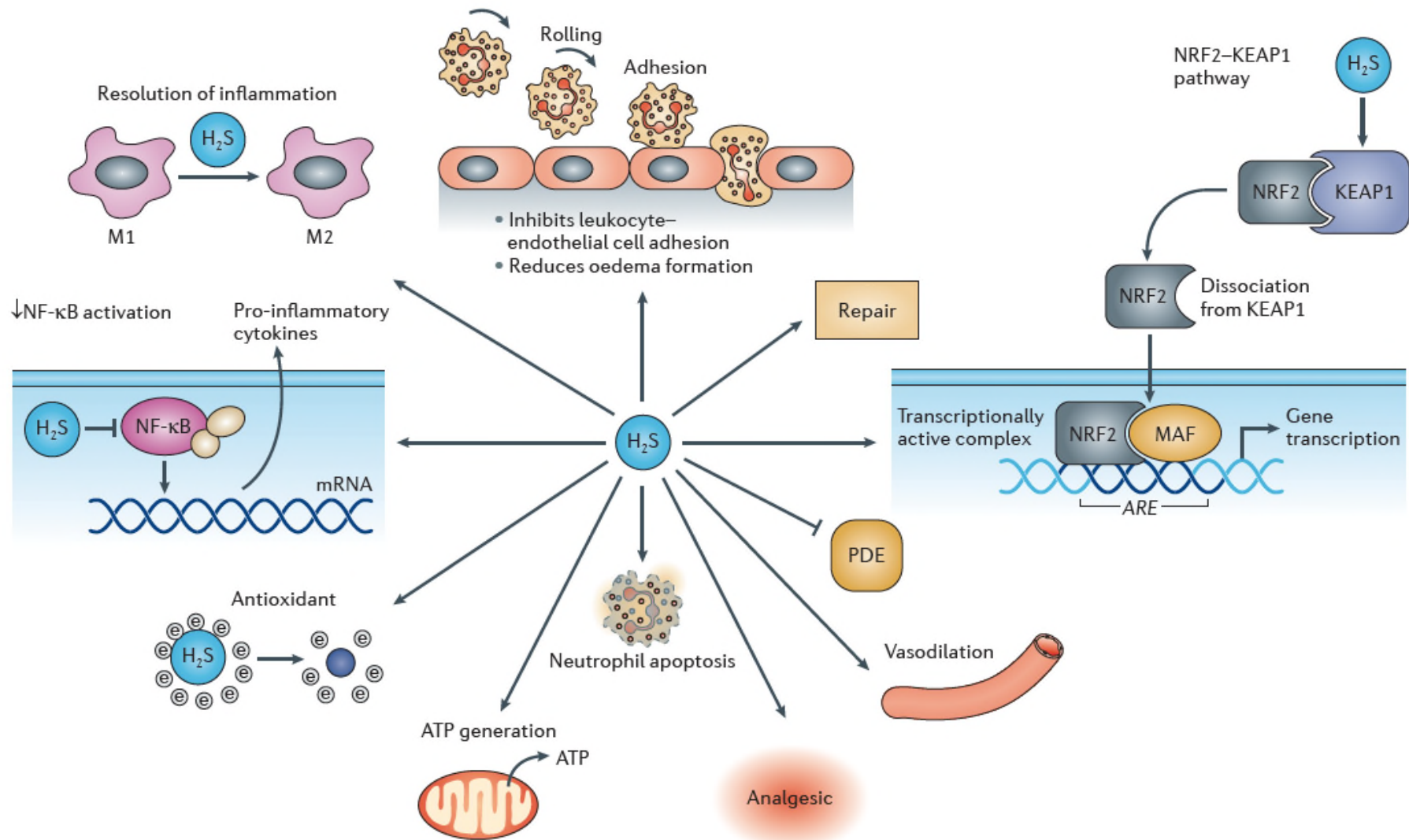


Development of GI-Safe NSAIDs

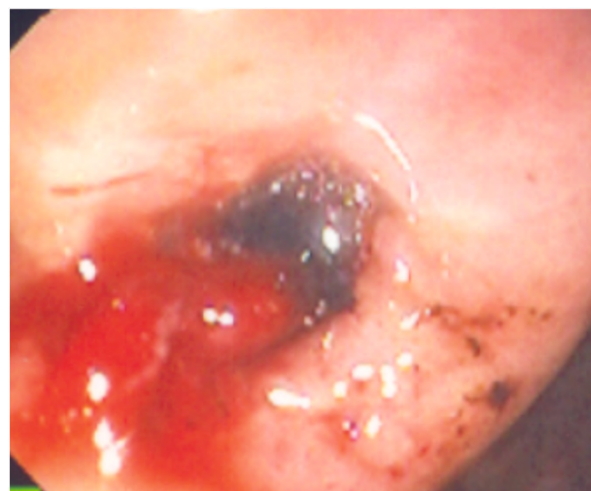


Hydrogen Sulfide is an Anti-Inflammatory, Pro-Healing Molecule



Wallace & Wang, 2015
Nature Reviews Drug Discovery

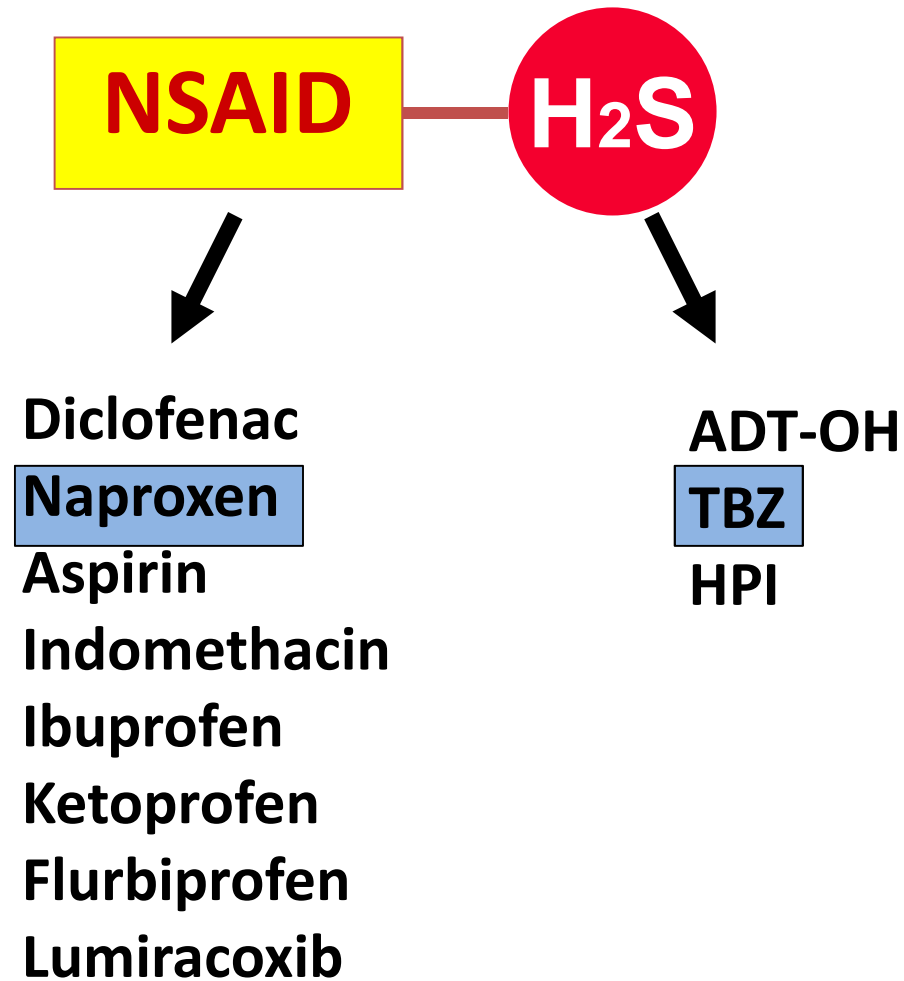
H₂S-Releasing Anti-Inflammatory Drugs



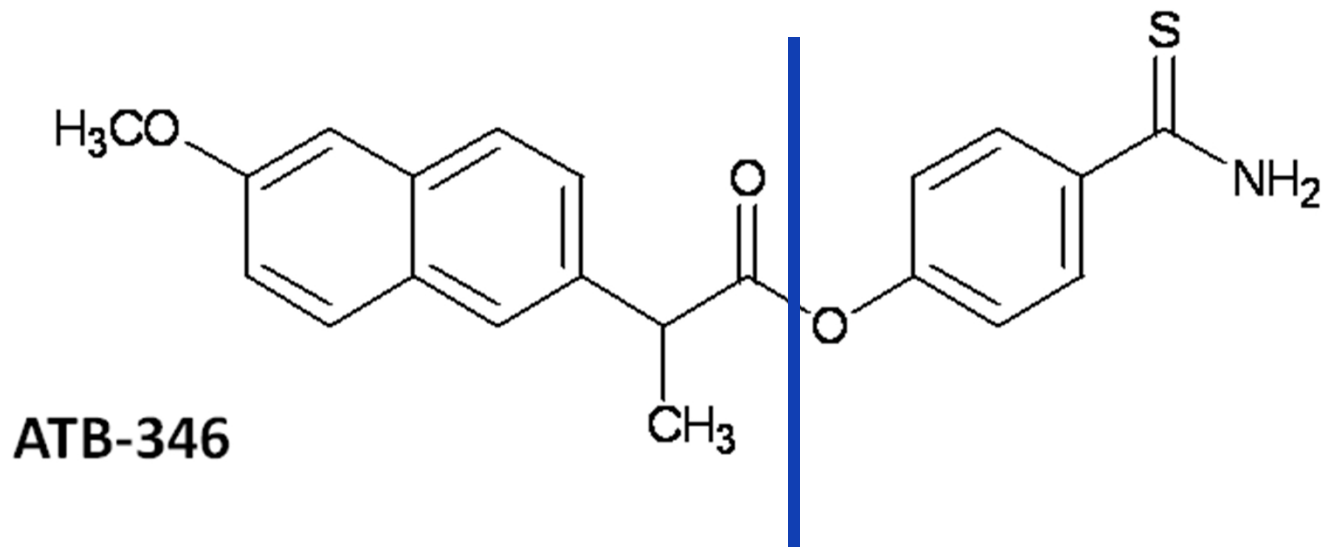
- 30 million people take NSAIDs on a daily basis
- 15.3 deaths per 100,000 users

Unmet Medical Need

H₂S-Releasing Anti-Inflammatory Drugs

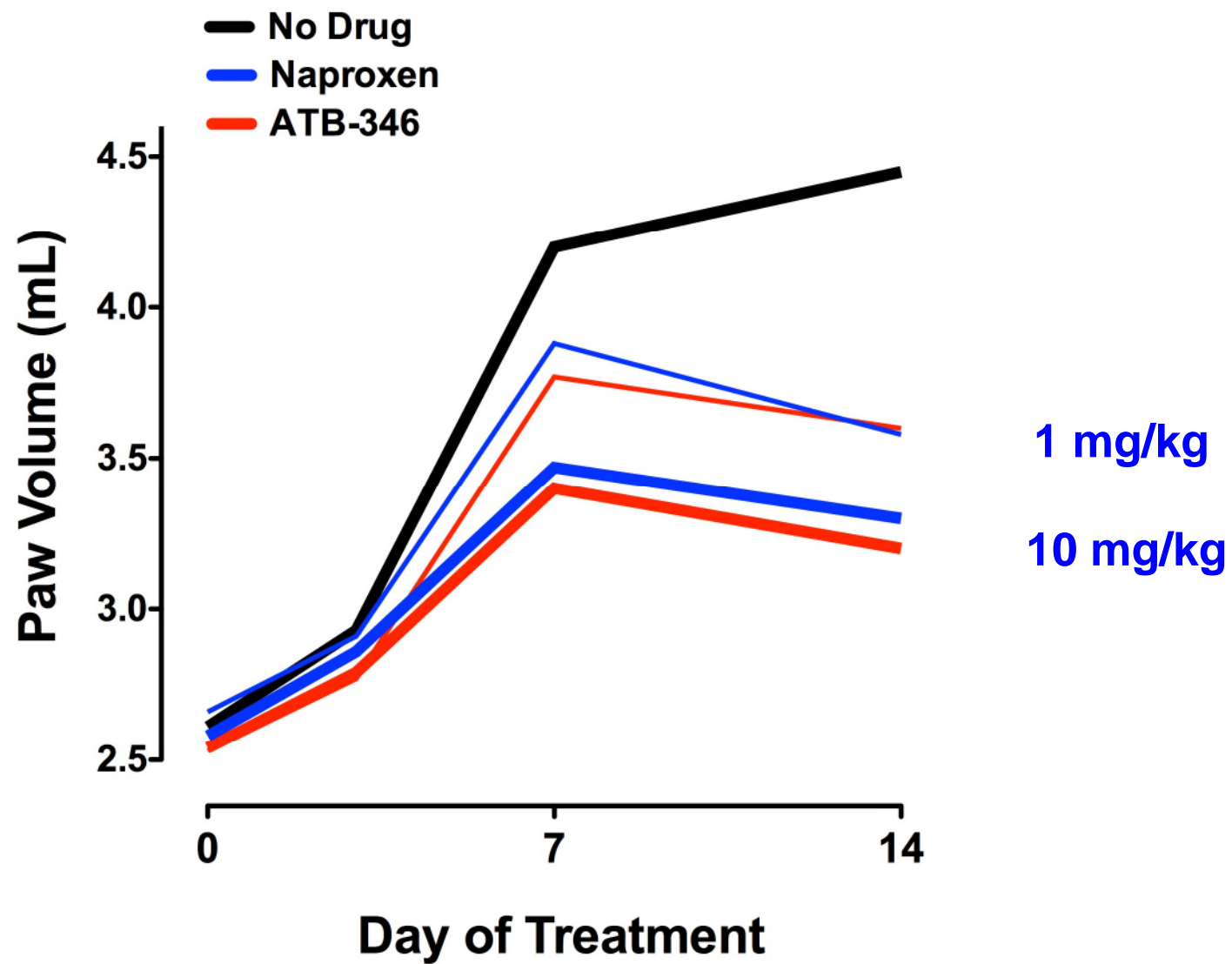


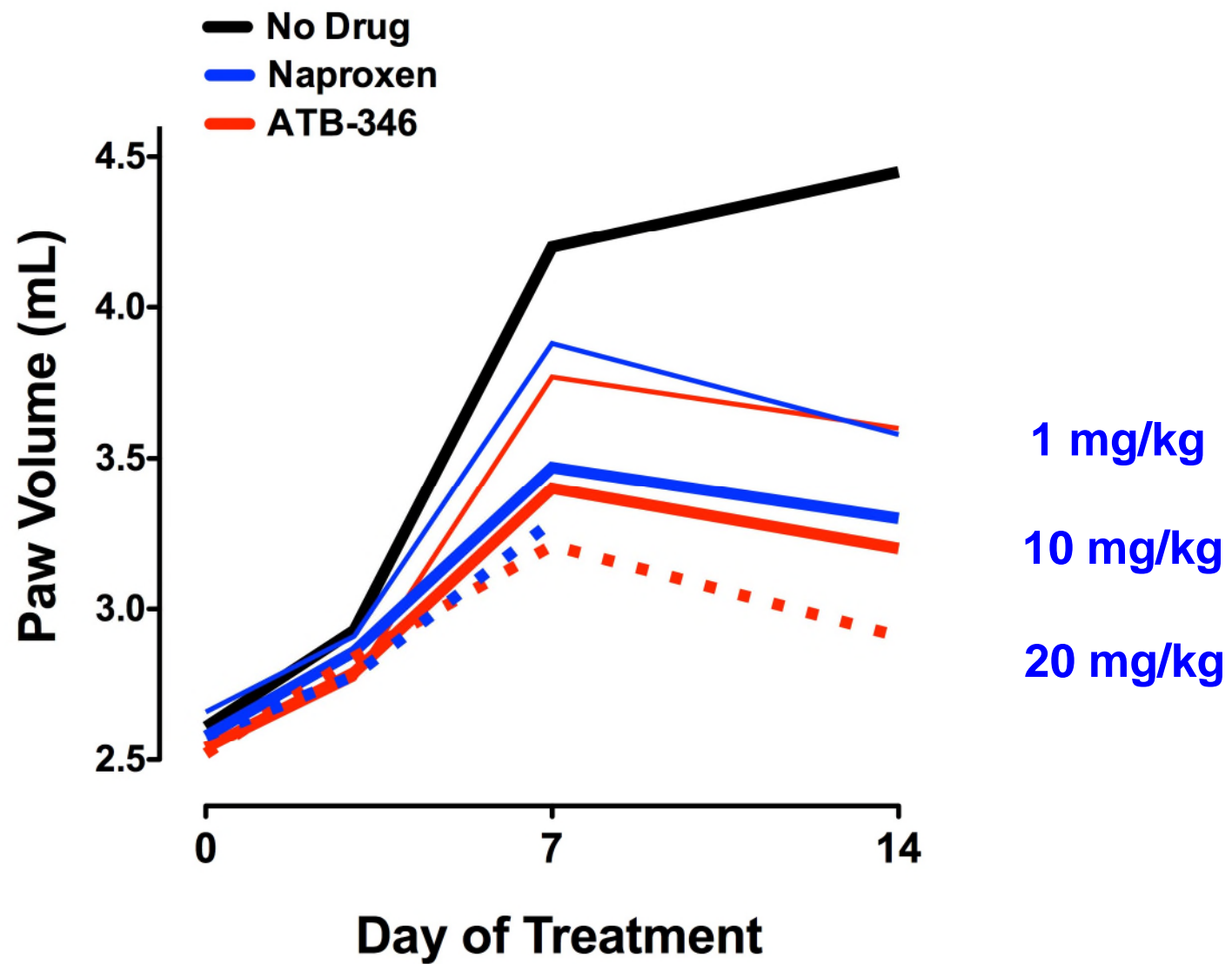
H₂S-Releasing Anti-Inflammatory Drugs



Effectiveness of ATB-346 compared to naproxen in adjuvant-arthritic rats

**Study performed in a blind manner
by independent contractor in France**

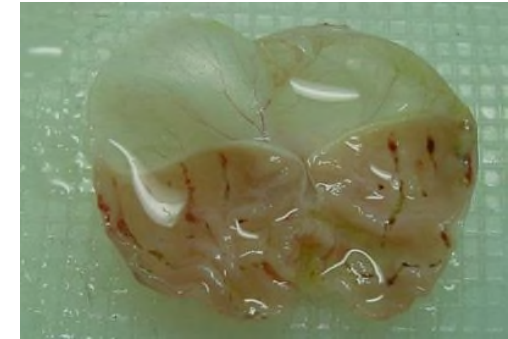
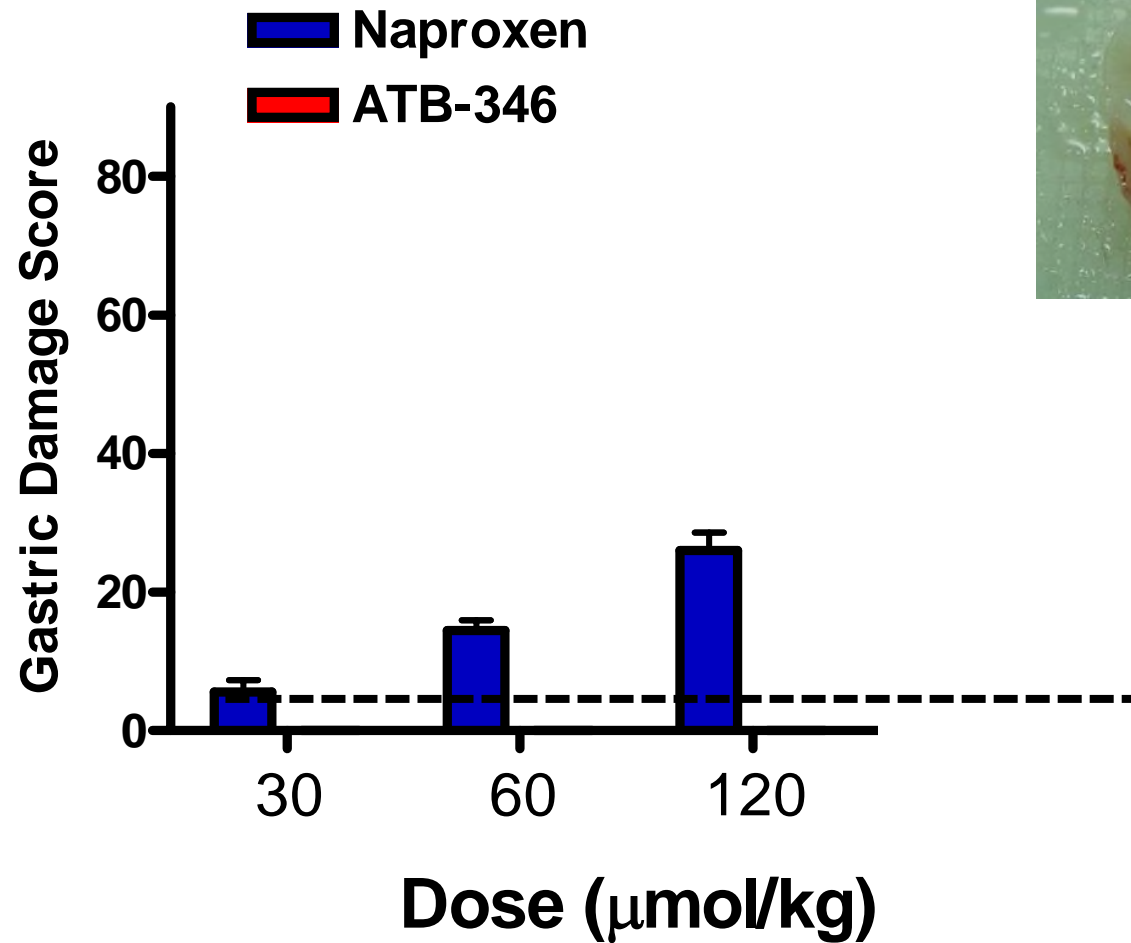


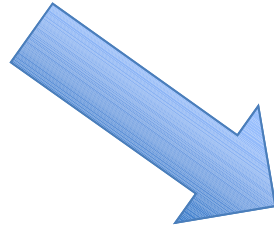


What About GI Safety?



ATB-346 Causes Negligible Gastric Damage (even at a very high dose)





Human Data on ATB-346

Phase 1 Trial

Single Ascending Doses (each cohort has 6 on drug and 2 on placebo)

First cohort: 25 mg single dose
75 mg single dose
150 mg single dose
300 mg single dose
500 mg single dose
1000 mg single dose
1500 mg single dose
2000 mg single dose

Fed vs fasted 750 mg single dose

Human Data on ATB-346

Phase 1 Trial

Multiple Ascending Doses

250 mg once-daily for 14 days

750 mg once-daily for 14 days

750 mg twice-daily for 14 days

Naproxen dose for arthritis: 500 mg twice-daily

Human Data on ATB-346

Phase 1 Trial Results

25 mg to 2,000 mg single doses were safe and well-tolerated

250 mg daily (14 days) – safe and well-tolerated



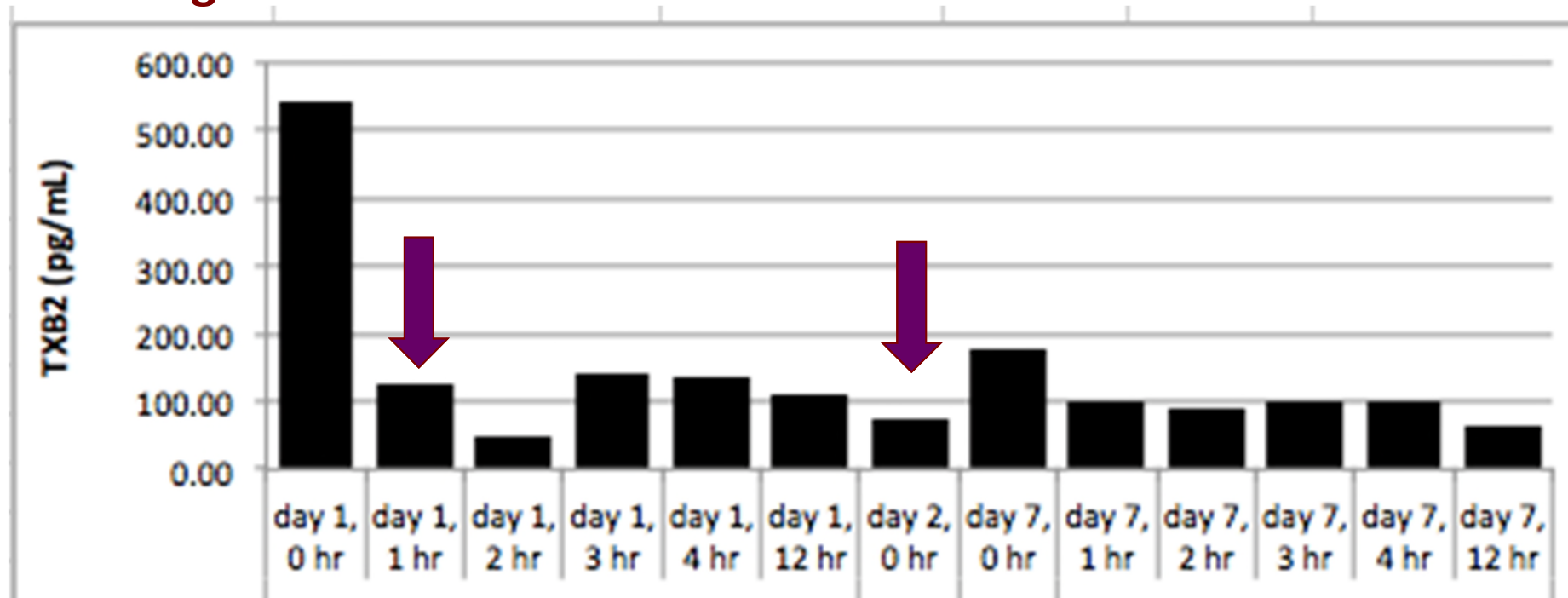
Subject #357 had prior history of hepatitis and was found to have a gallstone lodged in his bile duct when examined on Day 17 of this trial

Human Data on ATB-346

Phase 1 Trial

What about pharmacodynamics?

250 mg

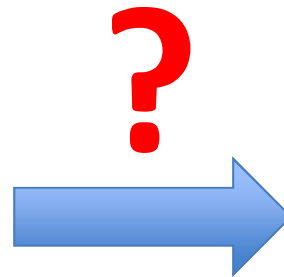


Human Data on ATB-346

Phase 1 Trial

Enhanced suppression of COX activity vs naproxen

Longer duration of suppression of COX activity



Phase 2 Trial

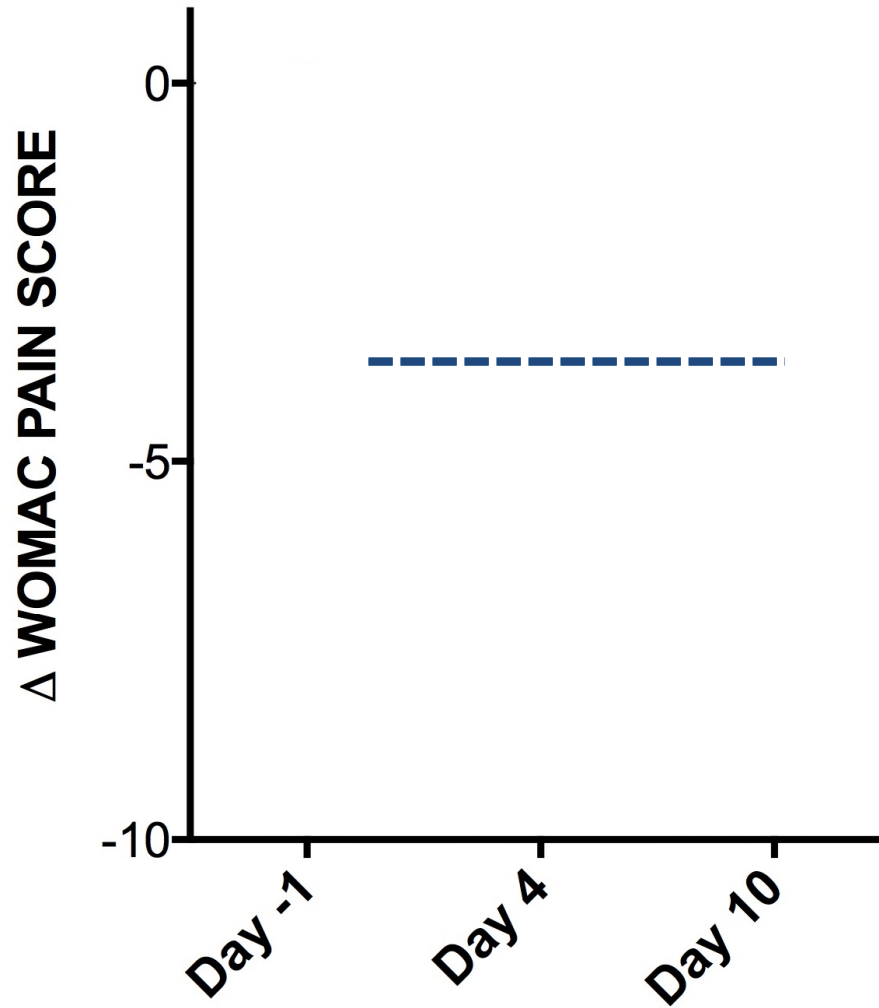
10-day treatment 250 mg once daily WOMAC

12 patients with osteoarthritis of the knee

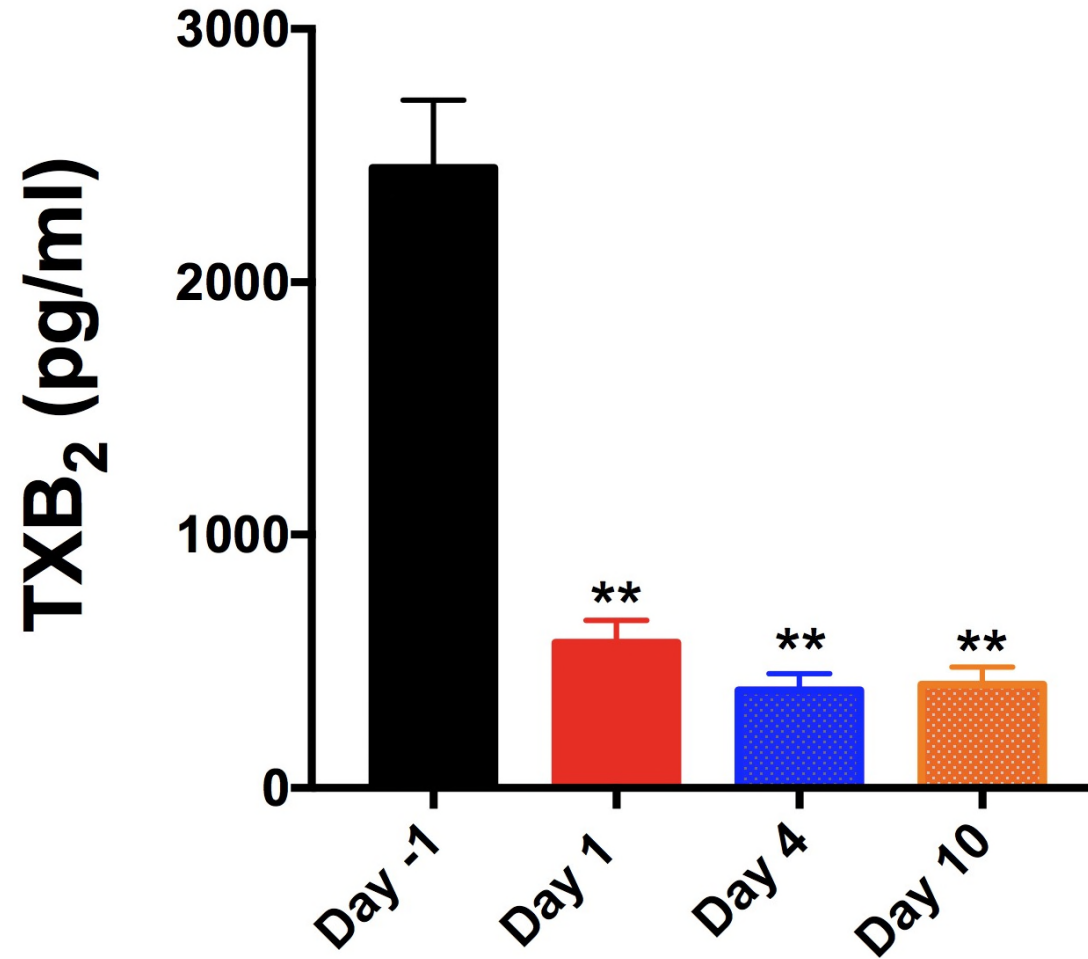
Started - April 2016 Toronto

Completed – August 2016

Change of Pain Severity in Osteoarthritis Patients Treated with ATB-346



Inhibition of Thromboxane Synthesis by ATB-346 in OA Patients



**Is ATB-346 GI-Safe in Humans at
an Effective Anti-Inflammatory Dose?**

Phase 2B Endoscopy Trial

~120 healthy volunteers per group

500 mg naproxen twice daily vs 160 mg ATB-346 once daily

14 days of drug treatment

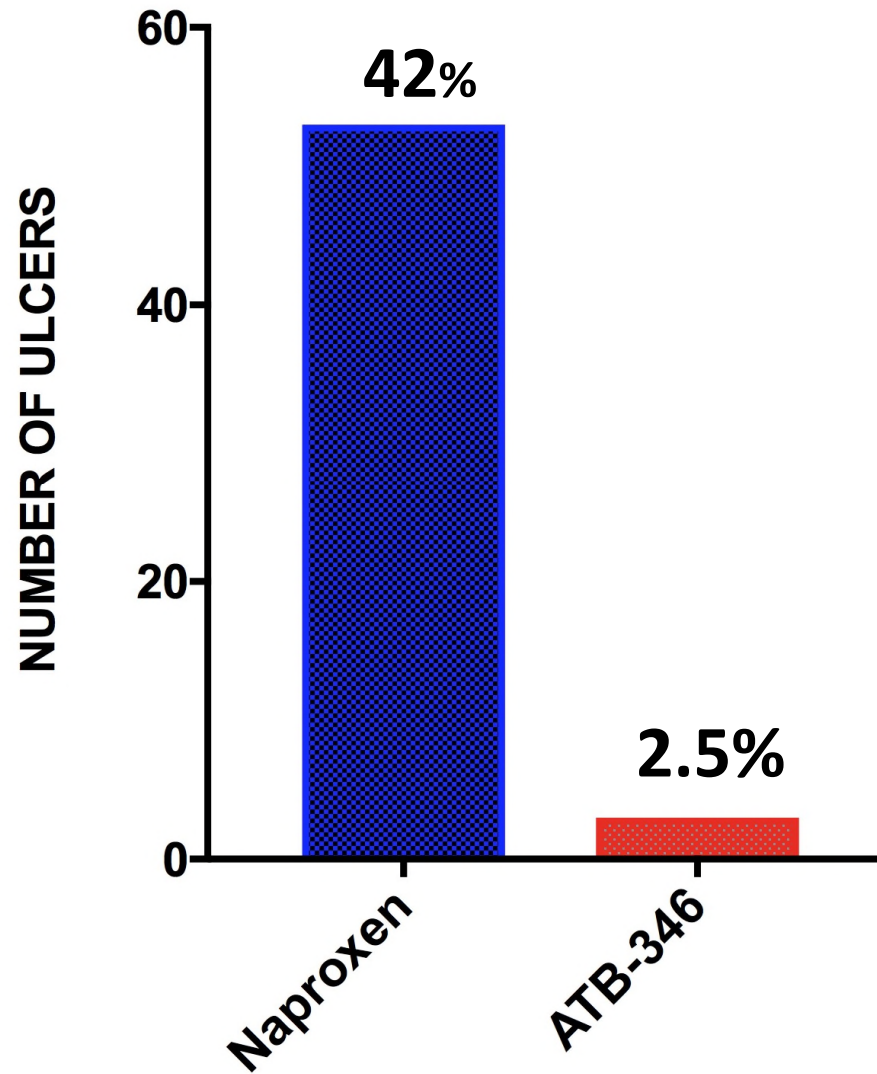
Upper GI endoscopy prior to study and on day 14

Primary endpoint: number of upper GI ulcers

Study powered based on a predicted ulcer rate of 20 in the naproxen group and 7 in the ATB-346 group

Primary endpoint results were released on Monday March 19

ULCER INCIDENCE



94% ↓
P<0.001

SUMMARY

Linking an H₂S-releasing moiety to an NSAID:

- **substantially reduces GI toxicity (animals & humans)**

Thank you !

Giuseppe Cirino - University of Naples
Jason McDougall - Dalhousie University
Marcelo Muscara - University of Sao Paulo
Gilberto de Nucci - University of Campinas
Andre Buret - University of Calgary
Wally MacNaughton - University of Calgary
Jose G Ferraz - University of Calgary

Jane Mitchell - Imperial College
Derek Gilroy - UCL
Rod Flower - QMUL
Mauro Perretti - QMUL