

# Sponsor Presentation (Bayer & Roche): Safety Data: Martin Huber MD

## JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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### Highlights

- **ANTI-PLATELET EFFECTS:** “it is a known property of naproxen to inhibit platelet aggregation and this has been substantiated by studies demonstrating an increase in bleeding time, etc.”
- **LONG TERM RANDOMIZED TRIALS:**
  - The VIGOR trial was already discussed (increase in CV risk with Vioxx compared with naproxen).
  - The TARGET trial was 2 sub-studies one with naproxen and one with ibuprofen. Versus lumiracoxib, naproxen “had a lower incidence” of stroke and myocardial infarction, whereas “ibuprofen actually had a higher rate than lumiracoxib”. However the incidence with lumiracoxib was higher in the naproxen comparison which “makes this a little tricky”.
- There was also a randomized trial comparing rofecoxib, naproxen and placebo (results not discussed).
- **META-ANALYSIS:** The White meta-analysis of celecoxib data did not show “an increased risk of myocardial infarction or stroke” with naproxen “compared to either celecoxib or placebo”.
- **OBSERVATIONAL STUDIES:** Observational studies, despite their limitations, did not suggest increased risk with naproxen. Of 11 studies, only one (the Graham Lancet study) suggested increased risk (14% increase, but the lower confidence limit “did hit 1.0”).

### Presentation Text

Thank you, Len. Good afternoon. I will try to go through this in a little abbreviated form as I will be repeating

data that has been summarized by other speakers.

What we looked at was: We did an evaluation of the available data to us, looking at the question of myocardial infarction and/or stroke based on the preliminary findings that were reported for the ADAPT study.

This evaluation included an overview of the clinical pharmacology, the clinical studies from both the NDA for the OTC as well as prescription filings. We also looked at our postmarketing safety data. Furthermore, we looked at the large randomized postmarketing clinical studies that were available in the literature, and finally spent some time on the observational studies.

With regard to the pharmacology, I think we have heard enough about COX-1 and COX-2 today to last most of us a lifetime so I am not going to spend any time, other than to remind you that it is a known property of naproxen to inhibit platelet aggregation and this has been substantiated by studies demonstrating an increase in bleeding time, etc.

With regard to the clinical trials in the NDA, I would just like to briefly touch on that. There have been more than 500 patients treated in the original NDA for naproxen, of which more than 300 were treated more than 6 months.

In addition, a little more than 4000 patients were in the OTC NDA--limited duration of treatment for these patients but in each of these data sets there was no signal for either myocardial infarction or stroke.

Furthermore, we reviewed the postmarketing data available in the Roche safety database which goes back to the launch of the product in the early

'70s and in that, with over 100 million patients exposed globally, we saw no signal for either MI or stroke. A similar review in the OTC postmarketing surveillance data did not identify a signal.

I am going to skip over this. We did some disproportionality. These are some internal signal checks we do. It is in your briefing package and the basic message is we didn't see a signal even going back retrospectively. If you have questions I will be happy to discuss this.

What I would like to focus on are some of the large randomized, postmarketing clinical trials. The selection criteria we looked at here were that they needed to be published. They had to have naproxen in them and they also had to have prolonged exposure. We weren't looking at short term. There are hundreds of trials looking at very short-term use of these agents.

The first trial is the VIGOR trial. I think this has been discussed extensively and I will not spend any more time on it.

I would like to spend a little more time on TARGET. This study has not really been discussed in detail today. Our colleagues, I am sure, from Novartis will be spending more time on this tomorrow, but just to quickly go over a few findings with relevance to naproxen. I am not here to discuss lumiracoxib but to focus on naproxen.

Of note, this is really two studies; it is two sub-studies. One of these studies was lumiracoxib versus naproxen and another of lumiracoxib versus ibuprofen. So, this offers us somewhat of an interesting opportunity to potentially

look at naproxen in relationship to another non-selective non-steroidal in a large randomized clinical trial.

In the first sub-study which was looking at naproxen versus lumiracoxib, with regards to stroke which included ischemic and hemorrhagic, as well as for acute MI, naproxen had a lower incidence of both of these events compared to lumiracoxib.

On the other hand, when we looked at the sub-study looking at ibuprofen, ibuprofen actually had a higher rate than lumiracoxib. What makes this a little tricky though is that if you look at lumiracoxib in the two arms it is not comparable. There was actually a higher rate in the second study the naproxen study. The authors of the publication attribute this to a higher cardiovascular baseline risk in the second sub-study. But for our purposes today, what we would like to emphasize is that we have to be careful in these comparisons that if you use lumiracoxib as a common reference arm-the doses, schedule, et., I understand to be the same in both sub-studies, you have ibuprofen higher than lumiracoxib here; naproxen lower than lumiracoxib here.

The other study, as noted, was the Alzheimer's trial. This is not the ADAPT study. This is a study that was done in patients with mild to moderate Alzheimer's disease, published by Aisen, in JAMA in 2003. This was a randomized trial between placebo, naproxen and rofecoxib. These data are based on the publication. Essentially what we see is that in the placebo arm there are 111 patients and what we have is death, MI, stroke and TIA. These data are the serious adverse event data as

reported in the paper. We are not aware of any specific adjudication or any further analysis.

There has been extensive discussion of the trials with celecoxib. The only reason I bring this up is it is part of White's meta-analysis. There were 2000 patients treated with naproxen. There are 4 events that were noted in that meta-analysis, 1 fatal stroke, 2 fatal MIs. The rate of these events for naproxen was comparable to the other groups of celecoxib and placebo as part of that meta-analysis. We did not see in this publication evidence of an increased risk of myocardial infarction or stroke compared to either celecoxib or placebo.

Given the lack of large long-term randomized, placebo-controlled studies, I would now like to review the observational studies. We recognize some of the limitations of observational studies but I would like to spend a little time emphasizing that there are some positive attributes of these studies as well.

First of all, these studies can be done in a fairly short period of time. I think all of us have noticed that since this question has been raised, there are multiple publications, 2002, 2003 and actually in fact even 2005, because you can do an investigation of chronic or prolonged exposure but by going retrospectively get the data in a relatively short period of time.

They also offer a tremendous opportunity to look at relatively rare events. You can say a one percent adverse event is not that rare but when you try to look at a 20-30 percent change in the risk of an event that is of one

percent frequency in a clinical trial, all of you are aware of the limitations of sample size. Looking at 10,000 patients is easy to do, or relatively easy to do in an observational study.

Maybe more importantly, it is real-world use of the drug. These are heterogeneous populations. There are concomitant medications; there are concurrent illnesses. I think what is the most important thing when we look at observational studies, we have already started to see isolated reports of limited observational data. Every observational study has intrinsic limitations, the database, how you identify the patients. We can have epidemiologists spend most of the afternoon or evening if they want in debating that, but at the end of the day there are limits. What is the real value of these studies is what do you see when you do multiple studies across multiple databases? Do you find a consistency of the finding?

These represent the observational studies that have been published for naproxen and myocardial infarction. That is the topic that was covered here. This was recently summarized in a meta-analysis by Juni et al. in Lancet in 2004, and there weren't any other ones out there besides these so we kind of borrowed the figure from Juni.

There has been a huge discussion in the literature regarding the validity, the strengths, the weaknesses of the meta-analysis which showed that the overall risk was 0.86, but I am not going to spend a lot of time on that. What I would rather focus on is just to briefly update the committee on the weight of these studies.

Each study is represented here. What you can see is one is in the center of the axis here, and this would show that there was essentially an equal risk of MI between naproxen and whatever the control group was for the study. This direction favors naproxen having a lower risk than the control. This direction favors the control.

What we find is most important about this data is there are 11 studies and 10 of them show the risk either equal to 1 or less than 1, which is striking consistency.

There is one study which had an increased risk. This is the Graham study which was recently published in Lancet, which showed a 14 percent increase in risk. Of note, in the publication in Lancet the lower limit of the confidence interval here did hit 1.0.

What we think is the important message here is not to spend time going through each of these but rather focus on the relative consistency of the findings. Based on these data, we do not see evidence of an increased risk of MI with naproxen.

A criticism of this analysis is that it includes multiple studies from the same database. It seems pretty intuitive that if you do multiple studies on the same database you will get similar findings. So, we did a sensitivity analysis where we took only one study from each database. The ones we excluded are here. If you look at the pooled relative risk it stays at 0.87. Remember, the original analysis was 0.86. The confidence interval gets wider, but you would expect this because there is a fewer number of observations. So, we

see no material change in the conclusions of Juni et al.

In summary, a review of the observational studies shows no increased risk of myocardial infarction with naproxen. A review of the postmarketing data also showed no signal for MI or cerebrovascular events. The published clinical trials do not provide evidence of an increased risk of MI or cerebrovascular events. And we would urge caution that the unadjudicated preliminary findings of ADAPT are inconsistent with the known data and pharmacologic properties of naproxen and need to be carefully considered in your deliberations.

In conclusion, the vast majority of data, collected over 30 years, indicates no signal for naproxen and myocardial infarction or cerebrovascular accident. We believe that naproxen, both prescription and Aleve over-the-counter remain safe and effective and that they remain important treatment options for patients.

Thank you.

# Presentation Slides

Note: Some of the slides presented may not be included below.

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**Post-Marketing Clinical Trials**

- VIGOR**
  - Randomized RA patients  $\geq 50$  yo (or  $\geq 40$  yo and receiving long-term glucocorticoid therapy) into either rofecoxib 50mg qd (N=4,047) or naproxen 500mg bid (N=4,029)
  - Overall rate of cardiovascular events reported in association with naproxen is consistent with that expected in this population
  - MI: Rofecoxib (0.4%) vs. naproxen (0.1%)
  - Ischemic cerebrovascular events: 0.2% in both

**Post-Marketing Clinical Trials**

- TARGET**
  - Randomized OA patients  $\geq 50$  yo into either lumiracoxib 400mg qd (N=9,156), naproxen 500mg bid (N=4,754) or ibuprofen 600mg bid (N=4,415)
  - Naproxen arm showed lower rates for cerebrovascular events and MI
    - Stroke: Lumiracoxib (0.34%) vs. naproxen (0.25%)
    - Ischemic stroke: Lumiracoxib (0.32%) vs. naproxen (0.23%)
    - Hemorrhagic stroke: 0.02% in both arms
    - Acute MI: Lumiracoxib (0.38%) vs. naproxen

**Post-Marketing Clinical Trials**

- TARGET (cont.)**
  - Rate of MI events was lower for naproxen than ibuprofen, using lumiracoxib as the reference point for both studies

Event*	Lumiracoxib	Ibuprofen
CV death	0.18%	0.23%
All MI	0.11%	0.16%
Stroke	0.18%	0.20%

\*Sum of percent of patients with confirmed or probable cardiovascular and cerebrovascular events

**Additional Post-Marketing Clinical Trials**

- Alzheimer's Trial**
  - Randomized mild to moderate AD patients (mean age 74 yo) into either rofecoxib 25mg qd, naproxen sodium 720mg bid, or placebo

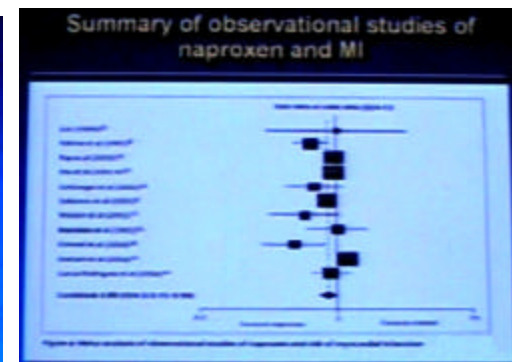
Events	Placebo (n=111)	Naproxen (N=118)	Rofecoxib (N=122)
Death	1	1	2
MI	1	0	3
Stroke/TIA	1	3	3

**Trials with Celecoxib**

- Pooled analyses of 41 celecoxib clinical trials (White et al)
- 2271 naproxen patients
  - 1 non-fatal stroke
  - 1 fatal stroke
  - 2 non-fatal MIs
- Naproxen (relative to celecoxib): 4/993 (1.01 per 100 patient years)
- Celecoxib (relative to NSAIDs): 5/64,949 (1.13 per 100 patient years)
- Placebo (relative to celecoxib): 3/300 (1.5 per 100 patient years)
- There is no evidence of an increased risk of MI or stroke compared to either celecoxib or placebo

**Observational Studies**

- Case control studies and retrospective cohort studies can be performed in a shorter period of time
- Opportunity to detect/evaluate relatively infrequent events
- Reflect "real world" use of the drug
  - More heterogeneous populations
  - Concomitant medications, concurrent illnesses
- Value of observational studies increases when these studies are done in multiple popul



## Sensitivity Analysis of Observational Studies

- Meta-analysis included multiple studies from same databases
- Performed analysis including only one study from GPRD and one study from Tennessee Medicaid
  - Excluded Jick, Watson, Schlienger studies with GPRD and Ray (Lancet 2002, 359:118-23) study with Tennessee Medicaid
- Resulting pooled RR = 0.87 (0.72-1.03)
- No material change in conclusions of Juni et al.

## Summary

- A review of the observational studies shows no increased risk of MI with naproxen
- A review of the postmarketing surveillance data shows no signal for MI or cerebrovascular events
- The published clinical trials do not provide evidence of an increased risk of MI or cerebrovascular events
- Unadjudicated preliminary findings of ADAPT are inconsistent with the known data and pharmacologic properties of naproxen

## Conclusions

- The vast majority of data collected for over 30 years indicates no signal for naproxen and myocardial infarction or cerebrovascular accidents.
- Naproxen Rx and Aleve OTC remain safe and effective
- Naproxen remains an important treatment option for patients