EXPAREL™, an investigational extended-release liposome injection of bupivacaine, delays time to first opioid and reduces opioid requirements for three days after hemorrhoidectomy

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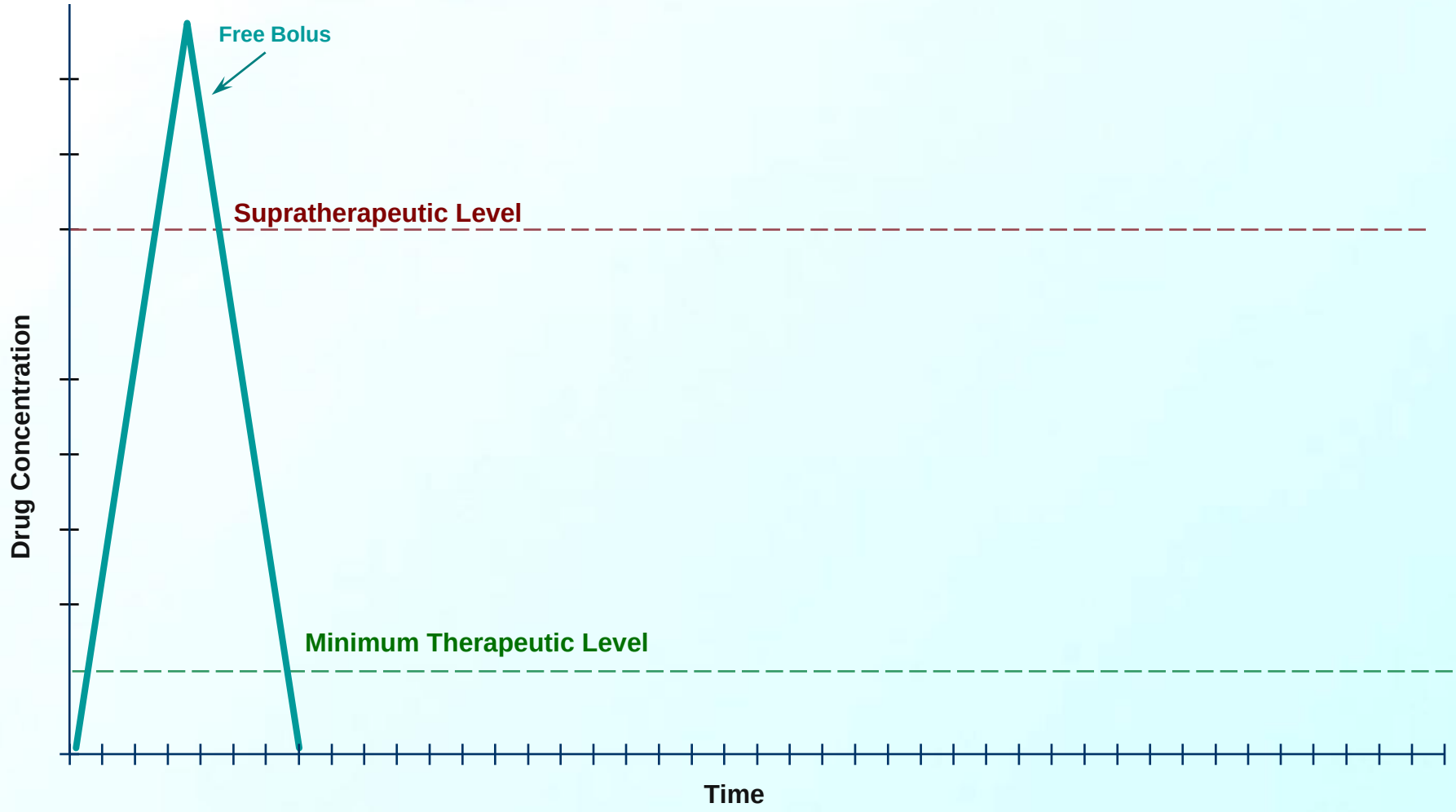
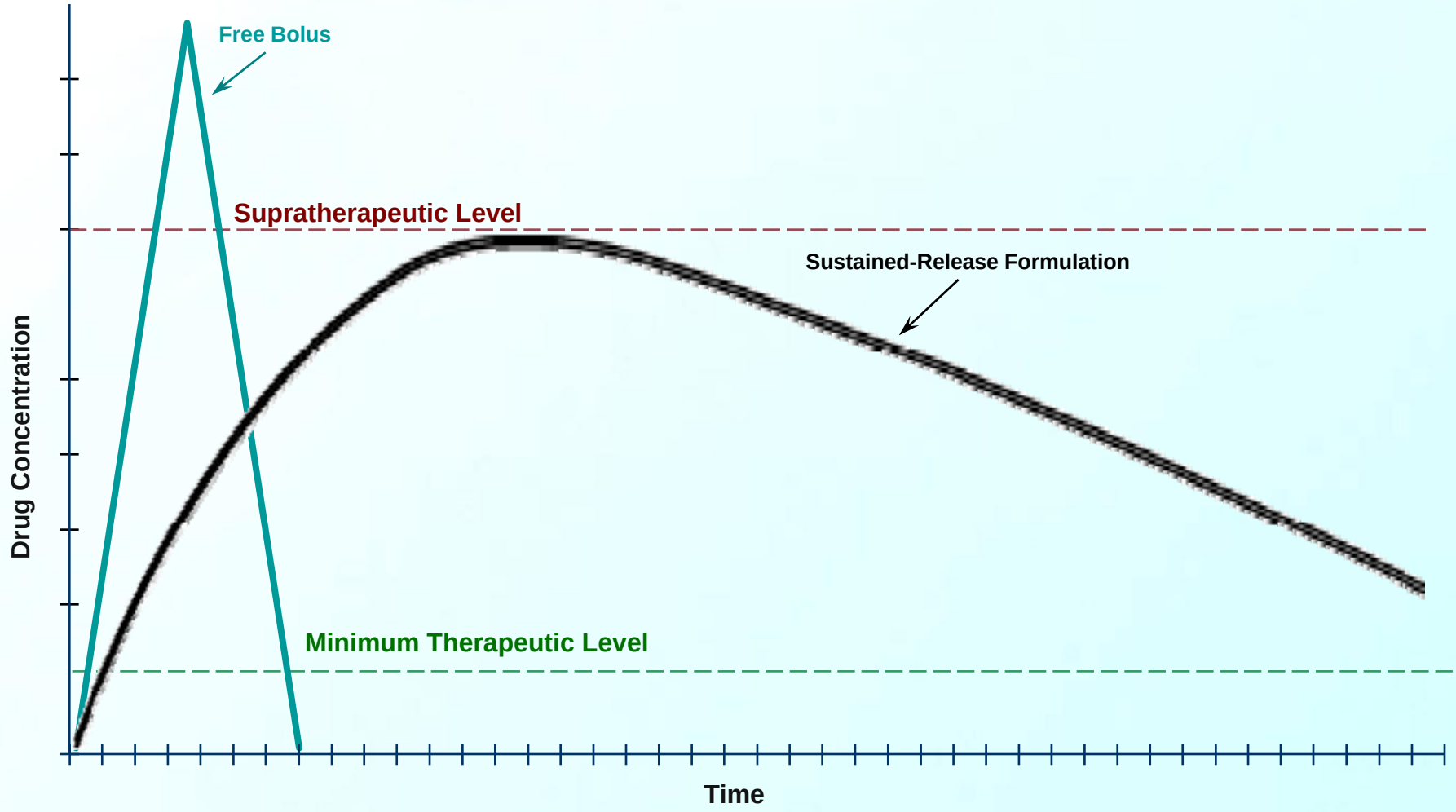
**Employed by Pacira Pharmaceuticals, Inc.*

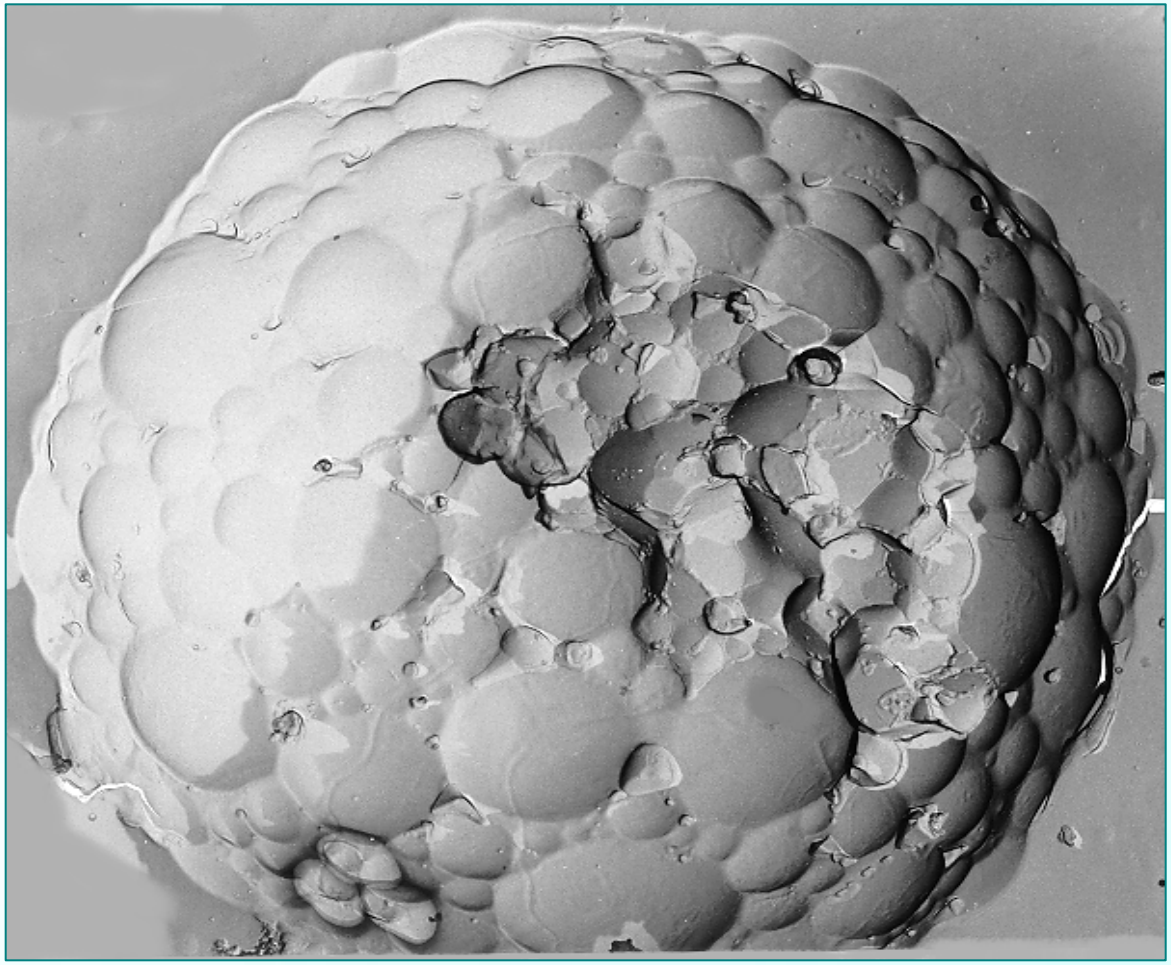
Injectable Drug: Release Profile

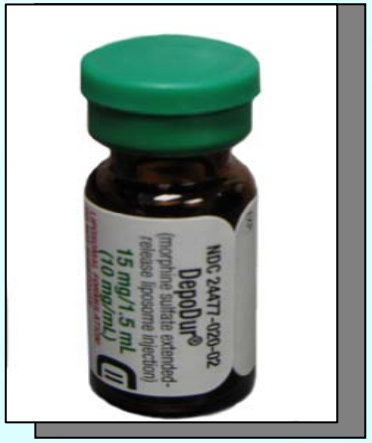


Injectable Drug: Sustained Release Profile



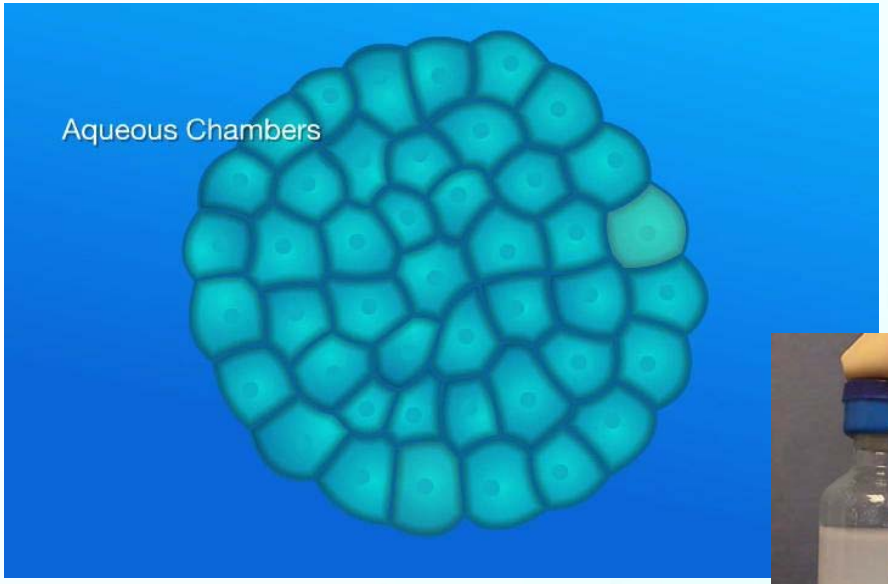
DepoFoam®
Multivesicular Liposomes

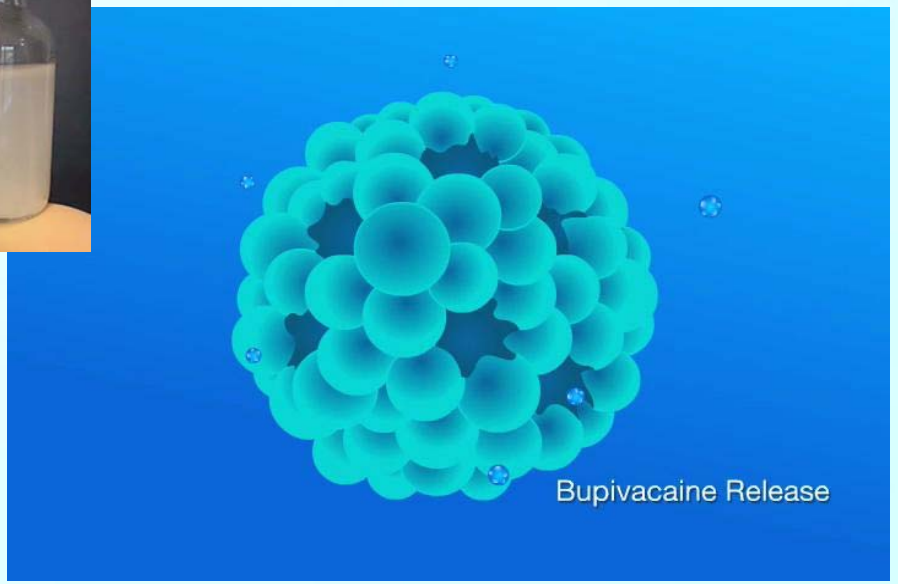




Scanning Electron Microscopy image

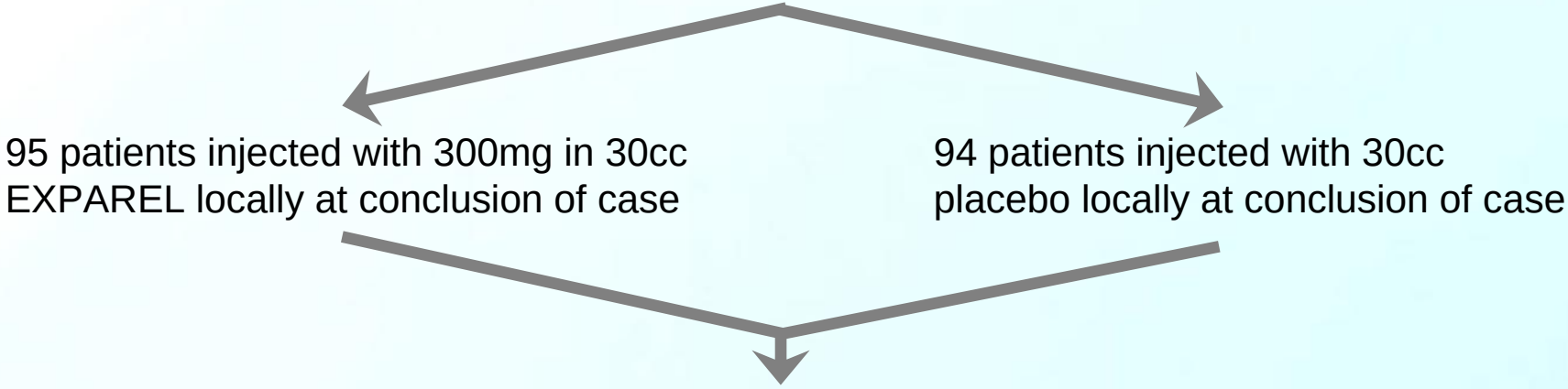
EXPAREL
DepoFoam Release of bupivacaine





Trial Design

189 patients having Milligan-Morgan hemorrhoidectomy were treated at 12 centers in Poland, Georgia, and Serbia; 25% patients also in nested pk study



Rescue Morphine 10mg IM q4 prn; NRS (at rest) at 0, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72; BPI at 0, 24, 72; Satisfaction at 24, 72; Discharge after 72hrs

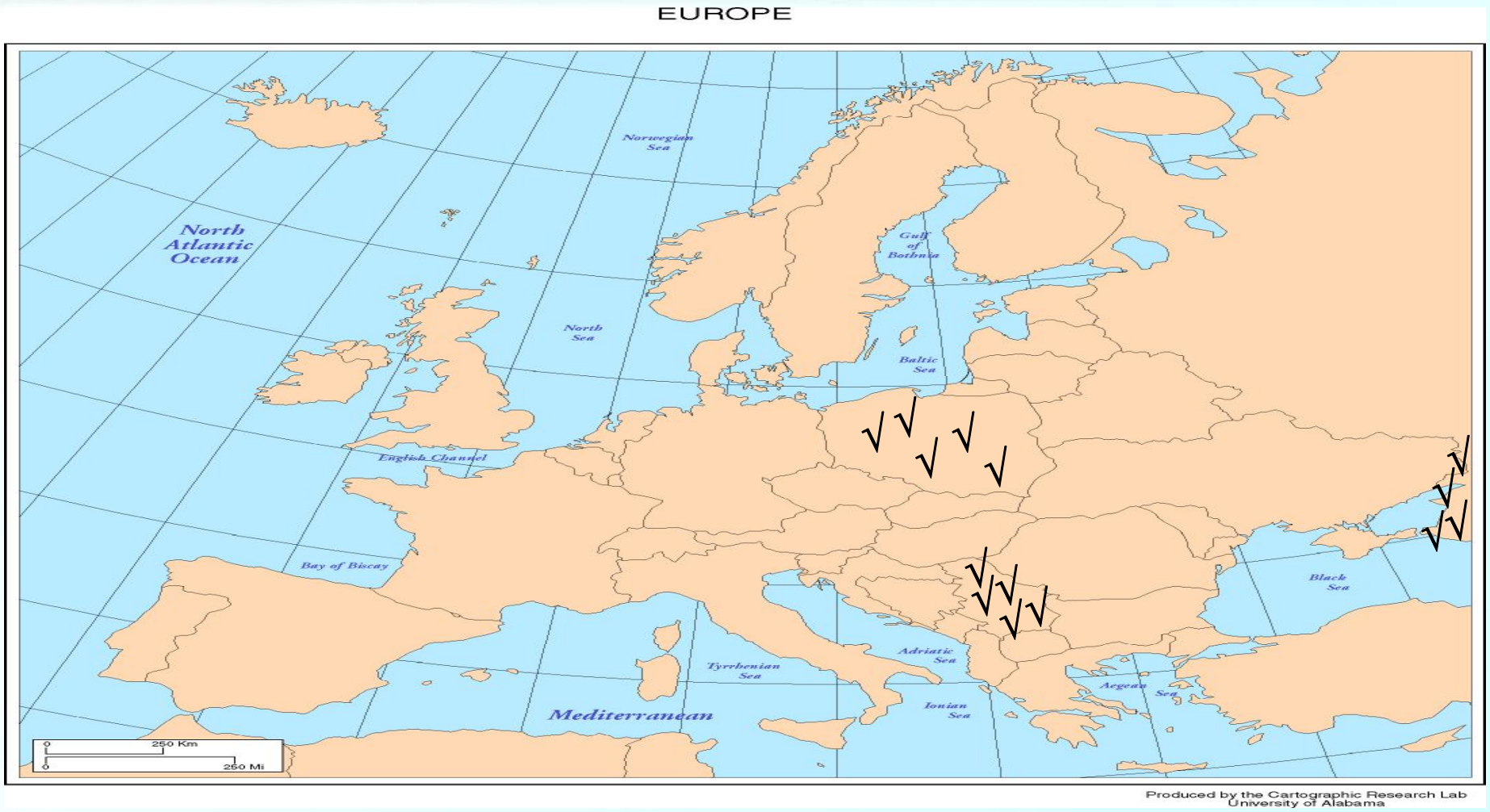
↓

Labs, Visit at day 8

↓

Wound check, BPI, End of study at day 30

Sites

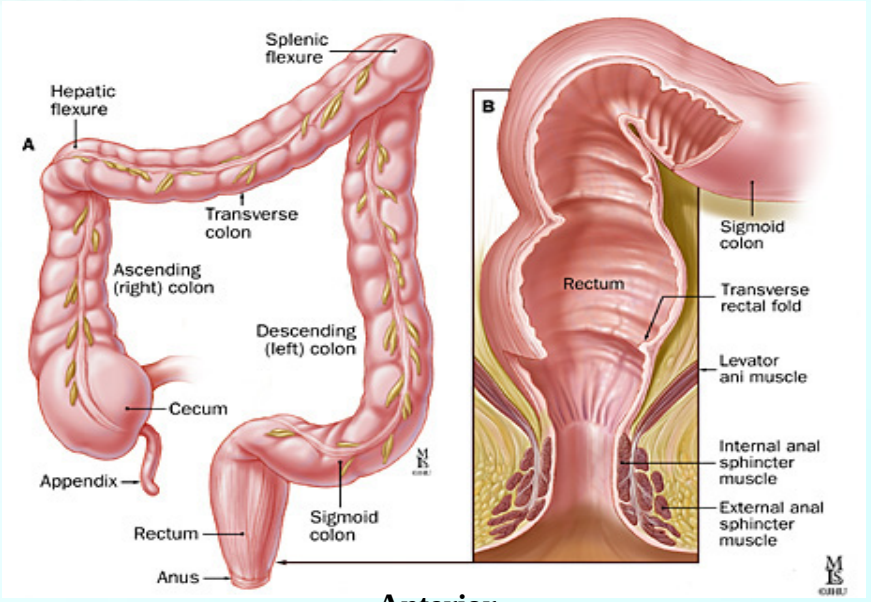

EUROPE
Norwegian Sea
North Atlantic Ocean
Gulf of Bothnia
North Sea
Baltic Sea
English Channel
Bay of Biscay
Black Sea
Adriatic Sea
Tyrrhenian Sea
Aegean Sea
Ionian Sea
Mediterranean
0 250 Km
0 250 Mi
Produced by the Cartographic Research Lab
University of Alabama

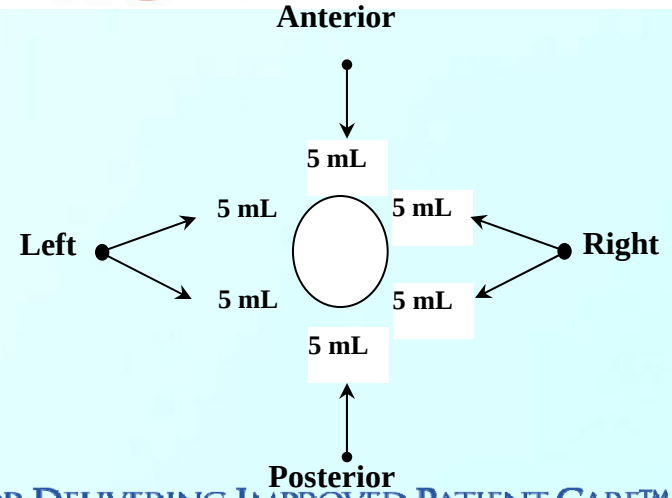
Demographics: Well Matched

	EXPAREL 300mg (n=95)	Placebo (n=94)
Age (Mean)	48.0y	48.7y
Male	66.3%	71.3%
Female	33.7%	28.7%
Race		
American Indian or Alaska Native	0%	0%
Asian	0%	0%
Black or African American	0%	0%
White or Caucasian	100%	100%
Ethnicity		
Hispanic or Latino	0%	0%
Not Hispanic or Latino	100%	100%
ASA		
1	60.0%	52.1%
2	37.9%	44.7%
Weight (Mean)	76kg	79kg
Height (Mean)	172cm	174cm
BMI (Mean)	25.5kg/m2	25.9kg/m2

Protocol

- General Anesthesia
- Milligan-Morgan technique
  - Instruments may vary
- 2 or 3 column
- Excisional
- Internal or Internal/External
- Cumulative Incision >3cm
- No Fissurectomy
- Double-Blinded



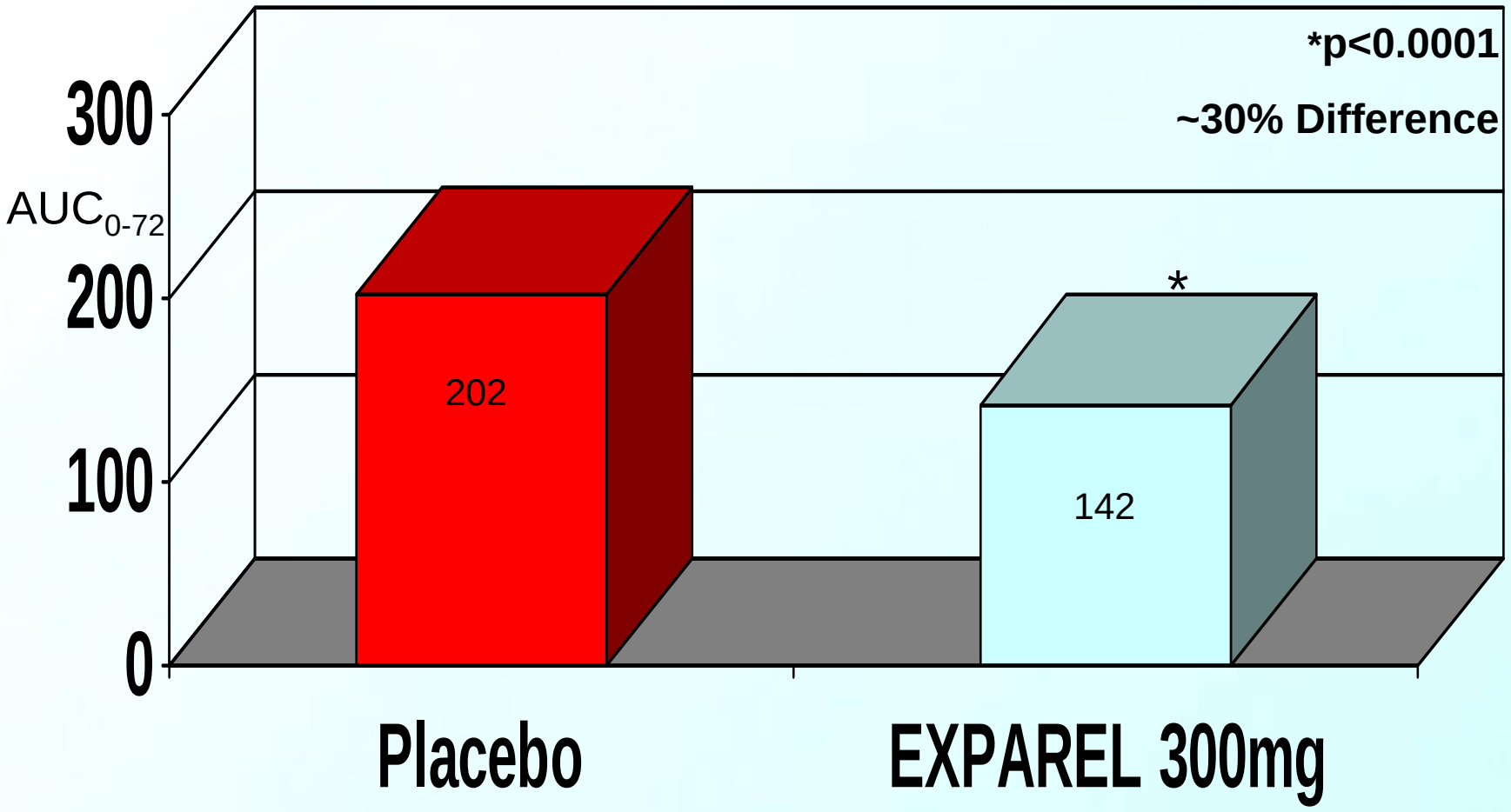


Primary Endpoint

- The primary endpoint is the area under the curve ($AUC_{0\text{-}72}$) of the numeric rating scale at rest (NRS-R) pain intensity scores through 72 hours for subjects receiving EXPAREL vs. placebo

- To assess: "On a scale of 0-10, where 0 = no pain and 10 = worst possible pain, how much pain are you having right now?"

Results:
Primary Endpoint - AUC_{0-72} of NRS

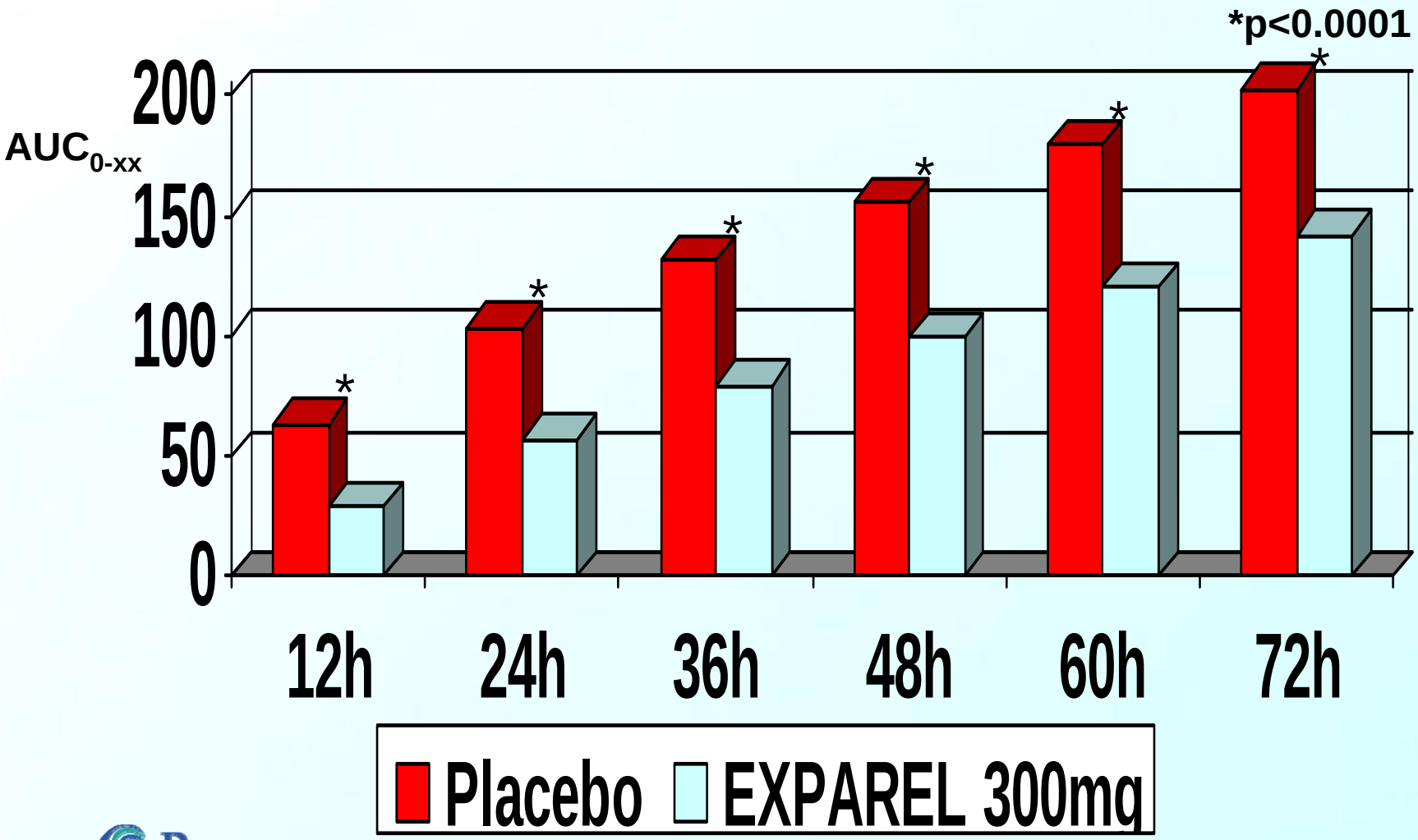


Results:
Summary

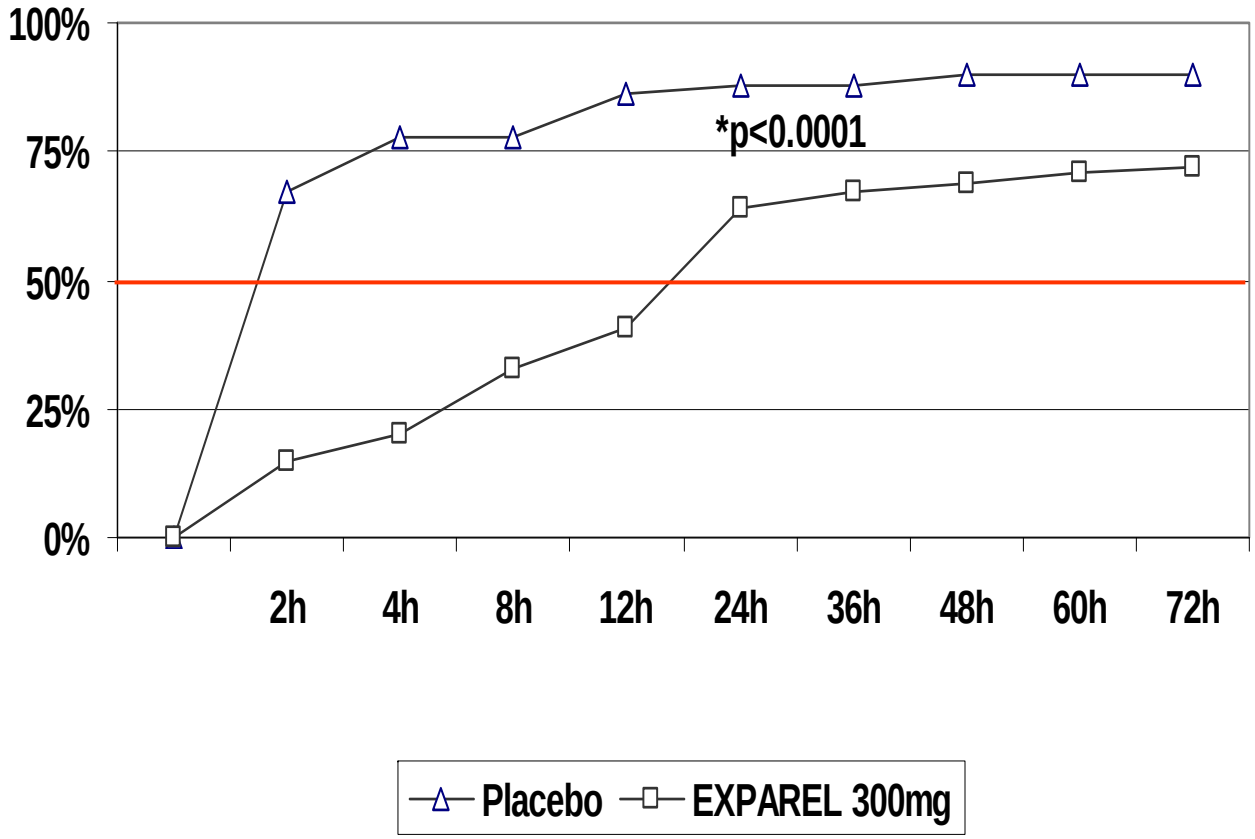
- The study met its primary endpoint with a statistically significant reduction in $AUC_{0\text{-}72}$ in the subjects receiving EXPAREL compared to placebo ($p<0.0001$)

- The difference was statistically significant at $p<0.0001$ at every tested timepoint from 0 hours to 72 hours (12, 24, 36, 48, 60, and 72 hours)

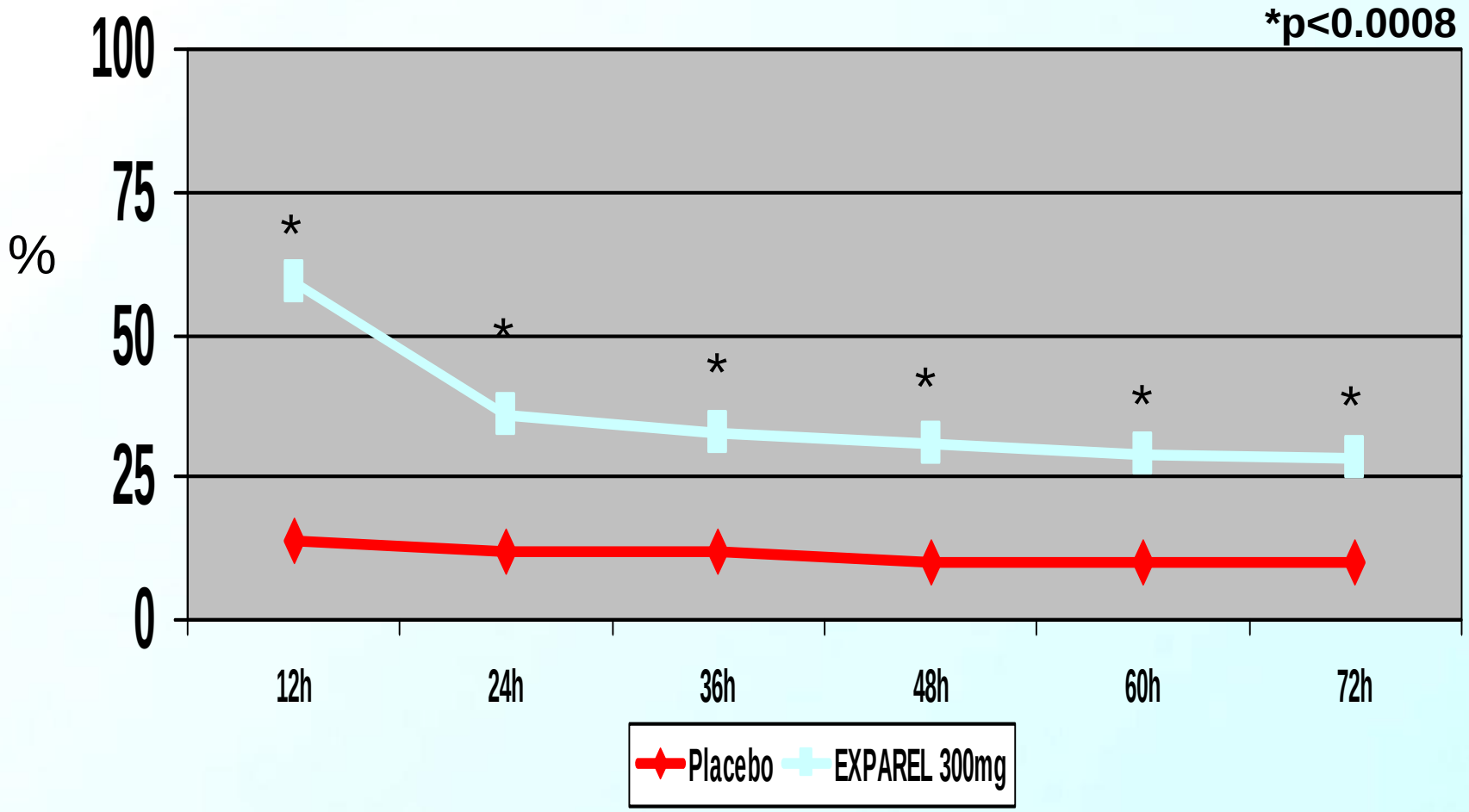
Results:
AUC Through Different Timepoints



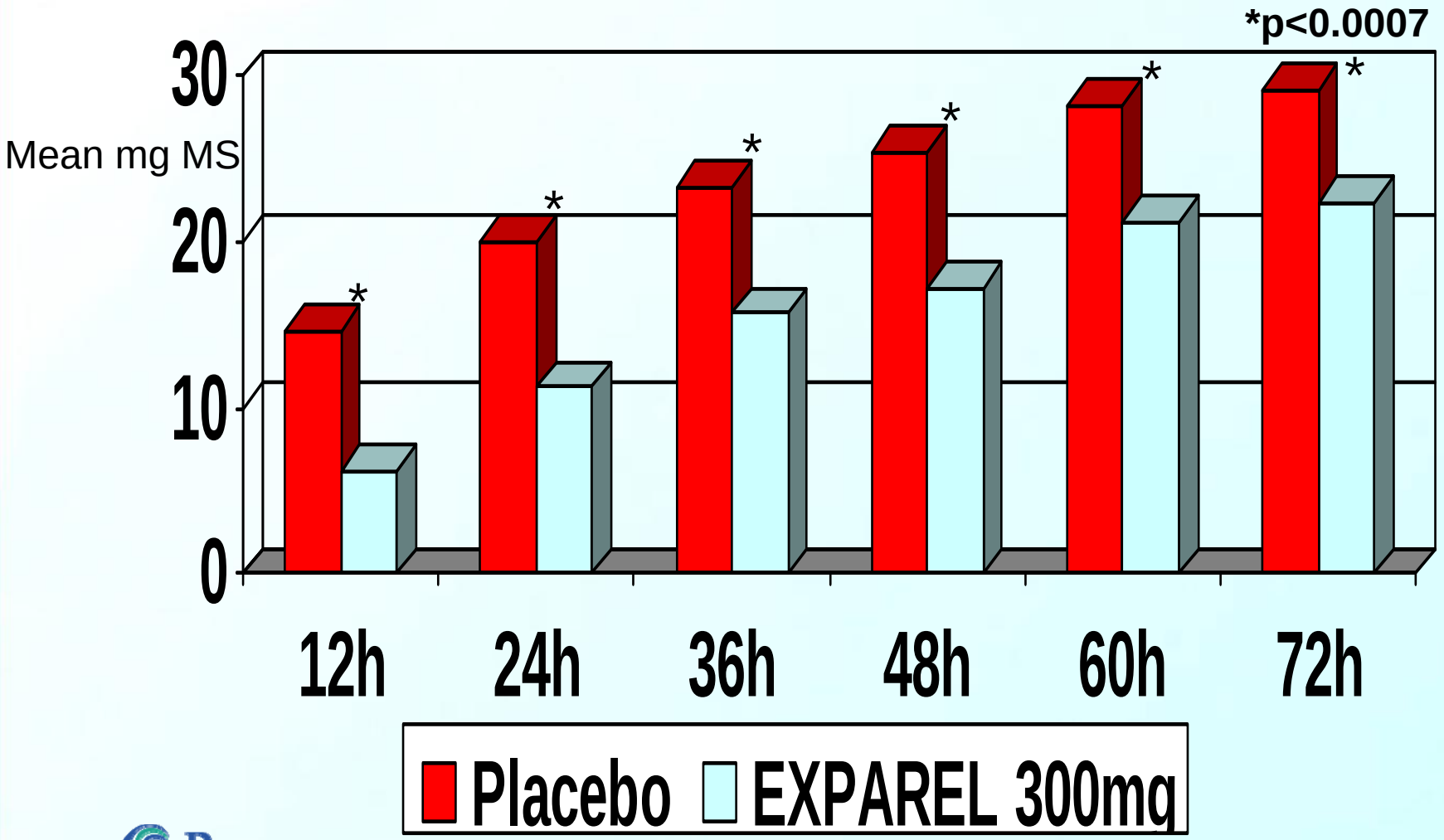
Median Time to First Opioid: 1h 10m vs 14hr 20m



Patients Avoiding Opioids (%): 14 vs 59 at 12h; 10 vs 28 at 72h



Total Opioid Consumption (mg): 15 vs 6 at 12h; 29 vs 22 at 72h



Safety:
Equivalent to Placebo

Patients who experienced:	Placebo	EXPAREL
At Least One TEAE	18%	17%
At Least One Related TEAE	0%	1%
Gastrointestinal AE (e.g., PONV)	14%	8%
SAE	1%	0%
Discontinuation Due to AE	0%	0%
Death	0%	0%

Benefits of a Non Opioid Platform

- ***Decreased opioid-related side effects***
  - Nausea, vomiting, constipation, urinary retention, pruritis, somnolence, respiratory depression
- ***Decreased hospital resource consumption***
  - Time from PACU to floor
  - Nursing time to monitor opioid-related side effects and PCA
- ***Faster ambulation***
  - Less need for patients to be tethered to IV pole
- ***Faster hospital discharge***
  - Increased patient satisfaction
- ***Effective pain control for patients who do not tolerate opioids***
  - Elderly, obese, sleep apnea, chronic opioid users

Conclusions

- ***EXPAREL provided pain control out to 72 hours***
- ***Reduced opioid consumption***
  - Patients needed fewer opioids
  - More patients remained opioid free
  - Patients stayed off opioids until later in hospitalization
- ***Safety equivalent to placebo***

EXPAREL has the potential to offer clinically meaningful analgesia and decrease the need for opioid analgesic drugs

Hvala
(Thank You)