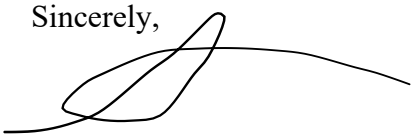
11/20/2023

Dear FDA Clinical Trials Review Board,

Please find attached the *study protocol and statistical analysis plan* document as requested on the PRS System.
This is for the study: *Intracanalicular Dexamethasone Insert for Post-Corneal Cross-Linking Inflammation and Pain- The LINK Study* (IND 146603; NCT04168112)
Please do not hesitate to contact me with any questions or concerns regarding this document.
Thank you for your time and consideration.

Sincerely,



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Intracanalicular Dexamethasone Insert for Post-Corneal Cross-Linking Inflammation and Pain- The LINK Study

Protocol in brief: This prospective, open-label, single-center, randomized, investigator-sponsored clinical study sought to investigate the efficacy of dexamethasone intracanalicular insert on post-corneal crosslinking inflammation and pain in keratoconus patients. This study planned to enroll 20 patients and follow patients over the course of several study visits [(postoperative day (POD) 1, POD-3, POD4-7, POW2, POW3 and POW4]. It is anticipated that corneal re-epithelialization will occur within the first postoperative week, but patients were be followed closely for documentation of therapeutic effect for 30 days due to duration of steroid therapy (i.e. dexamethasone intracanalicular insert or use of Prednisolone acetate 1% ophthalmic solution tapered over 1 month in the following schedule: 4 times daily x1 week, 3 times daily x 1 week, 2 times daily x 1 week, and daily x 1 week). All patients will receive postoperative fluoroquinolone antibiotic eye drops with instructions for use (i.e. 1 drop in operative eye 4 times daily x 10 days). All patients were evaluated for pain scores, rate of corneal re-epithelialization, ease of use of the post-crosslinking regimen, and need for rescue pain medication after standard bilateral epithelium-off crosslinking.

Biostatistics

Study variables were analyzed by appropriate statistical methods to assess for the differences between eyes treated as an entire group, and as broken down between dexamethasone implant and traditional prednisolone drop groups. Correlations between ease of use, intraocular inflammation, and epithelial healing were assessed using $\chi 2$, t-test, Pearson, and the Fisher Z-transformation test, evaluating the sample correlation r for significance. For independent samples, the t-test or Mann-Whitney-U test will be used for scaled data based on the outcome of the Kolmogorov-Smirnov test for normality of distribution. Ordinal data was analyzed using the Mann-Whitney-U test and chi-square or Fisher's Exact test for nominal data. P-values less than or equal to 0.05 were considered statistically significant. For non-inferiority or equivalency data, 95% confidence intervals were formulated and compared with equivalency margins. Sample size is small secondary to the incidence of the disease (1:2,000)

For any patient deciding to withdraw from the follow-up, the reasons for the withdrawal were recorded for the subsequent analysis in the interpretation of the results.
Reasons behind drop out were investigated and included in study results. The authors only analyzed complete cases, as imputing the missing data using single or multiple imputation methods would be confounded by the small sample size. ITT for ease of use was calculated utilizing extremely conservative estimates of a 70% +/- 10% for drops and 90% for dexamethasone insert, while utilizing a two independent sample study with a continuous endpoint, 1:1 enrollment ratio, alpha/beta of 0.05, and power of 95%. We calculated the minimum number of patients needed to enroll as 12.

In order to account for type I errors over multiple endpoints Bonferroni adjustment method was utilized.

Study results: Twenty patients (40 eyes) were enrolled in the study. In the prednisolone group, there was 60% male and 40% female (n=6, n=4, respectively). In the dexamethasone group, there was 40% male and 60% female (n=4, n=6, respectively). One patient in the prednisolone group dropped out from the study after POW1 as her family moved out of state and is continually followed by a cornea specialist in her new location. Another patient in the prednisolone group was lost to follow up after POW1 and despite multiple attempts at contacting her, including a certified letter she did not return for follow up. Results were analyzed for the remaining patients who completed the full study course (8 patients (16 eyes) in prednisolone group, 10 (20 eyes) in dexamethasone insert group).

Mean age in the prednisolone group was 26±3.89 years (range: 19-27), mean age in the dexamethasone group was 36.3±10.29 years (range: 25-47). Mean best corrected visual acuity (BCVA) at baseline was 20/40 (range: 20/20-20/100) in the prednisolone group and 20/40 (range: 20/20 to 20/400) in the dexamethasone insert group. There was no statistical difference between age, sex and whether or not patient received dexamethasone insert or prednisolone. In addition, there was no significant correlation between sex and final BCVA (t-test, *p=0.543*). No correlation was found between age and final BCVA (Pearson correlation, *p=0.372*)

No significant difference was found between BCVA at POW4 and whether the patient received dexamethasone or prednisolone (t-test, *p=0.554*). Mean POW4 BCVA was 20/40 in the prednisolone group and 20/30 in the dexamethasone insert group. There was no significant change in BCVA at POW4 as compared with baseline.

When assessing pain scores, a standardized visual analog pain scale (0-10) was used for each patient. Mean pain score on POD0 was 6.4±1.3 and 6.6±1.62 for the prednisolone and dexamethasone insert groups, respectively. Pain scores fell significantly on POD1 to 1.3±0.45 and 2±1.18 in the prednisolone and dexamethasone groups, respectively. By POD7, no patient complained of pain or discomfort (i.e., pain scale rating was "0"). No patient used 'rescue medications' longer than 2 days (POD0 and POD1) – the most commonly used self-reported medications were ibuprofen and acetaminophen. Seventy percent of patients in the prednisolone group vs. 60% of those patients in the dexamethasone insert group self-administered pain medications to help manage postoperative discomfort. No narcotics were prescribed or deemed necessary to help manage post-CXL pain in our study. Though not a large difference in pain scores, those in the prednisolone group reported statistically significantly lower pain scores at POD0(t-test, *p=0.021*) and POD1 (t-test, *p=0.036*) vs. those in the dexamethasone insert group.

Ocular surface inflammation was noted to be quite mild over the course of the study. Most patients demonstrated clear conjunctiva that was free of injection by POD1; only 4 eyes (2 in the prednisolone group, 2 in dexamethasone group) had trace injection noted at time of exam. No conjunctival injection was noted at the remainder of the study visits for any subject.

Trend in intraocular pressure (IOP) was assessed from baseline to POW4. There was no significant difference in baseline IOP between groups (t-test, *p=0.518*); mean IOP was noted to be 13.5±1.28mmHg and 13.9±1.64 mmHg at POD1 in prednisolone and dexamethasone insert groups, respectively. By POW4, mean IOP measured 14.25±1.64mmHg in the prednisolone

group and 13.65±2.26mmHg in the dexamethasone insert group. There was no significant rise or difference in intraocular pressure over time across both groups.

Rate of corneal re-epithelialization was assessed between groups. There was no significant difference between groups and rate of epithelial defect resolution at POD1 (t-test, $p=0.152$) and POD3 ($p=0.061$). Epithelial defect was noted to be resolved by POD7 in all subjects

Central corneal pachymetry (CCT) will often change over the course of post-CXL healing and as such was assessed at baseline and at the completion of the study between groups. As expected, there was no significant difference in mean CCT between groups at baseline (505.4±47.6µm in prednisolone group and 509±44.11µm in dexamethasone group), nor at POW4 (459±33.89 µm in prednisolone group; 473.15±43.78 µm in dexamethasone group).

At the end of the study, the patients were asked to complete an "ease of use" questionnaire regarding postoperative medications. The first question asked "Were directions regarding eye drop use post-CXL easy to follow"? All patients in both groups responded "yes" to this. The second question asked, "Was it cumbersome to use eye drops for more than 10 days" (this pertained to the prednisolone group), however 100% responded "no". The final question asked "Was it difficult to remember to use postoperative drops?"; 100% of patients responded "no". No patient experienced any adverse results in relation to treatment or CXL.