일반연제

Bridging Experience in MSD Korea: Etoricoxib 90 mg

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A bridging study is defined as a supplemental study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region according to ICH guideline. Bridging is basically a learning stage in drug development, thus modeling and exploratory data analysis method is preferred than test required in confirming stage.

Currently, there are 2 types of nonsteroidal anti-inflammatory drugs (NSAIDs) available on the market: nonselective NSAIDs that inhibit both the cyclooxygenase-1 (COX-1) and the cyclooxygenase-2 (COX-2) enzymes and the COX-2 inhibitors, which selectively inhibit the COX-2 enzyme over their clinical dose range. Etoricoxib is a highly selective COX-2 inhibitor.

Etoricoxib, when assessed in accordance with ICH E5 Guideline Appendix D, displays characteristics which show the low possibility of ethnic sensitivity such as the plasma concentration increased proportionally with dose and, flat pharmacodynamic curve, wide therapeutic range, low potential for drug interaction due to protein binding, high bioavailability, low interaction of drug-drug, drug-disease and drug-diet and little potential of inappropriate use. On the other hand, etoricoxib also has other properties such as moderate protein-binding rates and systemic mode of action, which may potentially have ethnic sensitivity across ethnic groups. However, when assessed with taking into account all characteristics holistically, etoricoxib has no clinically significant ethnic sensitivity among ethnic groups in terms of efficacy and safety.

Also, a pharmacokinetic study in Asian (Japanese) subjects did not reveal a clinically significant difference in the pharmacokinetic profile of etoricoxib between Japanese and Caucasian subjects.
Therefore, MSD Korea considered that etoricoxib has low possibility to show the ethnic sensitivity resulting in difference of safety and efficacy due to ethnic factors and submitted an application for bridging data waiver to KFDA with a report showing lack of ethnic sensitivity of etoricoxib based on

ICH E5 Guideline, foreign clinical data and Asian (Japanese) clinical data. However, as the results of KFDA review, they did not grant that there were no differences in safety and efficacy of etoricoxib across ethnic groups.

MSDK sponsored a bridging study in Korean rheumatoid arthritis patients and compared the pre-existing foreign clinical data and Korean data to examine whether there were clinically significant efficacy and safety differences and whether the foreign clinical data could be extrapolated to Koreans.

The bridging study of etoricoxib was an open-labeled, historical-comparative and safety and efficacy confirmatory study employing the tender joint count, swollen joint count, patient global assessment of disease activity and investigator global assessment of disease activity as the primary endpoints in Korean rheumatoid arthritis patients for 12 weeks with a design similar to the clinical studies in foreign clinical data package.

As the results of this study, each of the primary endpoints, consisting of the tender joint count, swollen joint count, patient global assessment of disease activity, and investigator global assessment of disease activity, showed statistically significant improvements from baseline. In terms of safety, general and non-specific adverse experiences were reported, without any extraordinary experiences within anticipated data variation

The similarity and consistency were evaluated as compared bridging data with pre-existing foreign clinical data. The extrapolation acceptance with foreign clinical data to Korean was also assessed.

The efficacy result in terms of patient global assessment of disease activity and the investigator global assessment of disease activity was similar between the two groups.

Meanwhile, when comparing the Korean bridging data with the foreign studies, the treatment results seemed to be different between the Korean and the historical control as the baseline values were starkly different for the tender joint count and the swollen joint count. However, similarity in terms of the treatment results was ensured by comparing the foreign results with Korean subgroup with the similar baseline value.

When Korean data and foreign data were analyzed with adjustment of covariate of baseline tender joint count and swollen joint count, treatment results were not different between two ethnic groups, and regression slopes were not different. Korean and foreign data were obviously self-explaining that the difference in reduction of tender joint count and swollen joint count is not due to ethnic sensitivity but due to baseline difference. In addition, less likelihood of ethnic sensitivity based on ICH E5 Guideline evaluation supported this conclusion.

However, the bridging result was not accepted by KFDA since similarity was evidenced by post hoc analysis. If there exist statistical analysis methods to adjust any bias, there is no reason we dont apply them for bridging study even it is post hoc.