

A Double-Masked, Randomised, Placebo-Controlled, Parallel-Group, 12 Week, Phase 2 Study to Investigate the Safety and Efficacy of Ripasudil (K-321) Eye Drops After Descemetorhexis in Patients with Fuchs Endothelial Corneal Dystrophy

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*Kowa Research Institute, Inc.*

*K-321-201*

*A Double-Masked, Randomised, Placebo-Controlled, Parallel-Group, 12-Week, Phase 2 Study to Investigate the Safety and Efficacy of Ripasudil (K-321) Eye Drops After Descemetorhexis in Patients with Fuchs Endothelial Corneal Dystrophy*

*08JUN2022*

Statistical Analysis Plan

**Version 2.0 Addendum**

Prepared by:



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## List of Abbreviations

| <b>Abbreviation</b> | <b>Definition</b>                          |
|---------------------|--|
| BCVA                | Best Corrected Visual Acuity               |
| BID                 | Twice Daily                                |
| CI                  | Confidence Interval                        |
| CSR                 | Clinical Study Report                      |
| ECD                 | Endothelial Cell Density                   |
| ETDRS               | Early Treatment Diabetic Retinopathy Study |
| FAS                 | Full-Analysis Set                          |
| LOCF                | Last-Observation-Carried-Forward           |
| QID                 | 4 Times Daily                              |
| SAP                 | Statistical Analysis Plan                  |
| SD                  | Standard Deviation                         |

## 1. Introduction

This statistical analysis plan (SAP) addendum to the primary SAP v2.0, dated August 25, 2021, is to describe additional analyses that were defined **after the Week 12 Unmasking** to support the final CSR. All analyses that were defined in the primary SAP v2.0 prior to the Week 12 unmasking will not be described again in this document.

## 2. Additional Analyses

The additional analyses will be performed for the Full-analysis set.

The following time-to-event endpoint will be analysed by pairwise log-rank tests comparing each active K-321 0.4% treatment regimen to placebo. Kaplan-Meier estimates and plots will also be presented up to Week 52. Patients who complete follow-up or discontinue the study without achieving the specified endpoint will be censored [REDACTED]

- Time to Intervention of Rescue Therapy\*

\*Patient is considered having received rescue therapy if the patient [REDACTED]

The following endpoints based on continuous measures will be analysed by pairwise Wilcoxon rank sum tests comparing each active K-321 0.4% treatment. For [REDACTED] Central corneal Endothelial Cell Density (ECD) assessments, the [REDACTED] data handling methods will be the same as primary analysis, or the Central corneal ECD assessments that could not be performed due to oedema. Otherwise, the [REDACTED] data will be [REDACTED]

[REDACTED]. Patients who receive a rescue keratoplasty will be [REDACTED] or [REDACTED] by [REDACTED], [REDACTED] or [REDACTED], respectively.)

For assessments other parameters, the [REDACTED] data will be [REDACTED]. Additionally, the mean values and standard deviation (SD) by visit will be graphically displayed.

- Central corneal ECD of study eye performed by specular microscopy at [REDACTED]
- Central corneal thickness change from [REDACTED] to [REDACTED].
- BCVA (letters) by ETDRS change from [REDACTED] to [REDACTED]

The following endpoint based on the number and percentage of patients achieving the endpoint will be analysed by Pearson chi-square test comparing each active K-321 0.4% treatment regimen to placebo. The 95% CI for the difference in percentage of patients achieving the endpoint will also be presented. Should the number of responders be less than 5 in either group, Fisher's exact test will be used instead. If Fisher's exact test is used, the unconditional confidence interval for the difference in response rates will be provided. The missing data will be [REDACTED]. Patients who receive a rescue keratoplasty will be [REDACTED]. Additionally, the number and percentages of subjects achieving endpoint by visit will be graphically displayed

- Number and percentage of patients who achieve no corneal oedema

The correlation between BCVA (letters) by ETDRS and Central Corneal ECD will be assessed by using Pearson's and Spearman's correlation coefficients. The correlation scatter plot will also be presented. The correlations and scatter plots will be based on data from all visits combined and analysed for all subjects overall as well as by each treatment arm. The correlations will be assessed separately using different data scenario:

- In the first correlation analysis, the data handling methods will be the same as primary analysis for [REDACTED] Central corneal ECD assessments, or the Central corneal ECD assessments that could not be performed due to oedema. Otherwise, the analysis will be [REDACTED]. Patients who receive a rescue keratoplasty will also be [REDACTED].
- The second correlation analysis will be the same as first except that the analysis visits where corneal oedema is observed or the Central corneal ECD assessments that could not be performed due to oedema will be [REDACTED].
- In the third analysis, the analysis visits where there are [REDACTED] Central corneal ECD assessments, or the Central corneal ECD assessments that could not be performed due to oedema will be [REDACTED]. Otherwise, the analysis will include the same data as the first correlation analysis.
- The fourth correlation analysis will be the same as third except that the analysis visits where corneal oedema is observed or the Central corneal ECD assessments that could not be performed due to oedema will be [REDACTED].

The BCVA (letters) by ETDRS will be summarized by the Central corneal ECD subgroups (defined below as sub-groupings (A) and (B)) at each visit and across all post-baseline visits by each treatment arm and all treatment arms combined. Box plots will also be presented for each at each visit and across all post-baseline visits by each treatment arm and all treatment arms combined for sub-grouping definition (A). Scatter plot and correlation coefficient (Spearman) will also be presented for each subgroup at each visit and across all post-baseline visits by each treatment arm and all treatment arms combined for sub-grouping definition (B). [REDACTED] Central corneal ECD include [REDACTED] Central corneal ECD assessments or the Central corneal ECD assessments that could not be performed due to oedema. Central corneal ECD assessments

that are [REDACTED] due to other reasons are [REDACTED]. Patients who receive a rescue keratoplasty will also be [REDACTED].

- (A) Central corneal ECD [REDACTED]
- (B) Central corneal ECD [REDACTED] ( $\leq$ Mean Central corneal ECD and  $>1$ ,  $>$ Mean Central corneal ECD, [REDACTED])

### **3. Appendix 1 – TLF shells**



**Table 14.2.1.42**  
Time to Achieve Intervention of Rescue Therapy  
(Full Analysis Set)

|   | K-321 QID<br>(N=XXX) | K-321 BID<br>(N=XXX) | Placebo<br>(N=XXX) |
|---|----------------------|----------------------|--------------------|
| Patients with Intervention of Rescue Therapy, n (%)           | XX (XX.X)            | XX (XX.X)            | XX (XX.X)          |
| Time to Archive Intervention of Rescue Therapy [day] (95% CI) |                      |                      |                    |
| 25th  | XX.X (XX.X, XX.X)    | XX.X (XX.X, XX.X)    | XX.X (XX.X, XX.X)  |
| 50th (Median)   | XX.X (XX.X, XX.X)    | XX.X (XX.X, XX.X)    | XX.X (XX.X, XX.X)  |
| 75th  | XX.X (XX.X, XX.X)    | XX.X (XX.X, XX.X)    | XX.X (XX.X, XX.X)  |

p-value [1]

Note: NA = Not Applicable

Patient is considered having received rescue therapy if the patient 1) received rescue surgical procedure (penetrating keratoplasty or endothelial keratoplasty) during the study. 2) withdrawal with potential for surgical procedure. 3) withdrawal with potential for Rho kinase Inhibitor treatment.]

Patient's study discontinuation date is used as the rescue therapy date if the patient withdrawal with potential for surgical procedure or Rho kinase Inhibitor treatment.

Patients who completed follow-up or discontinued the study without receiving rescue therapy were [REDACTED]

[1] Two-sided p-value is from the log rank test.

Table 14.2.1.43

Central Corneal ECD (cells/mm<sup>2</sup>) of Study Eye performed by Specular Microscopy by Visit (LOCF) via Wilcoxon Rank Sum Test (Full Analysis Set)

|                                   | K-321 QID<br>(N=XXX) | K-321 BID<br>(N=XXX) | Placebo<br>(N=XXX) |
|-----------------------------------|----------------------|----------------------|--------------------|
| Central Corneal ECD at Baseline   |                      |                      |                    |
| n                                 | XX                   | XX                   | XX                 |
| Mean (SD)                         | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       |
| Median                            | XX.X                 | XX.X                 | XX.X               |
| Q1, Q3                            | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         |
| Min, Max                          | XX, XX               | XX, XX               | XX, XX             |
| Difference to Placebo [1]         |                      |                      |                    |
| p-value by Wilcoxon Rank Sum Test | X.XXXX               | X.XXXX               |                    |
| Hodges-Lehmann Estimate           | X.X                  | X.X                  |                    |
| Moses 95% Confidence Interval     | (XX.X, XX.X)         | (XX.X, XX.X)         |                    |
| Central Corneal ECD at Week 1     |                      |                      |                    |
| n                                 | XX                   | XX                   | XX                 |
| Mean (SD)                         | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       |
| Median                            | XX.X                 | XX.X                 | XX.X               |
| Q1, Q3                            | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         |
| Min, Max                          | XX, XX               | XX, XX               | XX, XX             |
| Difference to Placebo [1]         |                      |                      |                    |
| p-value by Wilcoxon Rank Sum Test | X.XXXX               | X.XXXX               |                    |
| Hodges-Lehmann Estimate           | X.X                  | X.X                  |                    |
| Moses 95% Confidence Interval     | (XX.X, XX.X)         | (XX.X, XX.X)         |                    |

...  
 Note: LOCF = last-observation-carried, ECD = Endothelial Cell Density  
 Baseline is defined as the last measurement including unscheduled assessments prior to the administration of first dose of [REDACTED] treatment.  
 Central corneal ECD (both baseline and post-baseline) that are unable to be performed due to corneal oedema are [REDACTED]. Assessment images that are unable to be analysed and categorized as [REDACTED].

[REDACTED] and [REDACTED] by [REDACTED] are [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED] is based on the Wilcoxon rank sum test. The [REDACTED] between [REDACTED] treatment groups and the Moses CIs were estimated with the Hodge-Lehmann method.  
Source Data: Listing 16.2.6.1

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Prog Notes: 1. Repeat for scheduled visits.

Table 14.2.1.44

Change from Baseline in Central Corneal Thickness ( $\mu\text{m}$ ) of Study Eye by Visit (LOCF) via Wilcoxon Rank Sum Test  
(Full Analysis Set)

|   | K-321 QID<br>(N=XXX) | K-321 BID<br>(N=XXX) | Placebo<br>(N=XXX) |
|---|----------------------|----------------------|--------------------|
| Change from Baseline in<br>Central Corneal Thickness at<br>Week 1 [1] |                      |                      |                    |
| n   | XX                   | XX                   | XX                 |
| Mean (SD)   | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       |
| Median  | XX.X                 | XX.X                 | XX.X               |
| Q1, Q3  | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         |
| Min, Max  | XX, XX               | XX, XX               | XX, XX             |
| Difference to Placebo [2]   |                      |                      |                    |
| p-value by Wilcoxon Rank<br>Sum Test                                  | X.XXXX               | X.XXXX               |                    |
| Hodges-Lehmann Estimate   | X.X                  | X.X                  |                    |
| Moses 95% Confidence<br>Interval                                      | (XX.X, XX.X)         | (XX.X, XX.X)         |                    |

Note: Baseline is defined as the last measurement including unscheduled assessments prior to administration of first dose of study eye drops. The values for the change from baseline in central corneal thickness and the values for the change from baseline in corneal topography are [REDACTED].

Change from baseline is defined as the post baseline value minus the baseline value for the given assessment. For the change from baseline, only patients with a value at both baseline visit and the specific post-baseline visit are included.

[2] P-value is based on the Wilcoxon rank sum test. The median differences between the treatment groups and the Moses CIs were estimated with the Hodge-Lehmann method.

Source Data: Listing 16.2.6.3

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Prog Notes: Repeat for scheduled visits.

**Table 14.2.1.45**  
Proportion of Patients Who Achieve No Corneal Oedema of Study Eye by Visit (LOCF)  
(Full Analysis Set)

|   | K-321 QID<br>(N=XXX) | K-321 BID<br>(N=XXX) | Placebo<br>(N=XXX) |
|---|----------------------|----------------------|--------------------|
| Patients Achieved No Corneal Oedema at Baseline |                      |                      |                    |
| Achieved n(%)                                   | XX (XX.X)            | XX (XX.X)            | XX (XX.X)          |
| Not Achieved n(%)                               | XX (XX.X)            | XX (XX.X)            | XX (XX.X)          |
| Difference to Placebo [1]                       |                      |                      |                    |
| Response Rate Difference (%)                    | XX.X                 | XX.X                 |                    |
| 95% Confidence Interval                         | (XX.X, XX.X)         | (XX.X, XX.X)         |                    |
| p-value   | X.XXXX               | X.XXXX               |                    |
| ...   |                      |                      |                    |

Note: No corneal oedema is defined as absent of oedema in all three layers of cornea, including epithelial, stromal, and endothelial.

corneal oedema of study are .  
The p-value is based on the Pearson Chi-square test </the Fisher's exact test with unconditional confidence interval>.

Source Data: Listing 16.2.6.6

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMMYYYY hh:mm

Prog Notes: Repeat for scheduled visits.

**Table 14.2.1.46**  
Change from Baseline in BCVA by ETDRS of Study Eye by Visit (LOCF) via Wilcoxon Rank Sum Test  
(Full Analysis Set)

|  | K-321 QID<br>(N=XXX) | K-321 BID<br>(N=XXX) | Placebo<br>(N=XXX) |
|--|----------------------|----------------------|--------------------|
| Change from Baseline in BCVA<br>by ETDRS at Week 1 [1] |                      |                      |                    |
| n  | XX                   | XX                   | XX                 |
| Mean (SD)  | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       |
| Median   | XX.X                 | XX.X                 | XX.X               |
| Q1, Q3   | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         |
| Min, Max   | XX, XX               | XX, XX               | XX, XX             |
| Difference to Placebo [2]                              |                      |                      |                    |
| p-value by Wilcoxon Rank<br>Sum Test                   | X.XXXX               | X.XXXX               |                    |
| Hodges-Lehmann Estimate                                | X.X                  | X.X                  |                    |
| Moses 95% Confidence<br>Interval                       | (XX.X, XX.X)         | (XX.X, XX.X)         |                    |

....

Note: BCVA = Best Corrected Visual Acuity. ETDRS = Early Treatment Diabetic Retinopathy Study  
Baseline is defined as the last [redacted] measurement including unscheduled assessments prior to the  
[redacted] tration of first dose [redacted] plasty are  
[redacted] e given  
assessment. For the change from baseline, only patients with a value at both baseline visit and the  
specific post-baseline visit are included.  
[2] P-value is based on the Wilcoxon rank sum test. The median differences between the treatment groups and  
the Moses CIs were estimated with the Hodge-Lehmann method.  
Source Data: Listing 16.2.6.7

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Prog Notes: Repeat for scheduled visits.

**Table 14.2.1.47**  
Summary of BCVA by ETDRS by Central ECD Gradeability by Visit  
(Full Analysis Set)

Gradable Central Corneal ECD Images

|                          | K-321 QID<br>(N=XXX) | K-321 BID<br>(N=XXX) | Placebo<br>(N=XXX) | Total<br>(N=XXX) |
|--------------------------|----------------------|----------------------|--------------------|------------------|
| <b>All Post-baseline</b> |                      |                      |                    |                  |
| N                        | XX                   | XX                   | XX                 | XX               |
| Mean (SD)                | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       | XX.X (XX.XX)     |
| Median                   | XX.X                 | XX.X                 | XX.X               | XX.X             |
| Q1, Q3                   | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         | XX.X, XX.X       |
| Min, Max                 | XX, XX               | XX, XX               | XX, XX             | XX, XX           |
| <b>Baseline</b>          |                      |                      |                    |                  |
| N                        | XX                   | XX                   | XX                 | XX               |
| Mean (SD)                | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       | XX.X (XX.XX)     |
| Median                   | XX.X                 | XX.X                 | XX.X               | XX.X             |
| Q1, Q3                   | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         | XX.X, XX.X       |
| Min, Max                 | XX, XX               | XX, XX               | XX, XX             | XX, XX           |
| <b>Week x</b>            |                      |                      |                    |                  |
| N                        | XX                   | XX                   | XX                 | XX               |
| Mean (SD)                | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       | XX.X (XX.XX)     |
| Median                   | XX.X                 | XX.X                 | XX.X               | XX.X             |
| Q1, Q3                   | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         | XX.X, XX.X       |
| Min, Max                 | XX, XX               | XX, XX               | XX, XX             | XX, XX           |

....

Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study  
 ECD = Endothelial Cell Density  
 Baseline is defined as the last [redacted] measurement including unscheduled assessments prior to the  
 tion of first dose of [redacted]  
 [redacted] Central corneal ECD include [redacted] Central corneal ECD assessments or the Central corneal  
 o oedema.

Assessments after rescue keratoplasty are [REDACTED]

<DIRECTORY PATH>PROGRAM NA [REDACTED] ed: DDMMYYYY hh:mm  
Prog Notes: Continue with [REDACTED] Central Corneal ECD Images'.



**Table 14.2.1.48**  
Summary of BCVA by ETDRS by Central ECD Value by Visit  
(Full Analysis Set)

1 < Central ECD Value <= Mean

|                   | K-321 QID<br>(N=XXX) | K-321 BID<br>(N=XXX) | Placebo<br>(N=XXX) | Total<br>(N=XXX) |
|-------------------|----------------------|----------------------|--------------------|------------------|
| All Post-baseline |                      |                      |                    |                  |
| N                 | XX                   | XX                   | XX                 | XX               |
| Mean (SD)         | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       | XX.X (XX.XX)     |
| Median            | XX.X                 | XX.X                 | XX.X               | XX.X             |
| Q1, Q3            | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         | XX.X, XX.X       |
| Min, Max          | XX, XX               | XX, XX               | XX, XX             | XX, XX           |
| Baseline          |                      |                      |                    |                  |
| N                 | XX                   | XX                   | XX                 | XX               |
| Mean (SD)         | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       | XX.X (XX.XX)     |
| Median            | XX.X                 | XX.X                 | XX.X               | XX.X             |
| Q1, Q3            | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         | XX.X, XX.X       |
| Min, Max          | XX, XX               | XX, XX               | XX, XX             | XX, XX           |
| Week x            |                      |                      |                    |                  |
| N                 | XX                   | XX                   | XX                 | XX               |
| Mean (SD)         | XX.X (XX.XX)         | XX.X (XX.XX)         | XX.X (XX.XX)       | XX.X (XX.XX)     |
| Median            | XX.X                 | XX.X                 | XX.X               | XX.X             |
| Q1, Q3            | XX.X, XX.X           | XX.X, XX.X           | XX.X, XX.X         | XX.X, XX.X       |
| Min, Max          | XX, XX               | XX, XX               | XX, XX             | XX, XX           |

....

Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study  
 ECD = Endothelial Cell Density  
 Baseline is defined as the last [redacted] measurement including unscheduled assessments prior to the  
 administration of first dose of [redacted]  
 Assessments after rescue keratoplasty are [redacted]

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Prog Notes: Continue with 'Central ECD Value > Mean' and [REDACTED].

**Table 14.2.1.49**  
Correlation between BCVA by ETDRS and Central Corneal ECD (Include [REDACTED]) (Pearson and Spearman)  
(Full Analysis Set)

|                        | K-321 QID<br>(N=XXX) | K-321 BID<br>(N=XXX) | Placebo<br>(N=XXX) | Total<br>(N=XXX) |
|------------------------|----------------------|----------------------|--------------------|------------------|
| Pearson's Correlation  | 0.XX                 | 0.XX                 | 0.XX               | 0.XX             |
| Spearman's Correlation | 0.XX                 | 0.XX                 | 0.XX               | 0.XX             |

Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study  
 ECD = Endothelial Cell Density  
 Central corneal ECD assessments that are unable to be performed due [REDACTED].  
 Ass [REDACTED] be a [REDACTED] ed an [REDACTED] s [REDACTED].  
 or [REDACTED] by [REDACTED] [REDACTED] [REDACTED].  
 Ass [REDACTED] are [REDACTED].

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Table 14.2.1.50

Correlation between BCVA by ETDRS and Central Corneal ECD (Include [REDACTED] Data) (No Corneal Oedema)  
(Pearson and Spearman)  
(Full Analysis Set)

Same format as Table 14.2.1.49

Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study  
ECD = Endothelial Cell Density

Assessments before and after rescue keratoplasty are [REDACTED] as [REDACTED]  
or [REDACTED] by [REDACTED] are [REDACTED].  
Only [REDACTED] a observation [REDACTED].  
Assessments after rescue keratoplasty are [REDACTED].

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Table 14.2.1.51

Correlation between BCVA by ETDRS and Central Corneal ECD (Exclude [REDACTED] Data) (Pearson and Spearman)  
(Full Analysis Set)

Same format as Table 14.2.1.49

Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study  
ECD = Endothelial Cell Density

Central corneal ECD assessments that are unable to [REDACTED] and a [REDACTED] s  
[REDACTED] be analysed and categorized as [REDACTED] or [REDACTED]  
[REDACTED] are not included.  
[REDACTED] rescue keratoplasty are [REDACTED].

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Table 14.2.1.52

Correlation between BCVA by ETDRS and Central Corneal ECD (Exclude [REDACTED] Data) (No Corneal Oedema)  
(Pearson and Spearman)  
(Full Analysis Set)

Same format as Table 14.2.1.49

Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study

ECD = Endothelial Cell Density

Ass [REDACTED] be analysed and categorized as [REDACTED]

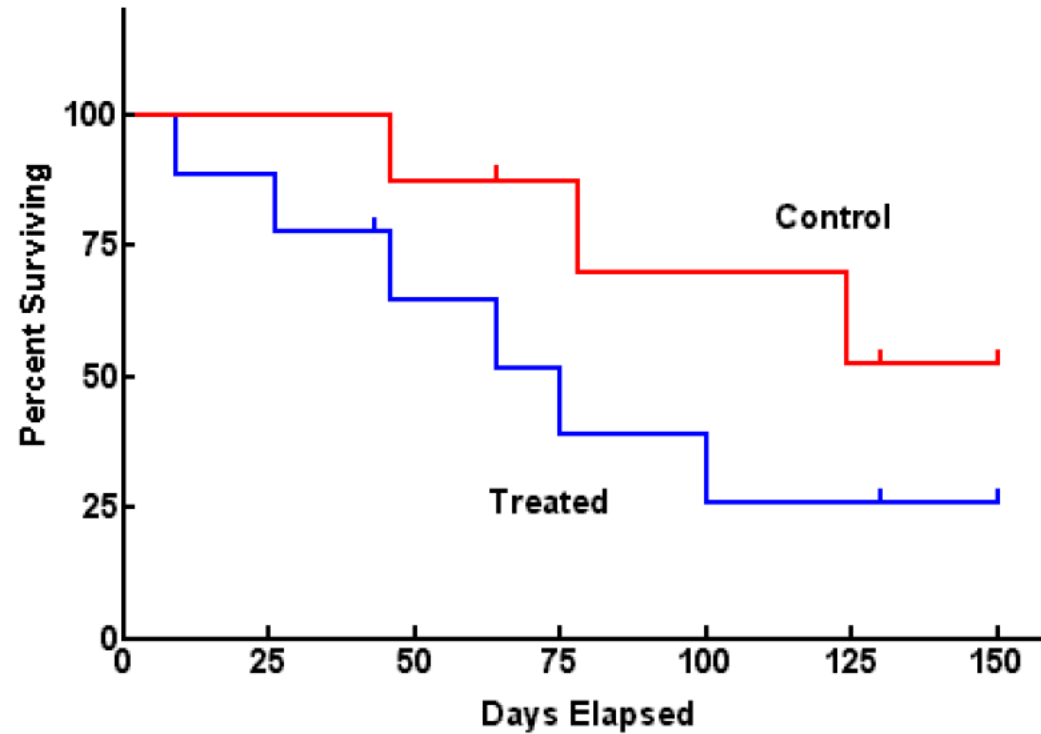
or [REDACTED] are not included.

Only [REDACTED] a observed are included.

Assessments after rescue keratoplasty are included using the collected values.

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Figure 14.2.1.42  
Time to Achieve Intervention of Rescue Therapy (Kaplan-Meier Plot)  
(Full Analysis Set)



Note: Time to Achieve Intervention of Rescue Therapy = Date of Achieving Intervention of Rescue Therapy - Day 1 + 1.

Patient is considered having received rescue therapy if the patient 1) received rescue surgical procedure (penetrating keratoplasty or endothelial keratoplasty) during the study. 2) withdrawal with potential for surgical procedure. 3) withdrawal with potential for Rho kinase Inhibitor treatment.]

Patient's study discontinuation date is used as the rescue therapy date if the patient withdrawal with potential for surgical procedure or Rho kinase Inhibitor treatment.

Patients who complete follow-up or discontinue the study without achieving the specified endpoint are

Source Data: T14.2.1.42

DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

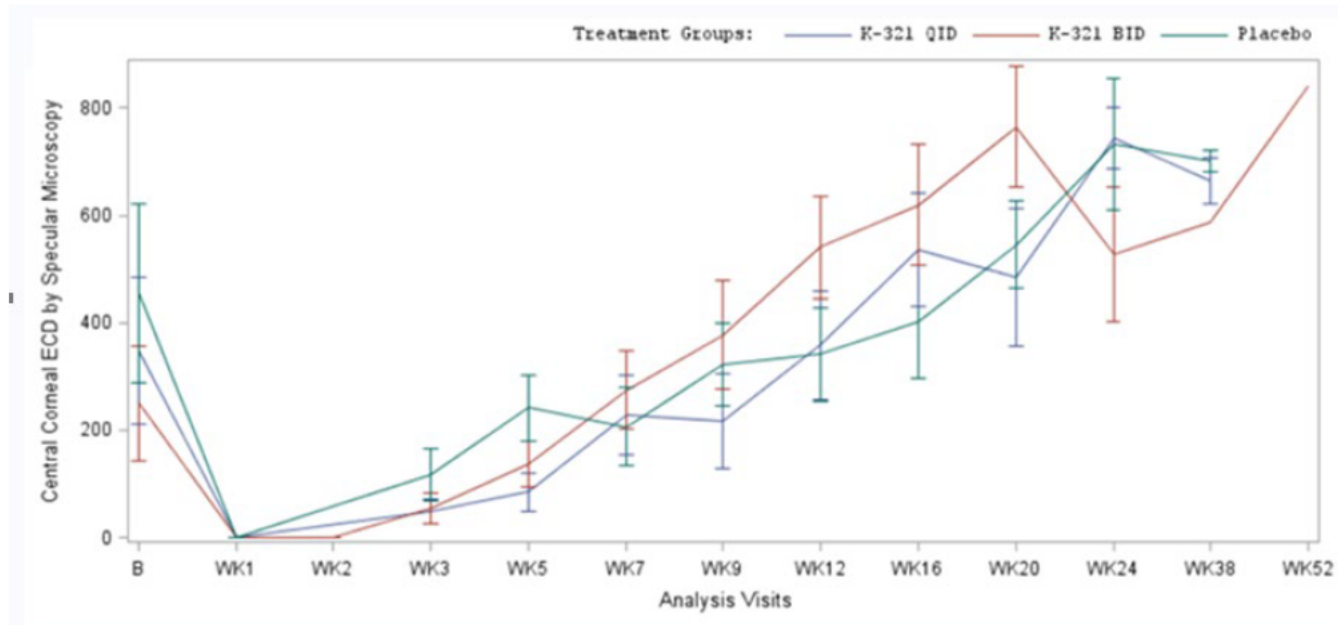
Programming note: Please show x-axis as Day 1 to Day 371. Please display y-axis label as 'Probability of Achieving Intervention of Rescue Keratoplasty (%)'.

Please display all treatment groups: K-321 QID, K-321 BID, Placebo



Figure 14.2.1.43

Central Corneal ECD (cells/mm<sup>2</sup>) of Study Eye performed by Specular Microscopy (LOCF) (Time Series Plot) (Full Analysis Set)



Note: LOCF = last-observation-carried forward, ECD = Endothelial Cell Density  
Baseline is defined as the last measurement including unscheduled assessments prior to the administration of first dose of treatment.  
Central corneal ECD (both baseline and post-baseline) that are unable to be performed due to

assessment and analysis and central corneal ECD by [redacted] are [redacted].

[redacted]

T14 43

DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Programming note: Please show x-axis according to the analysis visit. Please display y-axis label as 'Mean(+/-SD) Central Corneal ECD (cells/mm<sup>2</sup>) by Specular Microscopy'.  
Please display all treatment groups: K-321 QID, K-321 BID, Placebo  
Below the figure please include the N counts at each visit.  
Please include N counts for each treatment arm at the annotation.

Figure 14.2.1.44

Change from Baseline in Central Corneal Thickness ( $\mu\text{m}$ ) of Study Eye (LOCF) (Time Series Plot)  
(Full Analysis Set)

Repeat Figure 14.2.1.43 for Change from Baseline in Central Corneal Thickness

Note: Baseline is defined as the last [REDACTED] measurement including unscheduled assessments prior to  
inistration of first dose of st [REDACTED] n  
[REDACTED] central corneal [REDACTED]  
[REDACTED] atoplasty are [REDACTED]

[REDACTED] m baseline is defined as the post baseline value minus the baseline value for the given  
assessment. For the change from baseline, only patients with a value at both baseline visit and the  
specific post-baseline visit are included.

Source Data: T14.2.1.44

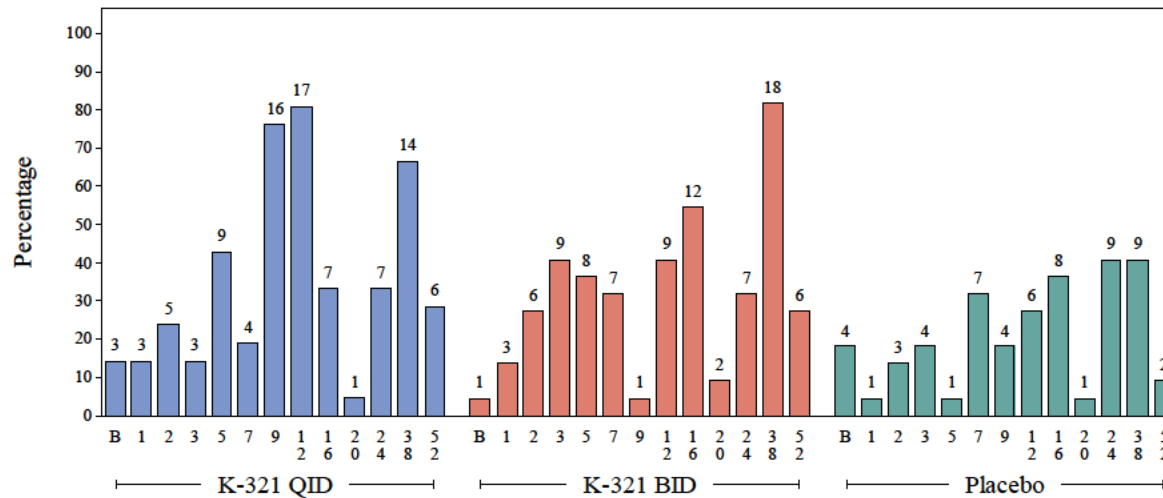
DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Programming note: Please show x-axis according to the analysis visit. Please display y-axis label as  
'Mean(+/-SD) Change from Baseline in Central Corneal Thickness ( $\mu\text{m}$ )'.

Please display all treatment groups: K-321 QID, K-321 BID, Placebo

Figure 14.2.1.45

Proportion of Patients Who Achieve No Corneal Oedema of Study Eye (LOCF) (Bar Chart)  
(Full Analysis Set)



Note: No corneal oedema is defined as absent of oedema in all three layers of cornea, including epithelial, stromal, and endothelial.

corneal oedema assessments are [REDACTED]. Patients who received a rescue keratoplasty are [REDACTED].

Numbers presented on the bars are the number of patients who achieve no corneal oedema of study eye for each visit under each treatment arm.

Source Data: T14.2.1.45

DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Programming note: Please show x-axis according to the analysis visit. Please display y-axis label as 'Proportion of Patients Who Achieve No Corneal Oedema'.

Please display all treatment groups on the same page: K-321 QID, K-321 BID, Placebo

Please include the n counts above each bar for each treatment arm and each visit for subjects who achieved the endpoint.

Figure 14.2.1.46  
Change from Baseline in BCVA by ETDRS of Study Eye (LOCF) via Wilcoxon Rank Sum Test (Time Series Plot)  
(Full Analysis Set)

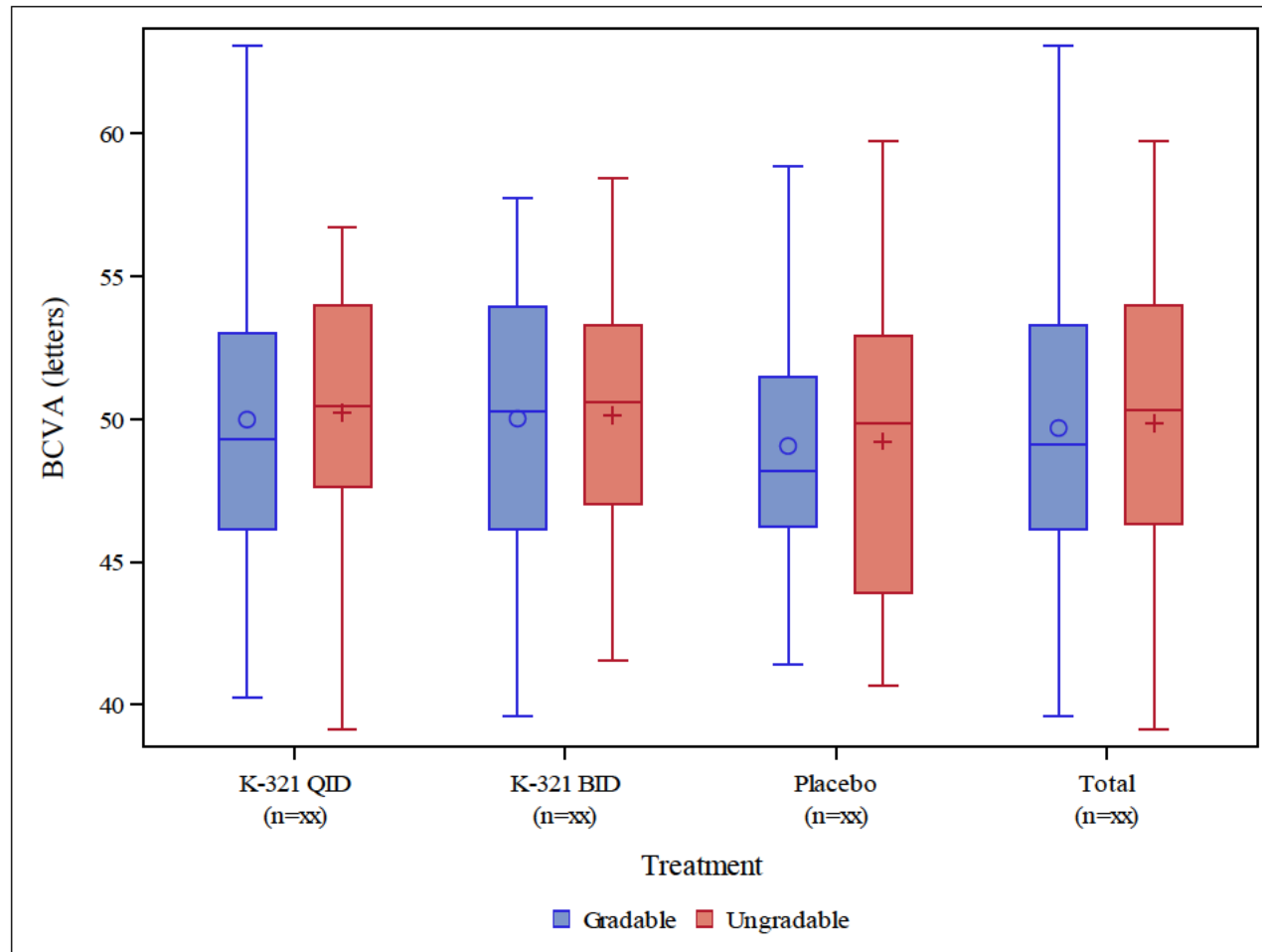
Repeat Figure 14.2.1.43 for Change from Baseline in BCVA

Note: BCVA = Best Corrected Visual Acuity; ETDRS = Early Treatment Diabetic Retinopathy Study  
Baseline is defined as the last measurement including unscheduled assessments prior to the  
administration of first dose. [redacted]  
[redacted] surgery are  
[redacted] ven  
assessment. For the change from baseline, only patients with a value at both baseline visit and the  
specific post-baseline visit are included.  
Source Data: T14.2.1.46

DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Programming note: Please show x-axis according to the analysis visit. Please display y-axis label as  
'Mean(+/-SD) Change from Baseline in BCVA by ETDRS Letter Score'.  
Please display all treatment groups: K-321 QID, K-321 BID, Placebo

Figure 14.2.1.47  
BCVA by ETDRS by Central ECD Gradeability by Visit (Box Plot)  
(Full Analysis Set)



Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study  
ECD = Endothelial Cell Density  
Baseline is defined as the last [REDACTED] measurement including unscheduled assessments prior to the  
[REDACTED] tion of first dose of [REDACTED]  
[REDACTED] Central corneal ECD include [REDACTED] Central corneal ECD assessments or the Central corneal  
[REDACTED] ments that could not be performed [REDACTED] o oedema.  
Source Data: Table 14.2.1.47

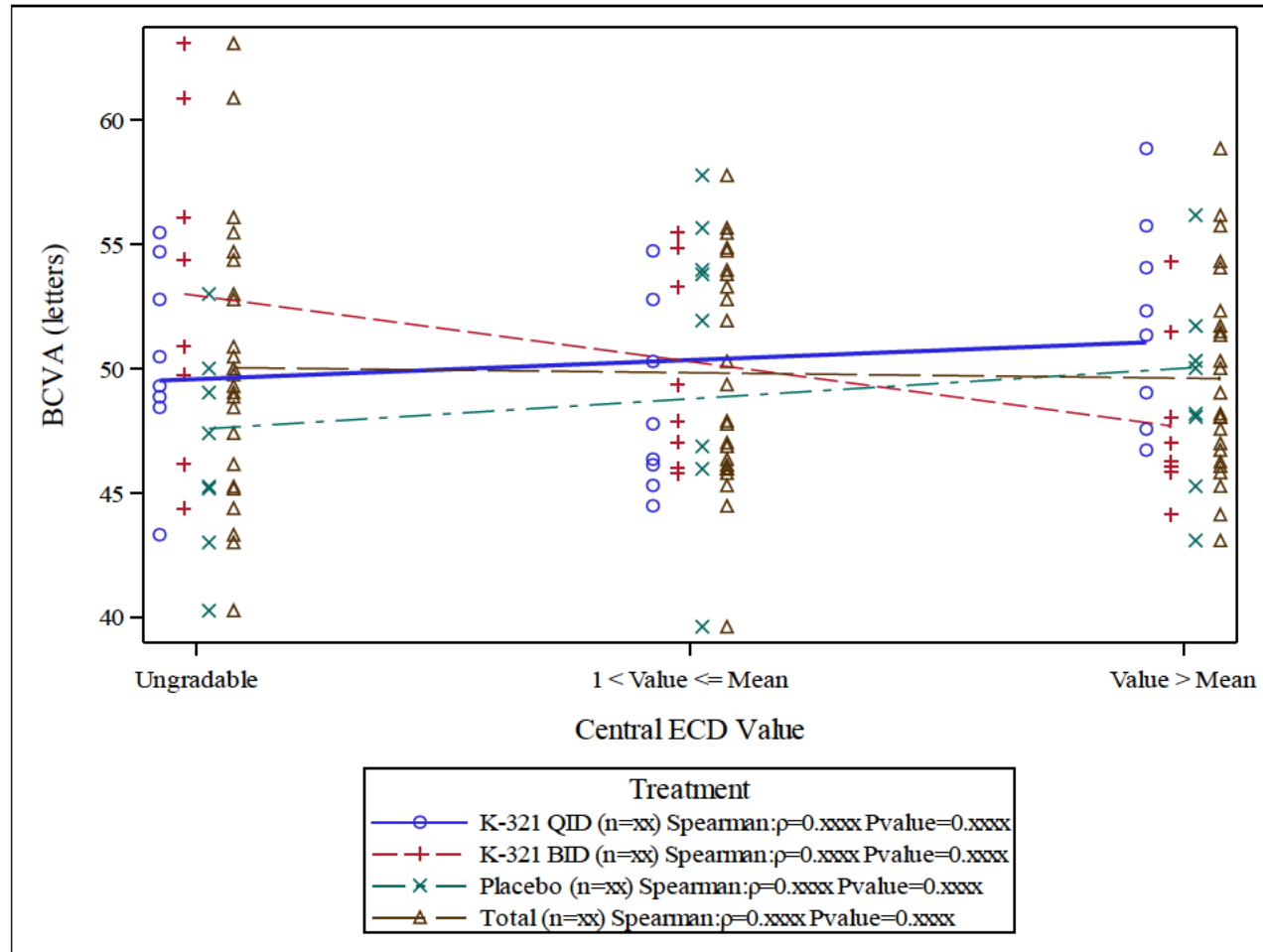
DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Programming note: Please show x-axis according to the subgroups [REDACTED] and [REDACTED]. Please  
display y-axis label as 'BCVA by ETDRS Letter Score'.

Please display 'All Post-Baseline Visits' in the first page, then start the second page with  
'Baseline', 'Week X'... Each visit should be on a separate page.

In each page please display all treatment groups and Total: Total, K-321 QID, K-321 BID, Placebo  
In each page please include number of subjects under each treatment arm and subgroups under the plot.

**Figure 14.2.1.48**  
BCVA by ETDRS by Central ECD Value by Visit (Scatter Plot)  
(Full Analysis Set)



Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study  
ECD = Endothelial Cell Density  
Baseline is defined as the last [redacted] measurement including unscheduled assessments prior to the administration of first dose of [redacted] ment.



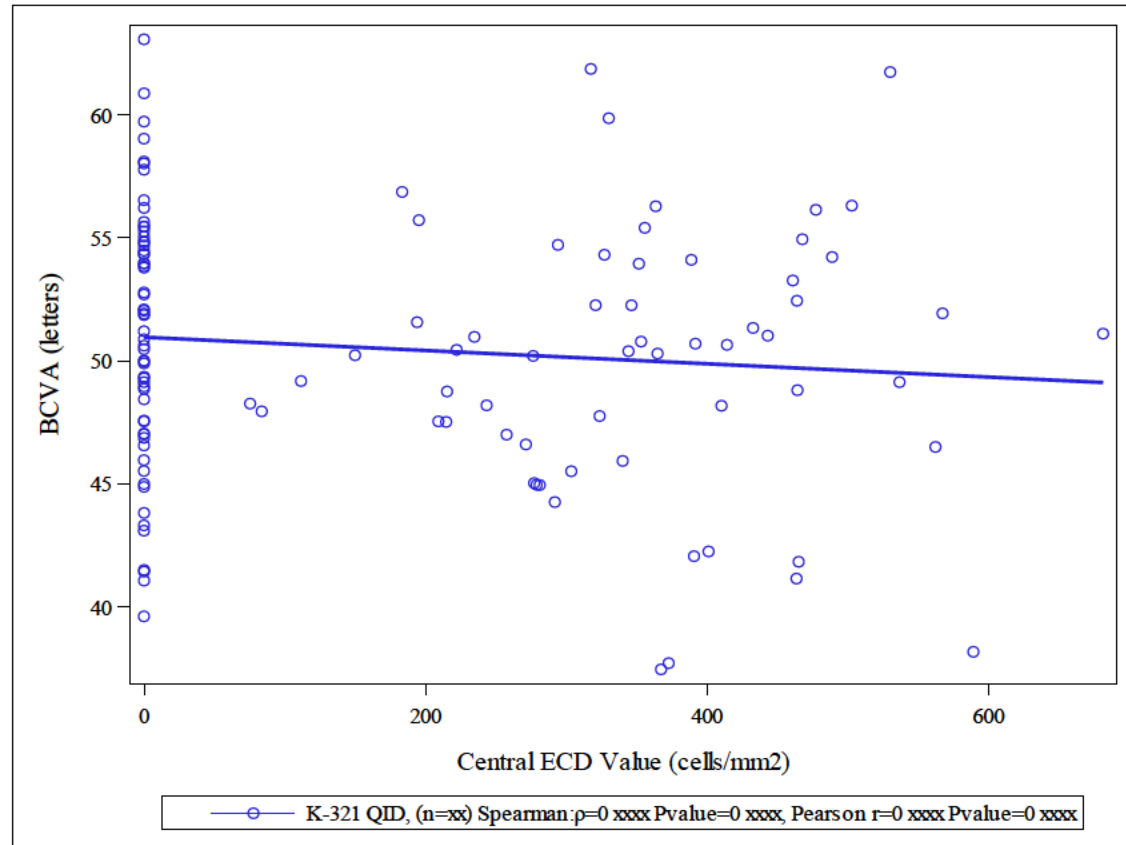
Source Data: Table 14.2.1.48

DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Programming note: Please show x-axis according to the subgroups '1 < Central ECD Value <= Mean', 'Central ECD Value > Mean' 'and [REDACTED]'. Please display y-axis label as 'BCVA by ETDRS Letter Score'. Please display 'All Post-Baseline Visits' in the first page, then start the second page with 'Baseline', 'Week X'... Each visit should be on a separate page.

In each page please display all treatment groups: Total, K-321 QID, K-321 BID, Placebo  
In each page please include number of subjects under each treatment arm and subgroups under the plot.  
Please display the spearman correlation and p-value under the figure for each treatment group and total.

Figure 14.2.1.49  
Correlation between BCVA by ETDRS and Central Corneal ECD (Include [REDACTED] (Pearson and Spearman)  
(Full Analysis Set)



Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study  
ECD = Endothelial Cell Density  
Central corneal ECD assessments that are unable to be performed due [REDACTED].  
Ass [REDACTED] be a [REDACTED] ed an [REDACTED] s [REDACTED].  
or [REDACTED] by [REDACTED] [REDACTED] [REDACTED] [REDACTED].  
Ass [REDACTED] are [REDACTED] [REDACTED] [REDACTED].  
Source Data: Table 14.2.1.49

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Programming note: Please display x-axis label as 'Central Corneal ECD (cells/mm<sup>2</sup>)'. Please display y-axis label as 'BCVA by ETDRS Letter Score'.  
Please display the scatter lot for total and each treatment group in separate pages.

Please include the spearman and perason correlation values and the corresponding p-values under the figure for each treatment group and total.

Figure 14.2.1.50

Correlation between BCVA by ETDRS and Central Corneal ECD (Include [REDACTED] Data) (No Corneal Oedema)  
(Pearson and Spearman)  
(Full Analysis Set)

Repeat Figure 14.2.1.49 but only include the visits where there is No Corneal Oedema.

Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study

ECD = Endothelial Cell Density

Ass [REDACTED] be an [REDACTED] sed an [REDACTED] as [REDACTED]  
or [REDACTED] by [REDACTED] are [REDACTED].  
Onl [REDACTED] a ob [REDACTED].  
Assessments after rescue keratoplasty are [REDACTED].  
Source Data: Table 14.2.1.50

Programming note: Please display x-axis label as 'Central Corneal ECD (cells/mm<sup>2</sup>)'. Please display y-axis label as 'BCVA by ETDRS Letter Score'.  
Please display the scatter lot for total and each treatment group in separate pages.

Please include the spearman and perason correlation values and the corresponding p-values under the figure for each treatment group and total.

**Figure 14.2.1.51**  
Correlation between BCVA by ETDRS and Central Corneal ECD (Exclude [REDACTED] Data) (Pearson and Spearman)  
(Full Analysis Set)

Repeat Figure 14.2.1.49 but only include the visits where there is no imputed data.

Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study  
ECD = Endothelial Cell Density  
Central corneal ECD assessments that are unable to [REDACTED] and a [REDACTED] es  
[REDACTED] be analysed and categorized as [REDACTED] or [REDACTED]  
[REDACTED] are not included.  
[REDACTED] rescue keratoplasty are [REDACTED].  
Source Data: Table 14.2.1.51

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Programming note: Please display x-axis label as 'Central Corneal ECD (cells/mm<sup>2</sup>)'. Please display y-axis label as 'BCVA by ETDRS Letter Score'.  
Please display the scatter lot for total and each treatment group in separate pages.  
Please include the spearman and perason correlation values and the corresponding p-values under the figure for each treatment group and total.

Figure 14.2.1.52

Correlation between BCVA by ETDRS and Central Corneal ECD (Exclude [REDACTED] Data) (No Corneal Oedema)  
(Pearson and Spearman)  
(Full Analysis Set)

Repeat Figure 14.2.1.49 but only include the visits where there is no imputed data and the visits where there is No Corneal Oedema.

Note: BCVA = Best Corrected Visual Acuity, ETDRS= Early Treatment Diabetic Retinopathy Study

ECD = Endothelial Cell Density

Ass [REDACTED] be analysed and categorized as [REDACTED]

or [REDACTED] are not included.

Only [REDACTED] a obs

Assessments after rescue keratoplasty are [REDACTED]

Source Data: Table 14.2.1.52

<DIRECTORY PATH>PROGRAM NAME Executed: DDMMYYYY hh:mm

Programming note: Please display x-axis label as 'Central Corneal ECD (cells/mm<sup>2</sup>)'. Please display y-axis label as 'BCVA by ETDRS Letter Score'.

Please display the scatter lot for total and each treatment group in separate pages.

Please include the spearman and perason correlation values and the corresponding p-values under the figure for each treatment group and total.