

Briefing package for Lumiracoxib

Preliminary review of GI and CV data from TARGET

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Background

The TARGET (Therapeutic COX189 Arthritis Research and Gastrointestinal Event Trial) study was a 52-week, large outcome study involving approximately 18,000 patients, ongoing at the time of the NDA submission. The study had two components: Study 0117 (LUM 400 vs. naproxen 500 mg bid), and Study 2332 (LUM 400 vs. ibuprofen 800mg bid), with approximately 4,500 patients in each treatment group. Approximately 25% of patients in this study were on concomitant low dose aspirin (ASA up to 100 mg/day) for cardiovascular (CV) prophylaxis.

The primary outcome of this study was the cumulative rate of POB (perforations, obstructions and bleedings) in the non-aspirin user population. The study was also intended to evaluate general safety and tolerability of LUM 400 as compared with the two active comparators. The study was not powered to evaluate specific organ safety other than GI, however, it provides a substantial safety database of approximately 7,000 patient years of exposure to LUM 400 mg.

Results

1) Gastrointestinal safety

Lumiracoxib 400 mg succeeded in the primary analysis (a composite endpoint of confirmed and probable complicated POBs in the non-ASA users) and in the overall population. For ASA users the advantage decreased but there were trends in favor of lumiracoxib as compared to naproxen or ibuprofen that was not statistically significant.

The definition of GI events included in the primary analysis in this study are not exactly the same as those used in VIGOR (rofecoxib outcome study) or CLASS (celecoxib outcome study), but definitively, TARGET showed a GI advantage over both NSAIDs in the non-ASA population with a smaller advantage (almost none over ibuprofen) for the ASA users.

2. Cardiovascular safety (Table 1)

In study 0117, the number of APTC (Anti Platelet Trialists Collaboration) endpoint (which includes a composite of confirmed and probable cardiac deaths as well as fatal and nonfatal myocardial infarctions and strokes) is greater for LUM as compared to naproxen. In study 2332, the number of APTC events with LUM and ibuprofen is similar, including total number of MI.

Table 1 Confirmed or probable APTC events

	Study 0117		Study 2332	
	LUM (4741)	Naproxen (4730)	LUM (4376)	Ibuprofen (4397)
All patients (N)				
Any APTC event	40	27	19	21
CV death *	11	8	8	10
Non fatal MI* *	16	9	5	5
Non fatal ischemic stroke	13	11	6	6

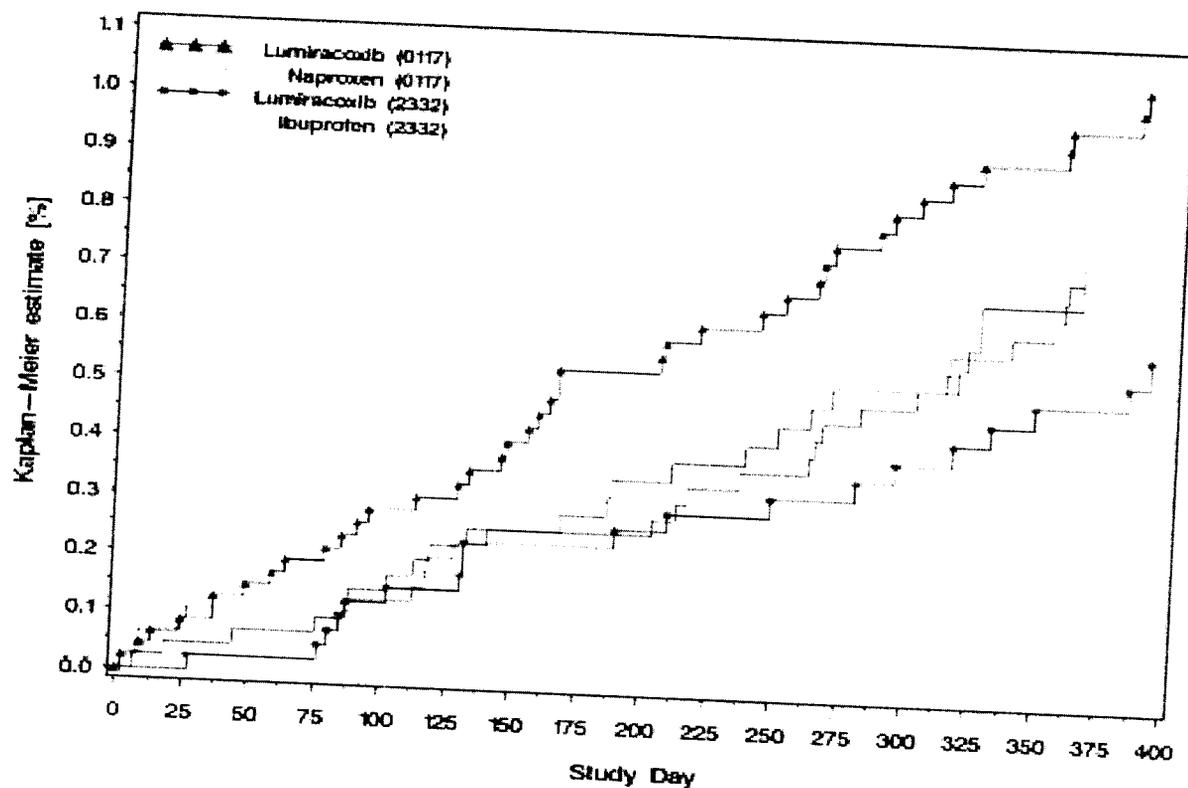
*Includes 2, 2, and 2 fatal MI in the LUM 0117, naproxen, LUM 2332 and Ibuprofen groups, respectively. ** Includes silent MI (ECG detected): 3 on LUM 0117, 3 on naproxen and 2 on ibuprofen (no silent MI in LUM 2332).

The difference in the number of APTC events in study 0117 was driven by non-fatal MIs in the non-aspirin user group. The numbers are small but suggest that low dose aspirin may prevent detecting a difference between LUM and naproxen. The numbers of MI in 2332 are small, particularly in the aspirin subgroup.

Interpretation of the findings is limited by the following issues:

1. The patient population was only OA. The study was initially designed as an OA/RA study and later amended to include only OA patients.
2. The study excluded patients at high cardiovascular risk (who had an indication for cardiovascular prophylaxis but were not taking asa).
3. The effective dose of lumiracoxib for OA and RA has not been identified yet.
4. The different number of CV/T events (MI, in particular) for lumiracoxib in each sub-study. The findings in study 0117 are consistent with findings for Vioxx as compared to naproxen in the VIGOR study. However, as observed in the following KM curve, naproxen, ibuprofen and lumiracoxib in study 2332 seem to behave similarly, while lumiracoxib in study 0117 was the outlier.

TARGET. Confirmed or probable APTC endpoint. KM plot (%).



Source: IND submission of TARGET final study report.

Conclusion:

This study has not definitively answered the question whether lumiracoxib increases cardiovascular thrombotic risk as compared to non-selective NSAIDs.