Pacira v. FDA: Summary of Declaration by Lee-Jen Wei, PhD Concluding that the Pivotal Hemorrhoidectomy Study for EXPAREL® Demonstrated a Treatment Effect for Up To 72 Hours After Surgery

Lee-Jen Wei, PhD
Declarant

- Professor of Biostatistics at the Harvard T.H. Chan School of Public Health
- Developed numerous novel statistical methods for designing, monitoring, and analyzing clinical studies, survival analyses, and meta-analyses
- Served on numerous Data and Safety Monitoring Boards ("DSMBs") for clinical trials, with extensive experience in the evaluation of efficacy and adverse event data from clinical studies
- Active involvement since 2004 in clinical research of pain medications, developing and publishing a number of new quantitative methods for analyzing data readily applicable to analgesic drug development

Background on Efficacy Measures in the Pivotal Soft-Tissue Trial for EXPAREL

- As part of the basis for approval, Pacira conducted a placebo-controlled, soft-tissue pivotal trial to demonstrate the safety and efficacy of EXPAREL in patients undergoing excisional hemorrhoidectomy

- The primary endpoint, **reduction in cumulative pain through 72 hours**, was met with statistical significance (*P*<0.0001)
  - Defined as the area under the curve of the numeric rating scale scores at rest through 72 hours (expressed as NRS-R $AUC_{0\text{-}72}$)
  - This is a common primary endpoint when studying analgesic medications to demonstrate a drug's magnitude and duration of effect

- Multiple secondary endpoints were also evaluated (e.g., median time to first rescue, use of rescue through 72 hours, percent of pain-free subjects)

The Efficacy of EXPAREL for up to 72 Hours is Substantiated Based on 3 Principles

1. The pre-specified primary endpoint was met with very high statistical significance
2. FDA's post-hoc analyses are not appropriate for use in undermining the primary outcome from the study
3. The effectiveness of EXPAREL for up to 72 hours after surgery is well-supported by other analyses from the study

1. The Pre-Specified Primary Endpoint was Met With Very High Statistical Significance

Cumulative Pain Scores for EXPAREL vs Placebo Through 72 Hours

Time from 0 to:	Statistics	EXPAREL (n=94)	Placebo (n=93)
72 hours	Mean	141.6	202.3
	SD	100.58	104.14
	Median	137.0	186.0
	Minimum, Maximum	0, 491	22, 529
	Adjusted Mean (SE)	141.751 (10.6800)	202.484 (10.7343)
	Difference (SE)	-60.733 (15.0532)	
	95% CI for Difference	(-90.434, -31.033)	
	P-value	<0.0001	

- The observed difference between EXPAREL vs placebo is -60.733 (-90.434, -31.033)
- Subjects treated with EXPAREL had cumulative pain scores as much as 90 points lower (where lower scores reflect less pain) than subjects in the placebo arm
- Even in the "worst-case scenario" in this study, EXPAREL patients had an approximate 31-point reduction in cumulative pain scores relative to the placebo over the entire 72-hour follow-up period

1. The Pre-Specified Primary Endpoint Was Met With Very High Statistical Significance

- In this study, the primary endpoint was met with a p-value of <0.0001
  - In clinical studies, a p-value of <0.05 is generally considered to be statistically significant
  - A p-value of <0.0001 is a highly statistically significant result, indicating that the observed difference was "real" and not simply a chance finding
  - The lower the p-value, the less likely it is that the observed difference is the result of chance

"Based on my extensive review and analysis of documents related to and data from [the hemorrhoidectomy study], I conclude that EXPAREL clearly demonstrated a reduction in pain intensity for up to 72 hours after surgery as compared to placebo" -- Lee-Jen Wei, PhD

2. FDA's Post-Hoc Analyses are not Appropriate for Use in Undermining the Primary Outcome From the Study

- During the NDA review process for EXPAREL, the FDA decided to conduct a post-hoc analysis to evaluate the mean pain intensity scores of subjects in each study arm at 10 time points during the study (i.e., from 1 hour to 72 hours following surgery)

- This post hoc analysis was not taken into account when the study protocol was developed

2. FDA's Post-Hoc Analyses are not Appropriate for Use in Undermining the Primary Outcome From the Study

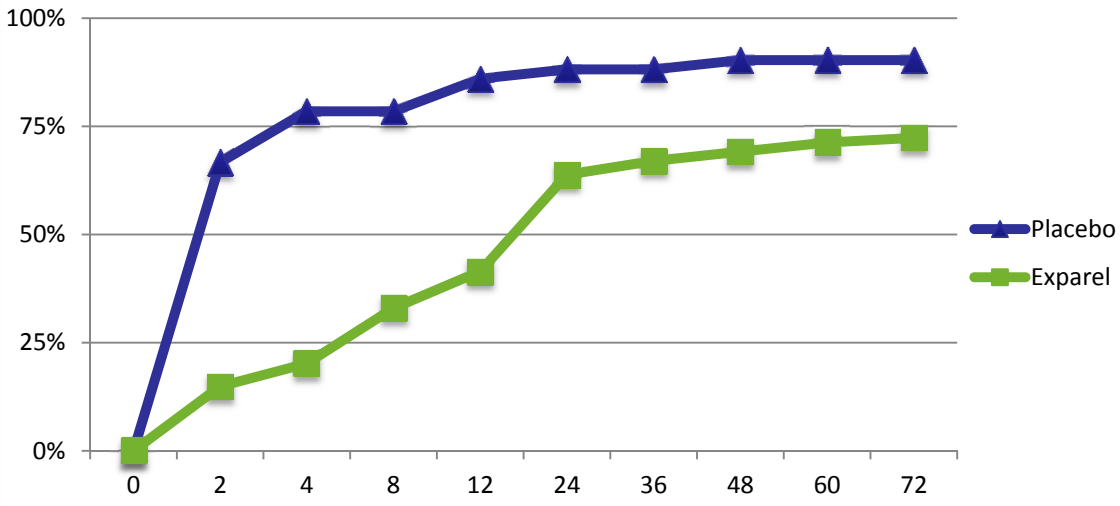
- The study was designed to detect cumulative pain scores through 72 hours (the FDA-agreed upon, pre-specified primary endpoint), and the size of the study was selected on that basis

- A much larger sample size would have been required for the study to have been statistically powerful enough to detect differences between the groups at each of those 10 different time points ***(~650 patients in each arm for a total of 1300 patients)***

"Post-hoc analyses…are exploratory. Using one to contradict the results of a pre-specified, FDA-accepted, primary endpoint of cumulative pain scores at 72 hours is simply not an appropriate statistical approach" -- Lee-Jen Wei, PhD

3. The Effectiveness of EXPAREL for up to 72 Hours After Surgery is Well-Supported By Other Analyses From the Study

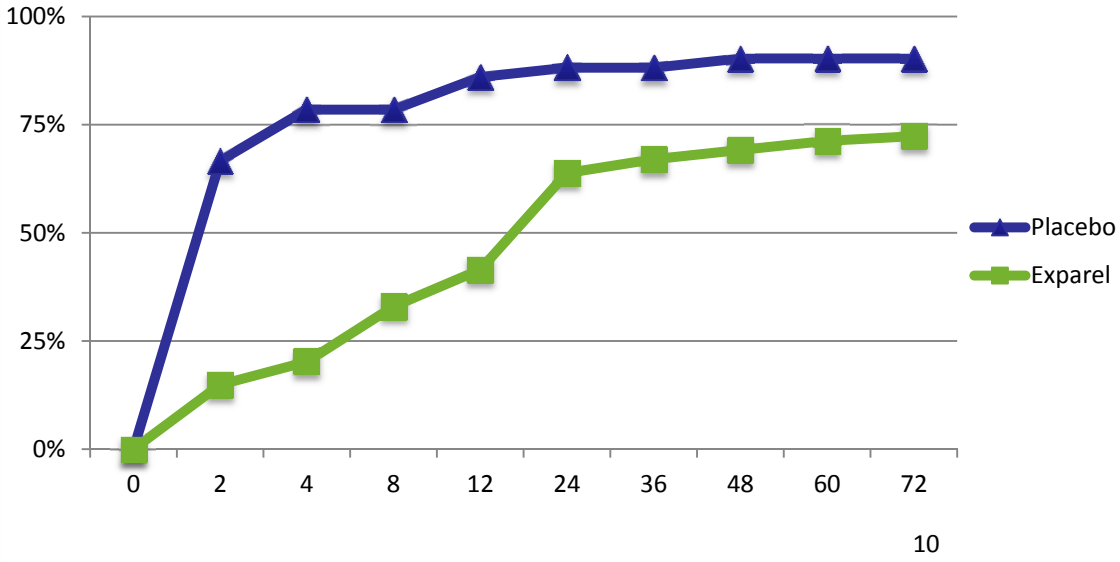
- One of the most informative ways to assess durability of a treatment effect is a "time-to-event" analysis, which measures the elapsed time until a meaningful event occurs
- First use of rescue medication is a meaningful "event" to analyze because it approximates the length of time during which a patient's pain is controlled



"The curve for the placebo arm is always above the curve for the EXPAREL arm for the full duration of the study. This means that EXPAREL is uniformly better than the placebo over the entire 72 hours with respect to the time to first use of rescue medication"
-- Lee-Jen Wei, PhD

3. The Effectiveness of EXPAREL for up to 72 Hours After Surgery is Well-Supported By Other Analyses From the Study

- At 72 hours after surgery, there remains a sizeable difference between two curves (72% EXPAREL vs. 90% placebo)
  - Put differently, only 10% of placebo patients required no rescue pain medication for the entire 72-hour period after surgery
  - Nearly *three times* as many EXPAREL patients (28%) required no rescue medication for that same period. This difference was highly statistically significant (*P*=0.0007)



"The fact that so many EXPAREL patients required no rescue pain medication for 72 hours after surgery further indicates that EXPAREL exerts a substantial analgesic effect for up to 72 hours"
-- Lee-Jen Wei, PhD

3. The Effectiveness of EXPAREL for up to 72 Hours After Surgery is Well-Supported By Other Analyses From the Study

- FDA's own analysis of "pain free" patients, when evaluated with appropriate statistical methods, shows that EXPAREL is effective for up to 72 hours after surgery
- This post-hoc measurement analyzed the percentage of “pain-free” subjects at 10 time points
  - “Pain-free” was defined as those having a pain score of <2 who had not taken rescue medication

3. The Effectiveness of EXPAREL for up to 72 Hours After Surgery is Well-Supported By Other Analyses From the Study

Percentage of Subjects That Were Pain Free

Treatment	Percentage of patients pain free and did not use rescue medication prior to that time point									
	1	2	4	8	12	24	36	48	60	72 hrs
Placebo	9	4	2	2	3	6	8	8	6	5
EXPAREL	48	45	46	39	30	23	24	20	17	16
p-value	*	*	*	*	*	0.001	0.002	0.01	0.02	0.02

- Over the entire 72-hour follow-up period, the percentage of subjects who are event-free is always higher for EXPAREL than for placebo
- Even at the 72-hour mark, the likelihood of being pain-free is tripled when using EXPAREL compared to placebo (5% for placebo vs 16% for EXPAREL)

3. The Effectiveness of EXPAREL for up to 72 Hours After Surgery is Well-Supported By Other Analyses From the Study

- In this analysis, all p-values are less than 0.05 (the conventional limit for determining statistical significance) for all time points
- The FDA statisticians in fact initially concluded on the basis of this analysis that "there was a significant treatment effect observed [for EXPAREL] out to 72 hours post-dose. . . ."

"That conclusion is correct. There should be no dispute about the efficacy of EXPAREL over the entire 72-hour follow-up period after surgery"
-- Lee-Jen Wei, PhD

3. The Effectiveness of EXPAREL for up to 72 Hours After Surgery is Well-Supported By Other Analyses From the Study

- FDA statisticians subsequently backed away from this conclusion, claiming due to the multiple time points captured, the method of controlling for error was not sufficiently rigorous
- Applying a more conservative method, which used an error rate of 0.005 rather than the conventional rate of 0.05, the statistical review team determined that statistical significance was demonstrated only to 36 hours after surgery

"A more standard and conventional statistical procedure to analyze [the data] is to use the Cochran-Mantel-Haenszel method …This method leads to a p-value of *P*<0.0002, indicating that such differences between the EXPAREL and placebo treatment arms are extremely unlikely to occur unless there was a true difference between the therapies"
-- Lee-Jen Wei, PhD

Conclusion

"In sum, my review of the [hemorrhoidectomy] data leaves me with no doubt that EXPAREL demonstrated a sustained treatment effect for up to 72 hours after surgery….FDA's post-hoc analyses are inappropriate to discredit these extremely impressive results on the primary endpoint. Furthermore, multiple other indicators provide additional support for the conclusion that EXPAREL's ability to control pain is long-lasting…FDA's allegations in the Warning Letter related to Pacira's 'misleading' promotion of the 72-hour pain control are not justifiable"

-- Lee-Jen Wei, PhD