

Record of Telephone Conversation - GLASSIA, May 20, 2010

RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA

Submission ID: 125325/0

Office: OBRR

Product: Alpha-1-Proteinase Inhibitor (Human)

Applicant: Kamada Ltd.

Telecon Date/Time: 20-May-2010 09:30 AM

Initiated by FDA? Yes

Telephone Number: Communication Categorie(s): 1. Information Request

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Telecon Summary: Request for updated PMR/PMC Letter

FDA Participants: L. Ross Pierce, Ewa Marszal, Jennifer Reed, Dorothy Scott, and Cherie Ward-Peralta

Non-FDA Participants: None

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body: FDA requested a telecon with Kamada to discuss clinical post-marketing requirements (PMR) and commitments (PMC) for Alpha-1-Proteinase Inhibitor (Human). Before the meeting began, FDA asked if Kamada performs -(b)(4)- visual inspections of the product during the packaging of the product and if this is a limited inspection.

Kamada confirmed visual inspections are done on the vials, and a filament inspection as stated in our responses within the recent amendments submitted to the BLA.

FDA requested Kamada to convert the requested Phase IV study in which they will measure viral PCR and anti-Alpha1-PI antibodies to a Post-Marketing Requirement, and to provide absolute (not relative to the date FDA accepts the protocol) calendar dates corresponding to estimated milestones for submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report to the BLA for all PMR/PMC.

The PMR study should also include design features which will permit the detection of possible adverse events (AEs) due to the presence of particulates in the product. The 5-week washout period needs to be justified or omitted and FDA recommends using a single licensed comparator rather than multiple comparators. The protocol needs to indicate which specific viral safety tests are to be performed at which time points. FDA requested Kamada to provide clarification regarding their statement in the protocol outline that each subject is to participate for 64 weeks since the treatment duration for the study is listed as 12 weeks.

Regarding the clinically meaningful endpoint stage 1 study, FDA requested to include the study duration, and power calculations used to determine the proposed sample size

for the study. The first study needs a reasonable sample size to be able to estimate the magnitude of the treatment effect in order to determine the sample size needed for the adequately powered stage 2 efficacy study. Other sponsors are conducting a fully powered stage 1 study, but this is for you to choose, i.e., whether to try to obtain a conclusive result from your initial study.

FDA requested the sponsor to provide a justification for the schedule of the CT exams. Kamada stated this information will be updated and provided to FDA. The dates could not be provided earlier as we are negotiating a collaborative study as suggested for the stage 2 clinical study.

FDA stated the option to consider a collaborative study (factorial design) was made only in regards to the Fully Powered Stage 2 study, since the latter may require substantial investment in time for recruiting. Also, each product is unique; FDA does not allow the efficacy results of one product to be included in the labeling of another product.

Kamada asked if FDA would accept the Stage 1, fully powered study, as a collaborative study.

FDA has not discussed this option as we originally expected the sponsor to have the resources to perform this with their own product. The number of subjects proposed should be used with your product at a minimum, but further discussion would be needed within the division if Kamada wishes to pursue a stage 1 collaborative study.

Kamada will provide a revised letter of commitment shortly and consider additional suggestions regarding study design after the approval.

FDA also recommended for the BAL Phase IV clinical study to include a small control group to allow detection of a problem with sample handling versus a problem with their product.

Kamada informed FDA that it may be difficult to recruit subjects for a BAL comparative study as the subjects may be participating in another study.

FDA recommended including naïve subjects or someone previously using Kamada Alpha1-PI in the BAL study with a perhaps a 3:1 or 4:1 randomization over the comparator. Kamada can also enroll anyone with previous Alpha1-PI products with a month washout period.

Kamada agreed including a comparator arm in the BAL study, but their original suggestion of utilizing one arm was due to recruitment difficulties, especially with an age criteria and meeting the timelines of the study.

FDA agrees to the proposal of enrolling a total of 16 subjects in the BAL study, if Kamada ensures enrolling evaluable subjects.

Kamada will contact FDA if there is a delay in recruiting subjects.

FDA suggested the possible use of previously frozen samples from the pivotal study to perform NAT testing for viruses, but should include data on how the analytes maintain in those storage conditions. The BAL study primary endpoint should be both antigenic and functional A1-PI levels in ELF after 10-12 weeks of treatment, not antigenic or functional A1-PI levels. Depending on the size of the comparator group, in addition to changes in ELF analytes from baseline to 10-12 weeks, we recommend you analyze as an exploratory analysis the difference between treatment groups in 10-12 week values using the baseline value as a co-variate.

FDA informed Kamada the revised letter of commitment should enumerate the three goals of the Phase IV PMR study, and the revision of your table of the PMR/PMCs with

calendar milestone dates. A written information request will be provided with all the requested and recommended information for the PMR and PMC. We request a response to be provided by May 28, and the more detailed recommended changes to the clinical protocols may be provided on the date written in the information request. FDA informed Kamada the possibility that the validation report for antibody testing may be converted to a PMR after discussions with the Safety Working Group, and CMC PMCs will be requested in the near future.

End of Meeting

<https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/default.htm>

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