 2) is: Right now, how satisfied are you with the appearance of the amount of redness on your face? This summary will be repeated for each of the two items.
- Proportion of subjects indicating Somewhat Satisfied or Very Satisfied with treatment on the FACE-Q Satisfaction with Skin Scale, by visit. There are 12 questions on the FACE-Q Satisfaction assessments regarding the subjects' rating of their satisfaction with skin. See Appendix 14.3 of the Protocol. This summary will be repeated for the response to each of the 12 questions, and for the average response to the 12 questions.
- Percentage change from baseline in rosacea facial redness using Digital Image Analysis (DIA) of standardized facial photographs, by visit/timepoint. This summary table will be presented if the rosacea facial redness data are obtained and such facial redness can be quantified. This summary table for the percentage change from baseline in rosacea facial redness will be provided.

5.3 Other Analyses of Efficacy Variable(s)

Not applicable.

5.4 Subgroup Analyses for Efficacy Variables

Not applicable.

6. Safety Analyses

All safety analyses will be based on the safety population. Safety will be assessed primarily in terms of the frequency count and the binominal incidence proportion of the adverse events of interest. The binomial incidence proportion for a given event of interest during a certain period is defined as the number of unique patients who have experienced the event of interest in the period divided by the number of patients in the safety population, then multiplied by 100. Note that, for the calculation of the incidence proportion, the numerator is counted at subject level. Specifically, if a subject has experienced the event(s) of interest (at a given summarization level) more than once during the period, he/she is counted only once into the numerator. The binomial incidence proportion of an event is also called the percentage of subjects who have had such an event. The two terms are used interchangeably. The 95% CIs for binomial incidence proportion will also be calculated using the Clopper and Pearson exact method (via SAS® procedure Proc Freq).

6.1 Exposure to Study Treatment(s)

Treatment duration in days will be calculated as: Date of last dose of study medication - Date of the initiation of the energy-based therapy + 1. Treatment duration will be summarized using descriptive statistics. Number of energy-based therapies administered and number of days in which Oxymetazoline 1.0% cream had been applied over the study period will be summarized using descriptive statistics.

Partial or missing start/end dates will be handled as per Section 2.3.3.

All treatment data will be listed.

6.2 Adverse Events

Adverse events will be coded using MedDRA version 20.1 or later to give a PT and a SOC term for each event.

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigational patient administered a pharmaceutical (investigational) product and which does not necessarily have to have a causal relationship with this treatment.

All AEs will be included in by-subject AE listings. A separate listing will be created with all the distinct levels of SOC and PT, and the verbatim investigator description reported in the study. Sorting will be by earliest observed SOC, PT within SOC and then verbatim description.

A treatment-emergent adverse event (TEAE) is a post-baseline AE where (i) there is no pre-treatment AE of the same MedDRA primary SOC and PT; or (ii) the maximum severity during the post-baseline period is greater than the maximal severity of any pre-treatment AE of the same MedDRA primary SOC and PT during the screening/baseline period. Note that the post-baseline period of the study starts upon the initiation of the energy-based therapy at Day 1.

Any AEs reported after signing of the Informed Consent Form and prior to the energy-based therapy on Day 1 are considered pretreatment AEs (PTAEs)

Relationship to study drug is categorized as 'related', 'possibly related', 'unlikely related', 'not related', and 'not assessable'. Relationship to trial medication as per investigator is not expected to be missing after data cleaning. However, if relationship is confirmed as missing, the AE will be considered as treatment related as per PI.

An overall summary of frequency count and the binomial incidence proportion with associated 95% CIs will be presented to describe the incidents of TEAEs. Note that 95% CIs of the binomial incidence proportion will be presented for the overall summary analyses of TEAEs, but not for the by-visit/timepoint analyses. Percentages and corresponding 95% CIs will be displayed to 1 decimal place.

Each type of AE will be tabulated by SOC and PT within SOC. The SOC and PT within SOC will be sorted by descending frequency. If a subject has multiple occurrences (start and stop) of an event associated with a specific SOC and PT, a patient will only be counted once in the incidence count for the SOC level and once at each PT within the SOC level.

The incidence of all TEAEs by SOC and PT will be presented for the following categories:

- Any TEAE
- Any TEAE related to energy-based therapy and leading to discontinuation of study medication
- Any TEAE related to treatment (i.e., study medication or energy-based therapy or both)

- Any TEAE by maximum severity
- Any PTAE

The following listings will be provided:

- Listing of all TEAE
- Listing of patients with TEAEs related to energy-based therapy and leading to discontinuation of study medication
- Listing of patients with TEAEs leading to discontinuation of treatment

6.3 Serious Adverse Events

A serious adverse event (SAE) is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Allergan considers all cancer AEs as SAEs. In addition, an abortion (spontaneous or non-spontaneous) is also considered a SAE. Any pre-planned surgery or procedure should be clearly documented in the source documents at the center by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a SAE and reported to Allergan.

If an unexpected AE is serious and suspected, it is a suspected "unexpected" serious adverse reactions (SUSAR). See Section of 7.1.2.1.2 of the Protocol for details, such as what is considered as "unexpected".

An overall summary of frequency count and the binomial incidence proportion with the associated 95% CIs will be presented to describe the incidents of treatment emergent SAEs. Note that 95% CIs of the binomial incidence proportion will be presented for the overall summary analyses of SAE, but not for the by-visit/timepoint analyses. Percentages and corresponding 95% CIs will be displayed to 1 decimal place.

The incidence of all treatment-emergent SAEs by SOC and PT within SOC will be presented for the following categories:

- Any SAE
- Any SAE related to energy-based therapy and leading to discontinuation of study medication
- Any SAE related to treatment (i.e., study medication or energy-based therapy or both)
- Any SAE by maximum severity
- Any SUSAR

The following listings will be provided:

- Listing of subjects who died
- Listing of subjects with treatment-emergent SAEs
- Listing of subjects with treatment-emergent SAEs related to energy-based therapy and leading to discontinuation of study medication
- Listing of patients with treatment-emergent SAEs leading to discontinuation of treatment
- Listing of patients with any SUSAR

6.4 Dermal Tolerability Assessments

Subject-assessed pruritus (itching), stinging/burning and dermatologist-assessed dryness and scaling will be summarized and displayed in terms of frequency count and proportion of subjects who reported at least a 1-grade worsening in severity from baseline at any time points over the study period.

For all dermal tolerability assessments, the scale (grade) was: 0 = none, 1 = mild, 2 = moderate, 3 = severe. A subject is classified as having had a at least 1-grade worsening from baseline for a timepoint if his change from baseline value ≥ 1 for the timepoint. The denominator used for calculating the proportion is the number of safety subjects who have baseline and at least one data of post-baseline dermal tolerability assessments.

There is no testing of any hypothesis or interval estimation of proportions with respect to dermal tolerability assessments.

Frequency count and proportion of subjects having had at least 1-grade worsening from baseline in dermal tolerability assessment parameters will be repeated and displayed by visit/timepoint. Summary statistics of dermal tolerability assessment parameters will also be presented by visit/timepoint.

6.5 Clinician's Telangiectasia Assessments (CTA)

Clinician's Telangiectasia Assessments (CTA) will be summarized and displayed in terms of frequency count and proportion of subjects who report at least a 1-grade worsening in severity from baseline at any time point over the study period.

For CTA, the scale was: 0 = clear skin, 1= almost clear, 2 = mild, 3 = moderate, 4 = severe. A subject is classified as having had a at least 1-grade worsening from baseline for a timepoint if his change from baseline value ≥ 1 for the timepoint. The denominator used for calculating the proportion is the number of safety subjects who have baseline and at least one data of post-baseline CTA.

There is no testing of any hypothesis or interval estimation of the proportions with respect to CTA.

Frequency count and proportion of subjects having had at least a 1-grade worsening from baseline in CTA will also be presented by visit/timepoint. Summary statistics of CTA will also be presented by visit/timepoint.

6.6 Vital Signs

Vital signs (e.g., systolic/diastolic blood pressure, heart rate, respiration rate, and body temperature) will be summarized by visit/timepoint using descriptive statistics.

6.7 Other Safety Analyses

All positive results of pregnancy tests will be listed.

6.8 Subgroup Analyses for Safety Variables

Not applicable.

7. Pharmacokinetic, Biomarker, Genomic, or Immunogenicity Data Analyses

Not applicable.

8. Health Outcomes Data Analyses

Analyses of certain patient reported outcome (PRO) measurements are described in Section 5.2. No other health outcomes data analyses will be conducted.

9. Interim Analyses

There is no interim analysis planned for this study.

10. Data Collected but not Analyzed

Not Applicable.

11. Deviations from Protocol

The modified Intent-to-Treat Population as defined in the Protocol (Oct 12, 2017) will not be used for reporting and analyses, since the intent-to-treat principle is commonly confined to randomized trials. Instead, an evaluable population, which is applicable for non-randomized trials, is defined in the SAP (See Section 2.1) and will be used for efficacy summaries.

Another deviation from the Protocol is that per protocol analysis population is defined and added into the SAP, and efficacy analyses will be repeated on the per protocol population if more than 20% of the evaluable subjects have had major protocol violations.

12. References

Journals or Software

SAS Institute Inc., Cary, NC (2013): SAS version 9.3

Allergan's Study Protocol

STUDY NUMBER	STUDY TITLE
CMO-MA-MED-0530	Multicenter, Open-Label, Interventional Study on the Safety and Tolerability of Oxymetazoline and Energy-Based Therapy in Subjects with Rosacea

13. Amendment(s)

Per protocol analysis population is defined and added to the SAP of Version 1.1. The per protocol population consists of all evaluable subjects who have not had any significant violations of the study protocol. Patients who have had significant violations of the study protocol will be identified before the analyses on the per protocol population being performed. Efficacy analyses will be repeated on the per protocol population if more than 20% of the evaluable subjects have had major protocol violations.

As those specified in the study protocol, major protocol violations (deviations) may include, but are not limited to:

(1) Inclusion/Exclusion criteria violations.
(2) Inadequate compliance with study drug.
(3) Prohibited medications and treatments taken. Refer to the Protocol sub-sections 5.6.10.1 and 5.6.10.2 for the list of prohibited medications and treatments.
(4) Significant deviations from the study drug administration schedule. Specifically, if a subject had ever deviated by more than 7 days from the scheduled visit windows, the subject will be considered as having had a major protocol violation.

The final list of the major protocol deviations will be defined during the data review meeting and before the final study database lock day.