Briefing package for Lumiracoxib (1/18/05)

Preliminary review of GI and CV data from TARGET

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1. 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.

2. 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 (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. Patients with Confirmed or Probable CCV[1] and APTC[2] events

	Study 0117		Study 2332	
	LUM	**Naproxen**	**LUM**	**Ibuprofen**
All patients (N)	**(4741)**	**(4730)**	**(4376)**	**(4397)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Pts with CCV event	*52*	*43*	*33*	*32*
Pts with APTC event	*40*	*27*	*19*	*23*
CV death	***11(0.2)***	***8 (0.2)***	***8 (0.2)***	***10 (0.2)***
All MI	*18*	*10*	*5*	*7*
MI	*15*	*7*	*5*	*5*
Fatal MI	*2*	*1*	*0*	*2*
Non fatal MI	***13(0.3)***	***6 (0.1)***	***5 (0.1)***	***3 (0.1)***
Silent MI [3]	*3*	*3*	*0*	*2*
All stroke	*16*	*12*	*8*	*9*
Ischemic stroke				
Fatal	*2*	*0*	*2*	*0*
Non fatal	***13(0.3)***	***11 (0.2)***	***6 (0.1)***	***6 (0.1)***
Hemorrhagic				
Fatal	*1*	*1*	*0*	*1*
Hemorrhagic	*0*	*0*	*0*	*1*

[1] CCV: cardiovascular and cerebrovascular events. [2] APTC: cardiovascular death, non-fatal MI (clinical or silent) and non-fatal stroke. [3] Silent MI= ECG detected. LUM: lumiracoxib 400 mg daily. Naproxen dose: 500 mg bid. Ibuprofen dose: 800 mg tid. Source: Sponsor's submission.

It is unclear why the total number of cardiovascular and cerebrovascular (CCV) events in sub-study 2332 is smaller than in sub-study 0117. Of particular note is the difference in the number of CCV between LUM in sub-study 0117 (n= 52) and LUM in sub-study 2332 (n= 33). As seen in Table 2., the difference in the number of CCV events in sub-study 0117 was driven by non-fatal MI, in the non-aspirin user group.

Table 2. Patients with Confirmed or Probable APTC[1] events by aspirin use.

	Study 0117		Study 2332	
	LUM	***Naproxen***	***LUM***	***Ibuprofen***
Non ASA user (N)	***(3549)***	***(3537)***	***(3401)***	***(3431)***
Pts with APTC event	*22*	*14*	*13*	*13*
CV death[2]	*7*	*5*	*5*	*6*
Non fatal MI	*10*	*1*	*4*	*1*
Non fatal ischemic stroke	*5*	*6*	*4*	*2*
ASA user (N)	***(1192)***	***(1193)***	***(975)***	***(966)***
Pts with APTC event	*18*	*13*	*6*	*10*
CV death[3]	*4*	*3*	*3*	*4*
Non fatal MI	*3*	*5*	*1*	*2*
Non fatal ischemic stroke	*8*	*5*	*2*	*4*

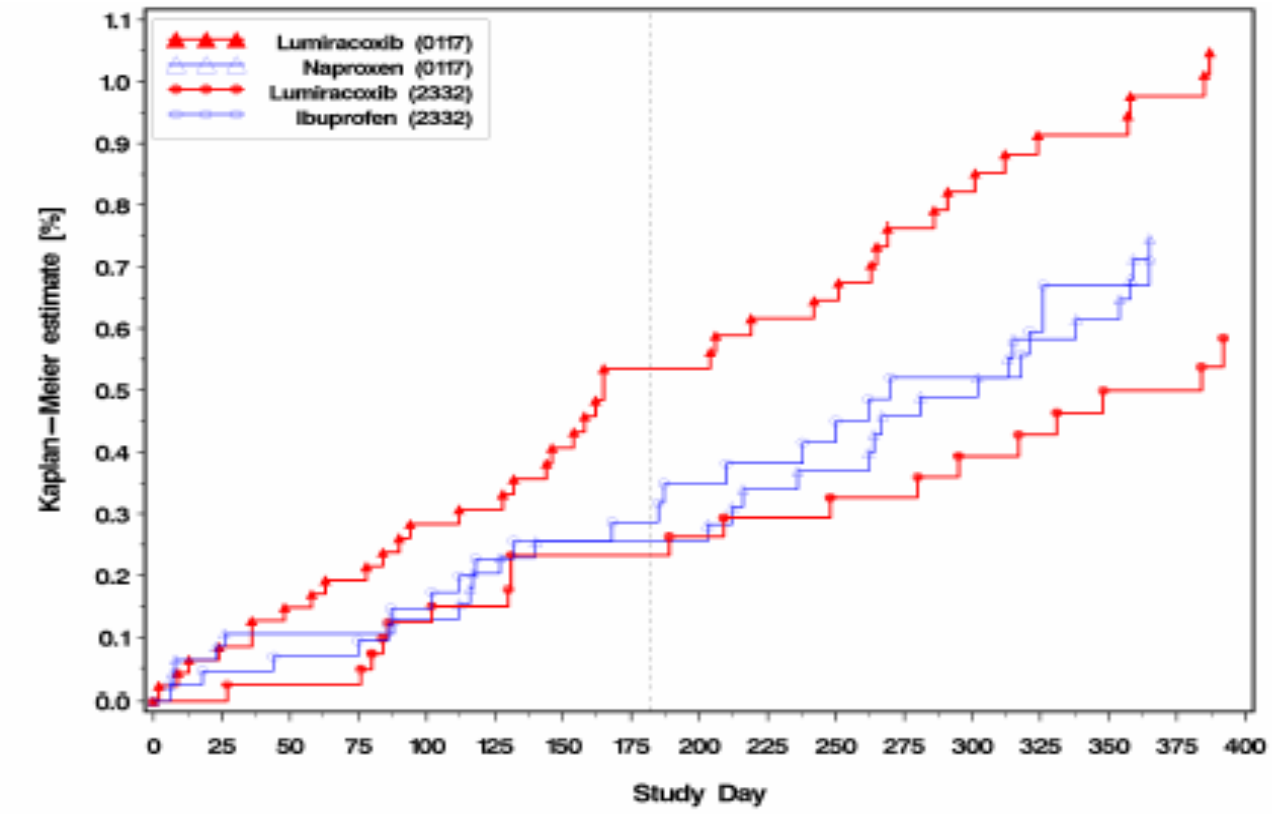
[1]APTC: cardiovascular death, non-fatal MI (clinical or silent) and non-fatal ischemic and hemorrhagic stroke. Numbers for non-fatal hemorrhagic stroke are not included in this table.
[2] Includes 1 and 2 fatal MI on naproxen and ibuprofen, respectively and 1 and 2 fatal ischemic stroke in the LUM 0117 and LUM 2332 groups, respectively.
[3] Includes 2 fatal MI and 1 fatal ischemic stroke on LUM 0117.

The numbers of MI in 2332 are smaller than 0117, particularly in the aspirin subgroups, however, they suggest that low dose aspirin may decrease the ability to detect a difference in the number of thrombotic events between LUM and these two non-selective NSAIDs.

Interpretation of the CV findings of this study are limited by the following issues:

1. *The study excluded patients at high cardiovascular risk (who had an indication for cardiovascular prophylaxis but were not taking ASA).*
2. *The patient population was only OA. The study was initially designed as an OA/RA study and later amended to include only OA patients. RA patients are known to be at higher CV risk than OA patients.*
3. *The effective dose of lumiracoxib for OA and RA has not been identified yet.*
4. *The different number of CCV 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 could have been the outlier.*

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



Source: IND submission of TARGET final study report.

3. Conclusion:

1.Sub-study 0117 suggests that LUM 400 mg daily is associated with increased risk of cardiovascular thrombotic events as compared to naproxen in patients not using low dose aspirin for cardiovascular prophylaxis. Aspirin seems to be "protective" for whatever is causing the difference between LUM and naproxen. High use of low dose aspirin in trials with COX-2 selective agents might blur differences between treatment arms.

2. Sub-study 2332 suggest that there are no differences in CV risk between LUM 400 mg daily and ibuprofen, except for a trend against LUM in the number of non-fatal MI. However, the number of events is small and precludes definitive conclusions.

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