# SYNOPSIS OF RESEARCH REPORT [redacted]

# (PROTOCOL BP25466)

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| COMPANY:<br><br>NAME OF FINISHED PRODUCT:<br><br>NAME OF ACTIVE SUBSTANCE(S): | (FOR NATIONAL AUTHORITY USE ONLY) |

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| TITLE OF THE STUDY / REPORT No. / DATE OF REPORT | Synopsis Clinical Study Report - An adaptive, multi-center, randomized, investigator-masked, subject-masked, multiple-dose, placebo-controlled, parallel study to investigate efficacy, safety, tolerability and pharmacokinetics of RO5093151 for up to 28 days in subjects with primary open angle glaucoma or ocular hypertension.<br>Report No. [redacted]. April 2013.<br>The Sponsor discontinued development of RO5093151 due to portfolio reprioritization. As a consequence, study BP25466 was terminated early following completion of Part 1 of the study and the results are, therefore, presented in synopsis format. Part 2 of the study was not conducted (for details of Part 2, please refer to Page 223). | | |
| INVESTIGATORS / CENTERS AND COUNTRIES | Participating centers: 3 centers in the United States, 2 centers in the Czech Republic, and 1 center in Hungary.<br>Details pertaining to the Ethics Committees and actions are provided on Page 382.<br>No audits were performed for this study. | | |
| PUBLICATION (REFERENCE) | Not applicable | | |
| PERIOD OF TRIAL | 01 December 2011 to<br>19 November 2012 | CLINICAL PHASE | IIa |
| OBJECTIVES | The objectives of Part 1 are presented below:<br>The primary objective of the study was:<br>• To assess the effect of RO5093151 on change from baseline in mean intraocular pressure (IOP) at 1 hour postdose following 7 days of treatment.<br>Secondary objectives of the study were:<br>• To assess the effect of RO5093151 on change from baseline in mean daily IOP following 7 days of treatment.<br>• To assess the effect of RO5093151 on change from baseline in mean IOP at each assessment time points following 7 days of treatment. | | |

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| | • To assess the IOP during a 1 week placebo lead-in phase.<br>• To assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of RO5093151 following multiple dosing.<br>For the planned objectives for Part 2, please see Page 223. |
| STUDY DESIGN | This was a Phase IIa, adaptive, randomized, investigator-masked, subject-masked, repeated-dose, placebo-controlled, parallel group study.<br>The total duration of the study for each subject was to be up to 15 weeks, divided as follows:<br>• A screening phase of up to 8 weeks including a wash-out period of up to 6 weeks for those subjects on glaucoma medications.<br>• A 1-week placebo lead-in phase with 2 pretreatment assessment days (Day -7 and Day -1). Assessments conducted on Day -1 were used as the baseline results.<br>• The study drug treatment phase began directly after Day -1 and lasted 1 week. Subjects were treated for 1 week with either 200 mg twice daily (BID) RO5093151 or a matching placebo in a ratio of 4:1, respectively.<br>• All subjects underwent follow-up visits 7 and 14 days (±1 day) after their last dose of study medication. |
| NUMBER OF SUBJECTS | Up to 25 evaluable subjects (active:placebo, 4:1) were needed for Part 1. The total number of subjects required followed an adaptive approach and included a Bayesian decision criterion (see Statistical Methods)<br>A total of 32 subjects were randomized (26 to RO5093151 and 6 to placebo) to achieve the target of 25 evaluable subjects. |
| DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION | Male and female subjects were ≥ 21 years of age with a diagnosis of ocular hypertension (OHT) or primary open angle glaucoma (POAG) in at least one eye.<br>Subjects with OHT had to have an IOP ≥ 22 mmHg at 8:00 am (±1hour) and ≥ 18 mmHg in the afternoon (between 3:00 and 6:00 pm) in at least one eye at both Screening and on Day -7. Subjects with POAG had to have an IOP ≥ 18 mmHg at Screening (at both the morning and afternoon assessment) and ≥ 22 mmHg on Day -7 in at least one eye. At all timepoints of Screening and Day -7, IOP had to be ≤ 32 mmHg in both eyes.<br>All subjects had to have a best corrected visual acuity score of 6/30 (20/100 Snellen, 0.7 LogMar) or better, central corneal pachymetry of 420 to 620 µ in the qualifying eye, as well as a cup-to-disk ratio of ≤ 0.8. |
| TRIAL DRUG / STROKE (BATCH) No. | RO5093151 - batch number: [redacted] |

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| DOSE / ROUTE / REGIMEN / DURATION | RO5093151 was provided as 100 mg film-coated tablets; 2 tablets to be taken orally BID at 8:00 am and 6:00 pm, approximately 30 min before breakfast and before dinner. Subjects were treated daily for 7 days (randomized treatment phase). |
| REFERENCE DRUG / STROKE (BATCH) No. | Matching placebo - batch number [redacted] |
| DOSE / ROUTE / REGIMEN / DURATION | Placebo lead-in phase:<br>• Matching 200 mg (2 × 100 mg tablets), oral administration, BID (at 8:00 am and 6:00 pm, approximately 30 minutes before breakfast and dinner, respectively) for 7 days<br>Randomized treatment phase:<br>• Identical as to the study drug. |
| CRITERIA FOR EVALUATION | |
| EFFICACY: | Primary efficacy endpoint:<br>• Change from baseline in mean IOP at 1 hour post-dose following 7 days of treatment (Day 7 vs. Day -1, time-matched)<br>Secondary efficacy endpoint:<br>• Change from baseline in mean daily IOP at each assessment timepoints, following 7 days of treatment<br>• Mean time-matched difference in IOP in the active treatment vs. placebo treatment<br>• Mean time-matched difference in IOP during the lead-in phase |
| PHARMACODYNAMICS: | • Urinary ratio of (5α-THF + THF) / THE |
| PHARMACOKINETICS: | • PK of RO5093151 and its 4 main active metabolites: RO5152953 (M9), RO5152954 (M7), RO5461860 (M4), and RO5509249 (M+32) |
| SAFETY: | • Adverse events (AEs)<br>• Physical examination<br>• Clinical laboratory safety tests<br>• Vital signs<br>• 12-Lead ECG |
| OTHER: | The following ophthalmological assessments were performed:<br>• IOP by Goldmann application Tonometry (primary efficacy endpoint, see above)<br>• General ophthalmological examination<br>• Visual acuity<br>• Biomicroscopy<br>• Pachymetry<br>• Gonioscopy<br>• Visual field<br>• Fundus examination under dilatation |

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| | • Optic disc measurement |
| STATISTICAL METHODS | The primary endpoint for the efficacy analysis was the absolute change of IOP (mmHg) from baseline to the value after the one-week treatment period, measured at 1 hour post-dose.<br>An analysis of covariance (ANCOVA) was used at the end of the study to evaluate the treatment effect on the change of IOP in the "worst" and "best" eye ("worst eye" defined as the eye with the highest IOP at baseline [Day -1] at time matching 1 hour post-dose. If the same IOP value was measured in both eyes at this timepoint, the eye with the higher IOP values over the diurnal curve was chosen as "worst eye"). The ANCOVA model had baseline IOP as continuous covariate and treatment group as a binary covariate.<br>The Bayesian Decision Criterion "Probability ($\Delta IOP \geq 5$ mmHg) $> 80\%$" was applied three times during Part 1, after the following number of evaluable subjects on RO5093151 was achieved: n=12 (15 including placebo), n=16 (20 including placebo), n=20 (25 including placebo) to assess whether the study could be stopped for success.<br>Descriptive statistics were used to analyze the PD data collected during this study. A sparse PK sampling approach was implemented. |

**METHODOLOGY**

Full details of the study methodology are presented in the protocol (Page 223). Details of the PK bioanalysis are provided on Page 83.

The study was designed as a Phase IIa proof-of-concept study in subjects with OHT and POAG to assess the potential of 11β-HSD1 inhibition in lowering the IOP following oral administration of RO5093151. This exploratory study was adaptive in nature in respect to the number of subjects to be included and the treatment duration (Bayesian decision criterion testing).

The Sponsor discontinued development of RO5093151 due to portfolio reprioritization. As a consequence, study BP25466 was terminated early following completion of Part 1 of the study and the results are, therefore, reported in synopsis format. Part 2 of the study was not conducted. Complete safety analyses were performed on the safety population, which consisted of all subjects who received at least 1 dose of treatment, analyzed as treated.

AEs were reported in frequency tables overall, by intensity, and by relationship to study treatment. PD parameters were summarized using descriptive statistics.

**STUDY POPULATION**

**Disposition of Subjects:** A total of 35 subjects were enrolled in the study; of these, 34 subjects entered the placebo lead-in phase (one subject was withdrawn prior to lead-in) and 32 subjects were randomized: 26 subjects were randomized to receive 200 mg BID RO5093151 and 6 subjects were randomized to receive placebo. Of the subjects randomized to receive active treatment, 1 subject [redacted] was randomized but withdrawn before receiving treatment (subject does not appear in the summary tables). All 31 subjects who were randomized and received treatment were included in the intention-to-treat (ITT) population. Six subjects were excluded from the per-protocol (PP) analysis (2 excluded due to compliance issues, 2 excluded due to inclusion criteria violation, and 2 excluded due to closure of a site (Page 392, Page 393). The PP population included 20 subjects on RO5093151 and 5 subjects on placebo. The "best eye" of Subject [redacted] was excluded from the PP analysis due to non-eligibility of his eye (previous trabeculectomy).

The decision to discontinue the conduct of the study at 1 site was made post-enrolment of 4 subjects and was due to concerns relating to data quality. Two of these subjects had not entered the randomization phase and therefore were not included in either the ITT or the PP population. The remaining 2 subjects had been randomized and received treatment and therefore were included in the ITT population but excluded from the PP population. All 4 subjects were included in the safety analysis population.

**Demographic and Baseline Characteristics:** Most subjects were female (19/31 subjects) and white (19/31 subjects) with a mean age of approximately 60 years (Table 1 and Page 16). Demographic data for individual subjects are listed on Page 394 and Page 396.

## Table 1 Summary of Demographic Data

dm11 Summary of Demographic Data by Trial Treatment
Protocol(s): BP25466
Analysis: ALL PATIENTS Center: ALL CENTERS

| | RO5093151 200 mg BID N = 25 | Placebo N = 6 |
|---|---|---|
| Sex | | |
| MALE | 10 ( 40%) | 2 |
| FEMALE | 15 ( 60%) | 4 |
| n | 25 | 6 |
| Race | | |
| ASIAN | [redacted] | [redacted] |
| BLACK OR AFRICAN AMERICAN | | |
| WHITE | [redacted] | [redacted] |
| n | 25 | 6 |
| Age in years | | |
| Mean | 59.4 | 61.0 |
| SD | 12.94 | 14.31 |
| SEM | 2.59 | 5.84 |
| Median | 63.0 | 65.0 |
| Min-Max | 24 - 80 | 41 - 76 |
| n | 25 | 6 |
| Weight in kg | | |
| Mean | 88.62 | 83.83 |
| SD | 16.827 | 18.004 |
| SEM | 3.365 | 7.350 |
| Median | 85.50 | 78.00 |
| Min-Max | 69.1 - 135.0 | 66.8 - 109.7 |
| n | 25 | 6 |
| Height in cm | | |
| Mean | 167.7 | 170.3 |
| SD | 14.24 | 10.35 |
| SEM | 2.85 | 4.22 |
| Median | 170.0 | 168.5 |
| Min-Max | 127 - 193 | 157 - 187 |
| n | 25 | 6 |

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Patient [redacted] was withdrawn from the study prior to receving randomized treatment and so is not summarized.
DM11 05APR2013:08:53:56 (1 of 2)

**Table 2 Summary of Demographic Data (continued)**

dm11 Summary of Demographic Data by Trial Treatment
Protocol(s): BP25466
Analysis: ALL PATIENTS Center: ALL CENTERS

| | RO5093151 200 mg BID N = 25 | Placebo N = 6 |
|---|---|---|
| Body Mass Index (kg/m2) | | |
| Mean | 31.813 | 28.812 |
| SD | 6.3187 | 5.1147 |
| SEM | 1.2637 | 2.0881 |
| Median | 31.080 | 27.625 |
| Min-Max | 22.56 - 45.06 | 22.84 - 37.58 |
| n | 25 | 6 |

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
Patient [redacted] was withdrawn from the study prior to receving randomized treatment and so is not summarized.
DM11 05APR2013:08:53:56 (2 of 2)

Baseline ophthalmic conditions are summarized in Table 3. The majority of subjects had POAG at baseline.

**Table 3 Summary of Ophthalmic Condition**

dm11_saf Summary of Ophthalmic Condition
Protocol(s): BP25466
Analysis: ALL PATIENTS Center: ALL CENTERS

| | RO5093151 200 mg BID N = 25 | Placebo N = 6 |
|---|---|---|
| Opthalmic Disease* | | |
| (Primary open angle) Glaucoma | 18 ( 72%) | 5 |
| Ocular Hypertension | 7 ( 28%) | 1 |
| n | 25 | 6 |

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
*Patients with both Ocular hypertension and Primary open angle glaucoma (POAG), are summarized under POAG.
DM11 05APR2013:08:54:58 (1 of 1)

Gonioscopy and pachymetry were performed at Screening:

- Gonioscopy: All subjects who participated in the study reported angular widths of > 20° (wide) and were classified to Shaffer Scale scores of 2 to 4.
- Pachymetry: All subjects reported central cornea pachymetry measurements of 454 to 610 μ in each qualifying eye (inclusion criterion 420 to 620 μ)

Gonioscopy and pachymetry data for individual subjects are listed on Page 397.

## EFFICACY RESULTS

Figure 1 displays the mean (±SEM) change from time-matched baseline for IOP (mmHg) over time on Day 7 in the "worst eye" (PP population). The corresponding display for "best eye" is attached on Page 578.

The primary efficacy endpoint was the absolute time-matched change from baseline IOP at 1 hour post-dose (equivalent to $C_{max}$ of RO5093151) following 7 days of treatment compared to Day -1 baseline. With an ANCOVA model adjusting for baseline level, there was no statistically significant difference in change of IOP for the primary efficacy endpoint. In the "worst eye", the adjusted least square mean change from baseline was -2.59 mmHg (95% CI -3.81, -1.37) in the RO5093151 and -2.37 (95% CI -4.86, 0.12) in the placebo group, with a mean difference between RO5093151 and placebo of -0.22 (95% CI -3.0, 2.56), in favor of RO5093151. In the "best eye", the adjusted least square mean change from baseline was -1.25 (95% CI -2.43, -0.08) in RO5093151 and -2.44 (95% CI -4.84, -0.05) in the placebo group, with a

mean difference between RO5093151 and placebo of 1.19 (95% CI -1.48, 3.85), in favor of placebo.

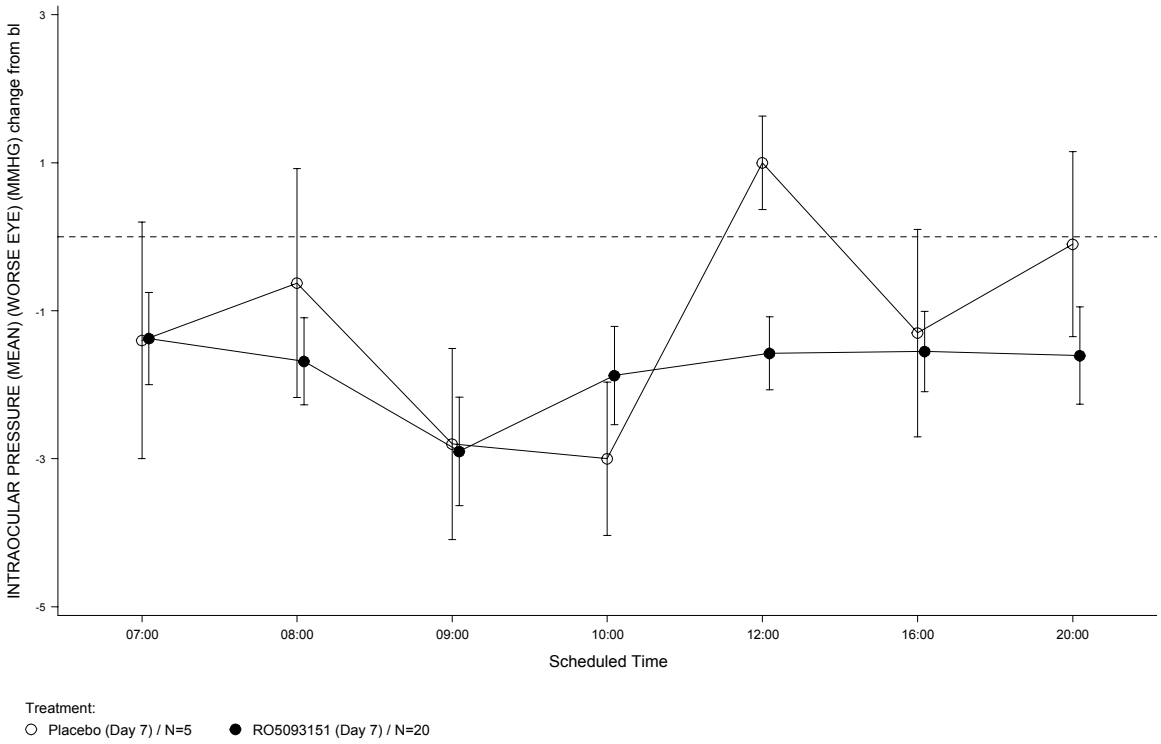
Overall, there was no indication for an effect of 200 mg BID of RO5093151, administered orally for 7 days, on IOP compared to placebo.

Mean ΔIOP values ranged from -1.4 to -2.9 mmHg for the worst eye and from -0.5 to -1.4 mmHg for the best eye at all timepoints. The highest decrease was observed at 1-hour post-dose.

The mean decrease in IOP observed in the study did not achieve the target of ≥ 5 mmHg (equivalent to a clinically relevant decrease of approximately 20% compared to baseline).

**Figure 1 Change from Time-Matched Baseline for IOP – Worst Eye**

Mean (±S.E.M.) Change from Baseline for INTRAOCULAR PRESSURE (MEAN) (WORSE EYE) (MMHG) on Day 7 (PP)




(B) Better eye, (W) Worse Eye. Baseline is the time-matched value at Day -1. Drug administration was at 08 00 and 18 00.
vs52c_iop_d7cbp_iopm-w 05APR2013 8 56 Project cdpt7590 Protocol bp25466

A listing and summary of absolute IOP results with change from baseline and percentage change from baseline are provided on Page 448 and on Page 572 , respectively. Corresponding mean graphs are provided on Page 578, whereas mean graphs of the 1h post-dose time-point only during the entire treatment phase are provided on Unresolved. Individual graphs of IOP results during the day are provided on Page 606 and the individual graphs of the 1h post-dose time-point only during the entire treatment phase are provided on Page 680. A boxplot of the change from BL on Day 1 and Day 7 in mean IOP for the PP population (worst and best eye) is provided on Page 710.

## PHARMACODYNAMIC RESULTS

A formal PD analysis was not performed due to study discontinuation. Data listings and plots of the raw data were generated for the ITT population and are available on Page 712 and Page 734.

## PHARMACOKINETIC RESULTS

A formal PK analysis was not performed due to study discontinuation. Details of sampling times are available on Page 379. Data listings and plots of the raw data are available on Page 18.

## SAFETY RESULTS

**Exposure to Study Treatment:**

Twenty-five subjects received RO5093151 during this study. Treatment administration details for individual subjects during the scheduled visits at the site are listed on Page 24. An overview of RO5093151/placebo intake compliance on the days between the site visits is given on Page 294.

**Adverse Events:**

Glossaries of super class terms, preferred terms, and verbatim terms for AEs and medications are provided on Page 384 and Page 385.

Common Adverse Events

No subject who received placebo reported an AE. In addition, no subject (either placebo or RO5093151) reported an AE during the lead-in phase.

Three subjects who received RO5093151 reported 4 AEs during the study (Page 738). The AEs reported were:

- Diverticulum and osteoporosis (Subject [redacted]): Both events were considered mild in intensity and unrelated to study treatment by the Investigator. These events were recorded after 1 day on randomized study treatment and were both unresolved at the final study visit.
- Urinary tract infection (Subject [redacted]): This event was considered mild in intensity and unrelated to study treatment by the Investigator. The event was recorded after 4 days on randomized study treatment and was considered resolved 16 days later with no sequelae.
- Protein urine present (Subject [redacted]): This event was considered mild in intensity and unrelated to study treatment by the Investigator. The event was recorded after 7 days on randomized study treatment and resolved 1 day later with no sequelae.

Related Adverse Events

There were no AEs reported that were considered related to R05093151.

Adverse Events by Intensity

All AEs reported were mild in intensity.

Serious Adverse Events

There were no serious adverse events (SAEs) reported during this study.

Adverse Events that Led to the Withdrawal of Study Drug

There were no AEs reported that resulted in the withdrawal of study drug.

Deaths

There were no deaths during this study.

**Laboratory Safety Tests:** Individual laboratory safety test results are summarized on Page 34 and are listed on Page 739 and Page 752. Out-of-range laboratory data are listed on Page 815. No trends in any laboratory safety parameters were observed.

Cortisol and adrenocorticotropic hormone (ACTH) concentrations were assessed in plasma at Day -1, Day 7, and at Follow-Up (Page 60, Page 62). In RO5093151-treated subjects, mean plasma ACTH concentrations at Day 7 were slightly increased above baseline (+8.64 pg/mg), whereas no change was apparent in placebo-treated subjects (+0.45 pg/mg).

Mean plasma cortisol concentrations at Day 7 in RO5093151-treated subjects were slightly decreased compared to baseline (-20.98 ng/mL), whereas no relevant change was observed in placebo-treated subjects (+5.34 ng/mL). At Follow-Up, mean cortisol levels in RO5093151-treated subjects still displayed values slightly below baseline (-9.26 ng/ml), whereas the values of placebo-treated subjects were slightly above baseline (11.26 ng/mL).

Marked abnormalities in laboratory values are summarized on Page 68 and listed on Page 752. The majority of marked abnormalities were present at a single assessment. Only 1 event (high proteinuria) was reported as an AE.

With the exception of ACTH and cortisol levels described above, there was no evidence for changes in safety laboratory parameter values due to R05093151.

**Vital Signs:** Individual vital sign data, including change from baseline, are listed on Page 818. Abnormal vital signs included high diastolic blood pressure (BP) (3 subjects receiving RO5093151), high systolic BP (7 subjects receiving RO5093151 and 2 subjects receiving placebo), low pulse (1 subject receiving RO5093151), and low temperature (7 subjects receiving RO5093151 and 2 subjects receiving placebo) ( Page 79 ). For the majority of subjects, vital sign measurements remained within standard reference ranges following study drug administration. Where abnormal diastolic or systolic blood pressure and pulse rate were observed, the anomaly was either present pre-dosing or, following drug administration, recorded at an isolated timepoint, after which parameters returned to within the standard reference range in subsequent readings. There was no evidence for changes in vital sign parameters due to RO5093151.

**ECGs:** Electrocardiograms (ECGs) were taken at Screening and at the 14-day Follow-Up Visit. ECG tracings were reviewed and assessed as normal or abnormal by the Investigator. Abnormal ECG results were recorded at Screening for 8/25 subjects who received RO5093151 and 2/6 subjects who received placebo. At Day 14, abnormal ECGs were recorded for 6/24 RO5093151 subjects and 3/6 placebo subjects ( Page 80 ). No study drug-related trends were observed during the study. Abnormal ECG results are listed on Page 833. There was no evidence for ECG changes due to RO5093151.

**Ophthalmological Assessments:**

**-Intraocular Pressure:** see efficacy section.

**-Biomicroscopy:** Biomicroscopy was performed at Screening, Day -7, Day -1, Day 1, Day 4, Day 7, and at Follow-Up (Day 14). No abnormal findings were reported during the study. Full results are listed on Page 838.

**-Fundus Examination:** Fundoscopy was performed at Screening and at 14-day Follow-Up.

- Optic disc atrophy: In RO5093151-treated subjects, no subject reported worsening or new appearance of atrophy at Follow-up. In the subject who reported severe atrophy at Follow-Up, no assessment was performed at Screening and therefore no comparison can be drawn. In subjects who received placebo, no subject reported worsening or new appearance of atrophy from Screening to Follow-Up.
- Neuroretinal rim: No subject (RO5093151 or placebo) reported any changes in either eye from Screening to Follow-Up.
- Cup disc ratio: No subject (RO5093151 or placebo) reported a cup disc ratio that was >0.8 $mm^2$ in either eye (inclusion criterion specified a cup disc ratio at Screening of <0.8 $mm^2$).
- No abnormal findings were reported for rim hemorrhages, retinal hemorrhages, and macular degeneration.

Full results are listed on Page 397 .

**-Visual Acuity:** Visual acuity testing was performed at Screening, Day -7, Day -1, Day 1, Day 4, Day 7, 7-day Follow-Up, and 14-day Follow-Up.

- All subjects (RO5093151 and placebo) showed scores of 60/30 (0.7 LogMar) or better in each eye for the duration of the study. No subject showed a notable improvement or decline after treatment.

Full results are listed on Page 838.

**-Visual Field Assessment by Perimetry:** Visual field testing was performed at Screening and at Follow-Up (Day 14). In general, abnormal visual field test results were identified as consistent with glaucoma. There was no notable improvement or decline after treatment.

Full results are listed on Page 397 and Page 1093.

**CONCLUSIONS**

RO5093151 was well tolerated in all subjects in this study with no related AEs reported. No clinically significant changes in vital signs, clinical laboratory values, general safety ophthalmological assessments, and ECG readings were noted during this study.

The IOP at 1 hour post-dose on Day 7 in the RO5093151 and placebo-treated groups displayed a similar trend of decrease from baseline. Thus, there was no clear indication for an effect of 200 mg BID of RO5093151 on IOP when administered orally for a duration limited to 7 days. The mean decrease in IOP observed in the study did not achieve the target of $\geq$ 5 mmHg (equivalent to a clinically relevant decrease of approximately 20% compared to baseline).