

Vonoprazan: The promise and current status

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Disclosures

Consultant

- Allakos, Clexio, EndoStim, ISOThrive, Phathom, RedHill Biopharma

Speaker

- Alynlam, RedHill Biopharma

Stockholder

- Antibe Therapeutics

Potassium-competitive acid blockers (P-CABs)

Licensed in some Asian and South American countries

Faster onset of action and more profound control of acid secretion than PPIs

Current examples include revaprazan, vonoprazan, tegoprazan and fexuprazan

Phase 3 trials with vonoprazan in US and Europe

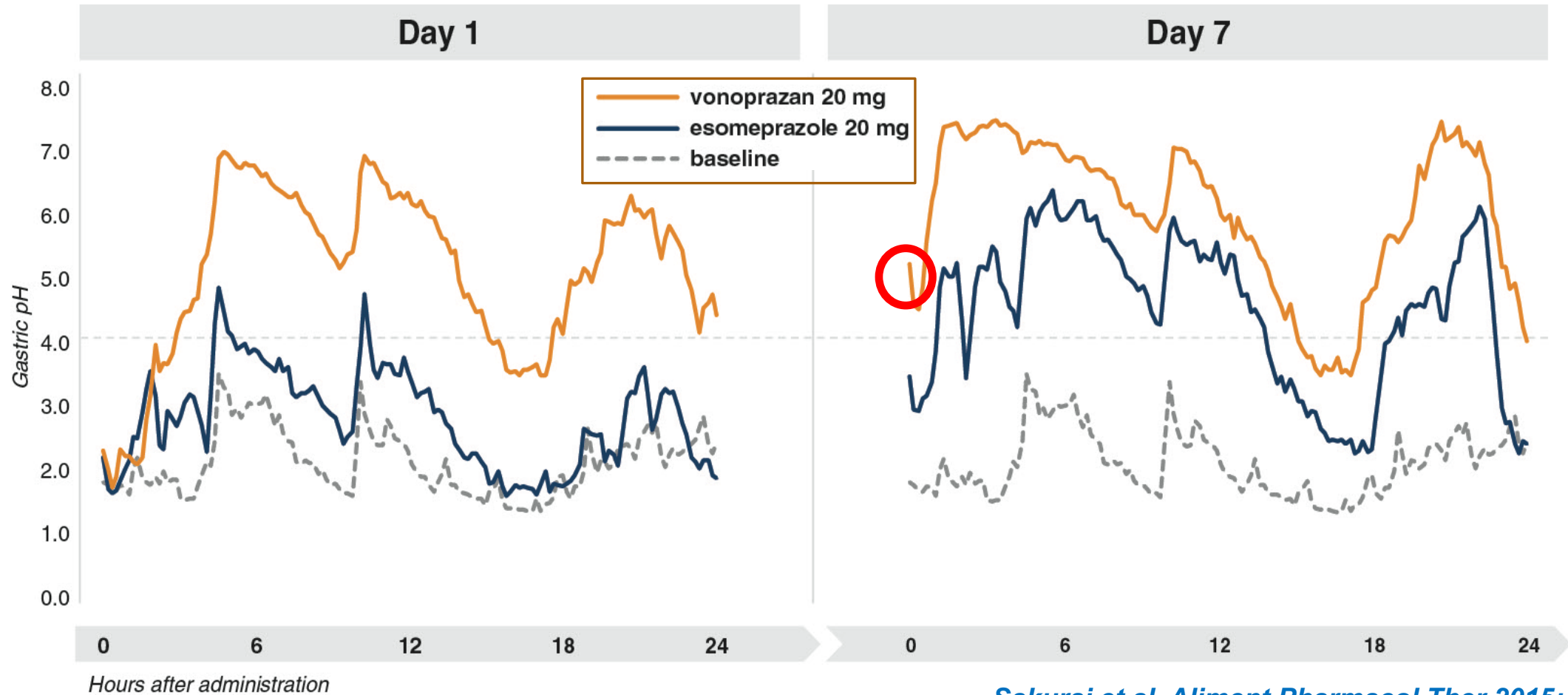
- *H. pylori* infection
- erosive esophagitis

Mechanisms of action of P-CABs and PPIs

| P-CABs | PPIs |
|---|---|
| Act directly (after protonation) on H ⁺ ,K ⁺ -ATPase | Require transformation to sulfenamide |
| Super-concentrate in parietal cell acid space (100,000-fold higher than in plasma) | Concentrate in parietal cell acid space (1000-fold higher than in plasma) |
| Bind competitively to the K ⁺ binding site of H ⁺ ,K ⁺ -ATPase | Sulfenamide binds covalently to H ⁺ ,K ⁺ -ATPase |
| Reversible binding | Irreversible binding |
| Duration of effect related to plasma half-life | Duration of effect related to half-life of sulfenamide-enzyme complex |
| Full effect from the first dose | Full effect after repeated doses |

Scarpignato & Hunt Aliment Pharmacol Ther 2015; 42: 1027
Abdel-Aziz et al, Aliment Pharmacol Ther 2021; 53: 794

Comparison of vonoprazan and esomeprazole on 24-hour intragastric pH (Japan)



Control of intragastric acidity with vonoprazan 20 mg daily (UK)

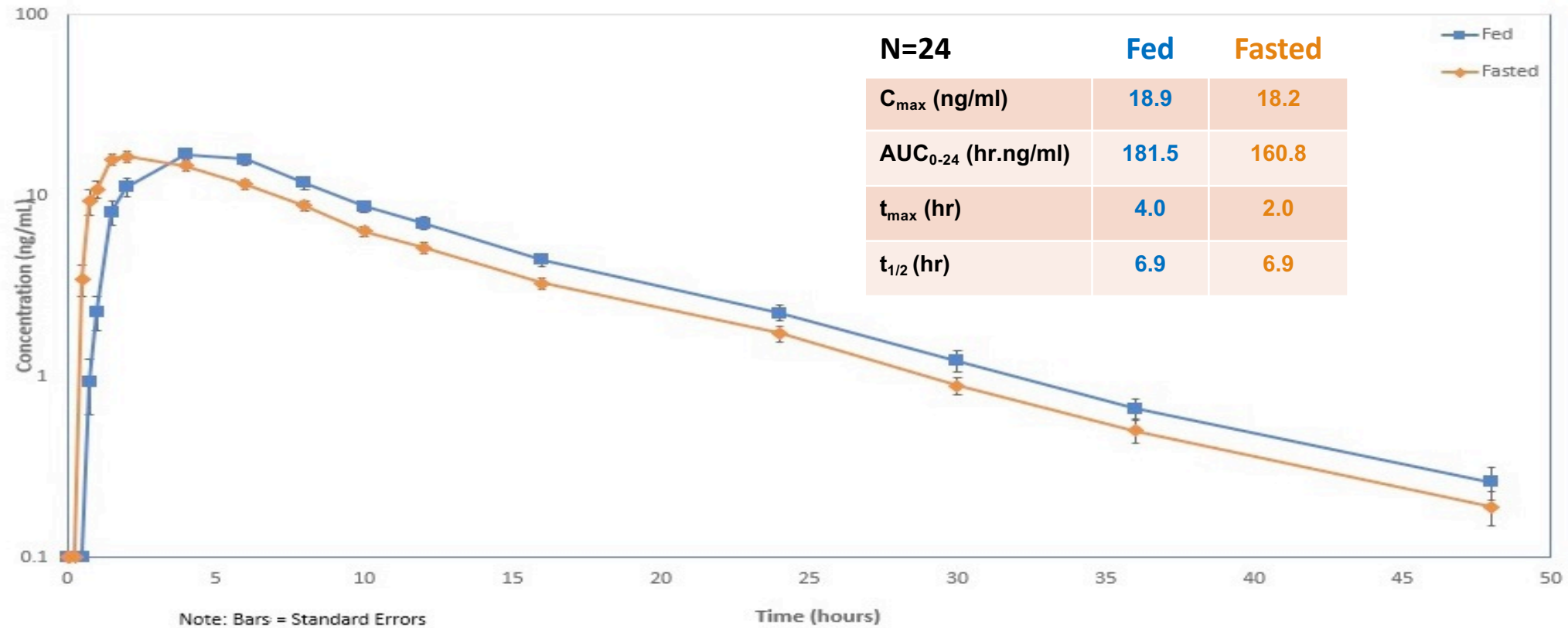
| | pH holding time (% of 24h) ¹ | |
|--------------|---|------|
| | > 4 | > 5 |
| Day 1 | 62.7 | 49.2 |
| Day 7 | 85.2 | 78.6 |

For comparison, esomeprazole 40 mg daily for 5 days: pH > 4 for 70%²

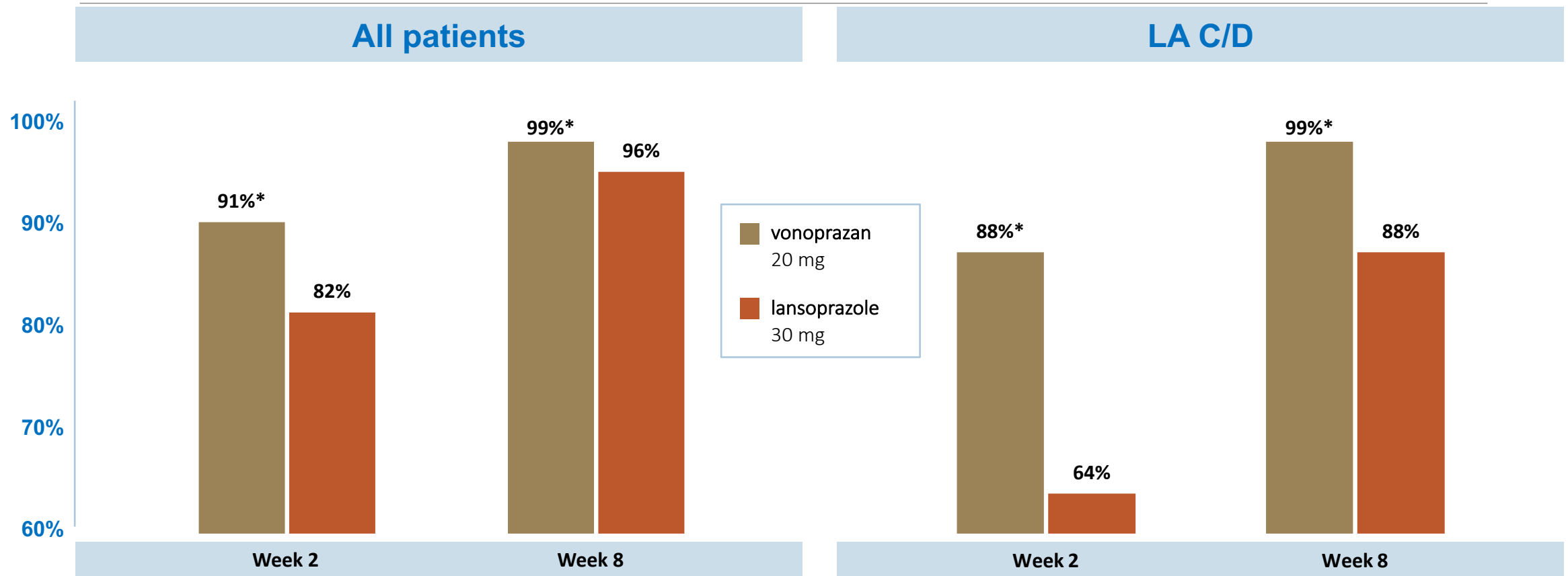
1. Jenkins et al, *Aliment Pharmacol Ther* 2015; 41: 636-48

2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022101s004,021153s034,021957s007,021689s015lbl.pdf

Oral pharmacokinetics of vonoprazan 20 mg in fed and fasted states



Comparison of vonoprazan and lansoprazole in erosive esophagitis (Japan)

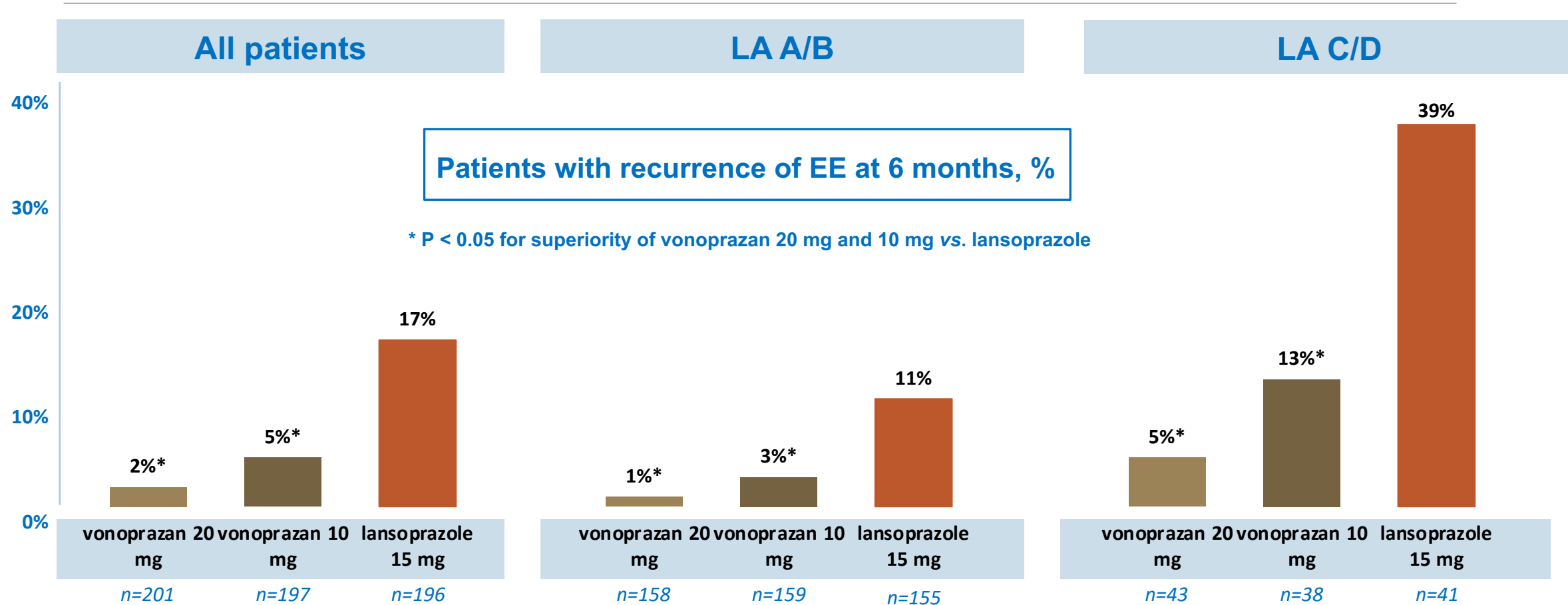


n=404; * P < 0.05 for superiority versus lansoprazole

n=147; * P < 0.05 for superiority versus lansoprazole

Ashida et al, Aliment Pharmacol Ther 2016; 43: 240

Comparison of vonoprazan and lansoprazole in erosive esophagitis (Japan)

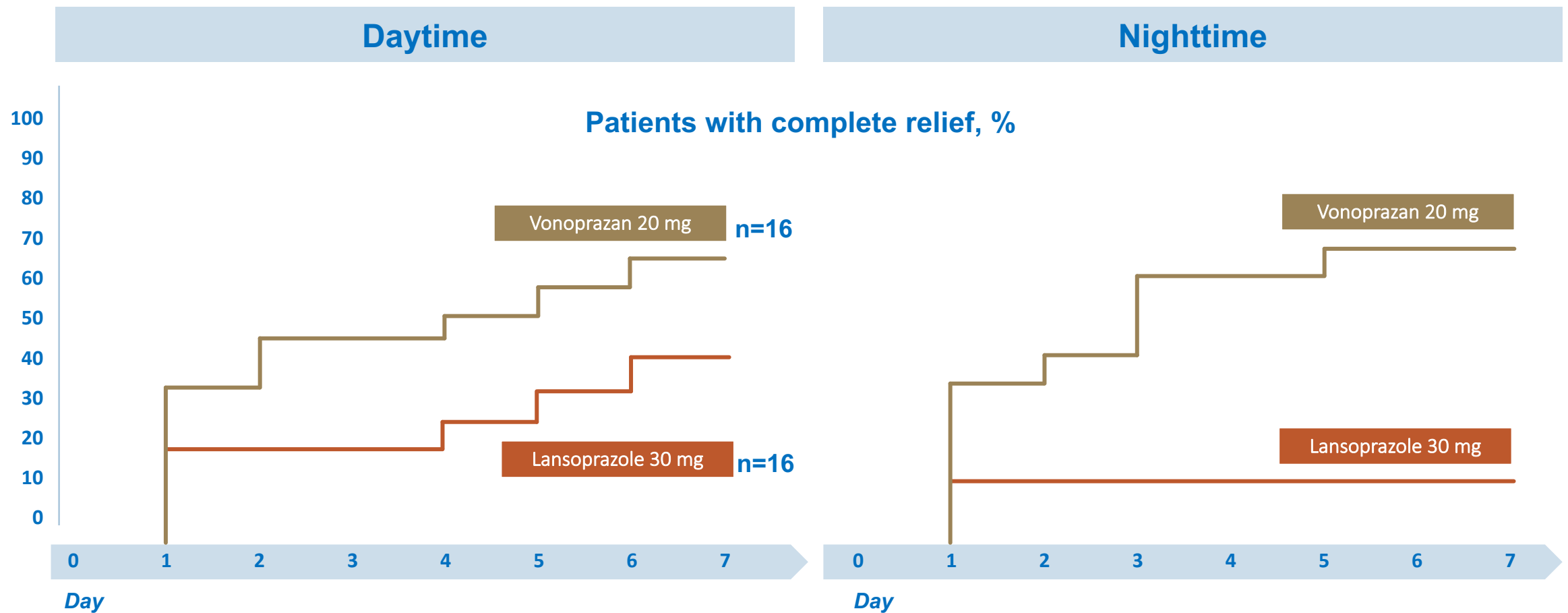


Comparison of vonoprazan and lansoprazole in erosive esophagitis (Japan)

Cumulative 8-week healing rates according to *CYP2C19* status

| | Vonoprazan 20 mg <i>qd</i> | Lansoprazole 30 mg <i>qd</i> | P |
|---------------------------|-------------------------------|---------------------------------|-------|
| Extensive metabolizers | 98.9% | 94.3% | 0.029 |
| Poor metabolizers | 100% | 100% | NS |

Comparison of vonoprazan and lansoprazole on speed of heartburn relief in EE (Japan)



Oshima et al, Aliment Pharmacol Ther 2019; 49: 140

Phalcon-EE trial (NCT04124926)

Phase 3 trial in US and Europe

Healing phase

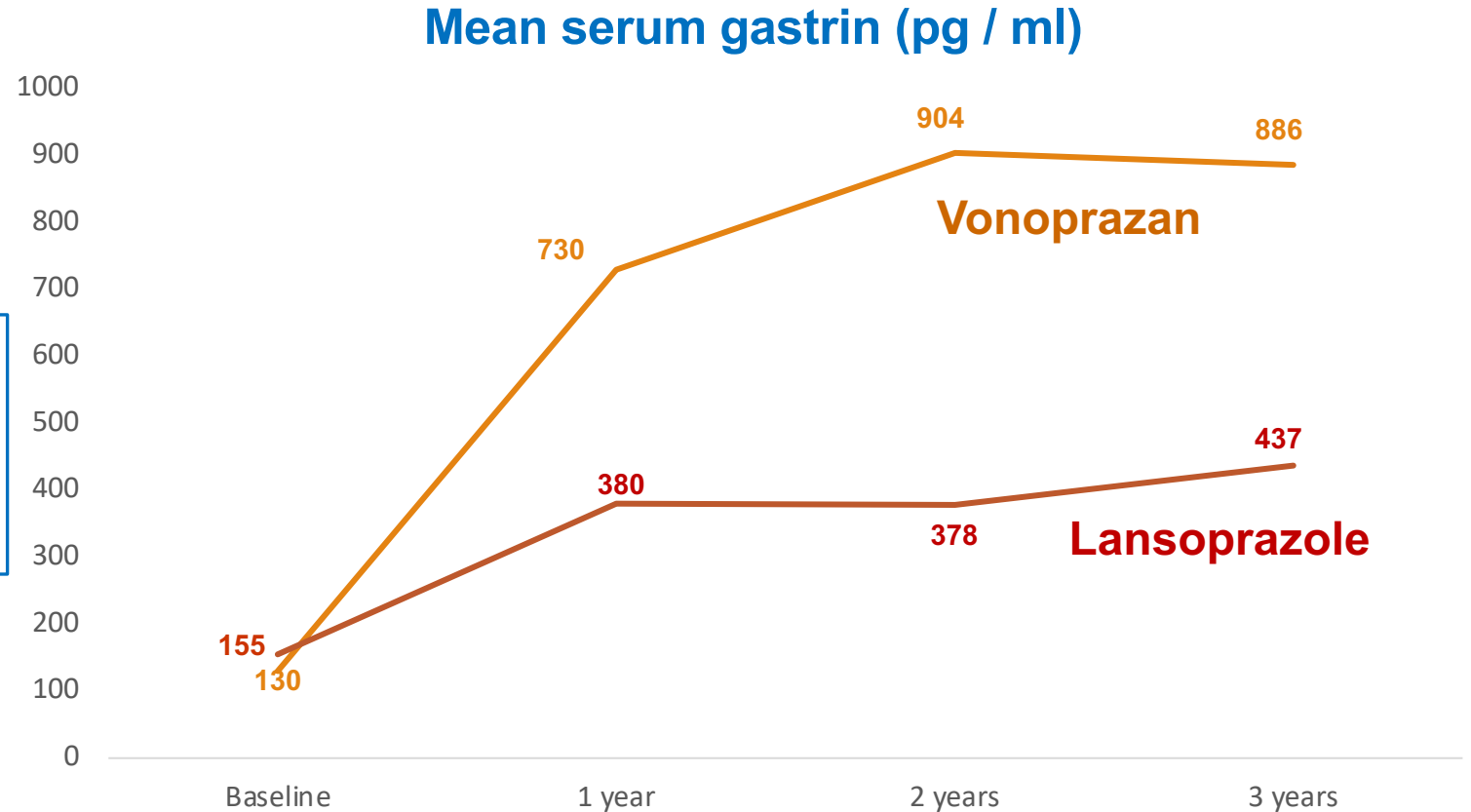
- Randomized to vonoprazan 20 mg *qd* or lansoprazole 30 mg *qd* for up to 8 weeks
- EGD at 2 and 8 weeks

Maintenance phase

- Healed EE at 2 or 8 weeks
- Re-randomized to vonoprazan 10 or 20 mg *qd* or lansoprazole 15 mg *qd* for up to 6 months

Prospective safety evaluation (Japan)

- 202 patients with healed EE
- Re-randomized 2:1 on healing to vonoprazan or lansoprazole
- Followed prospectively



Prospective safety evaluation (Japan)

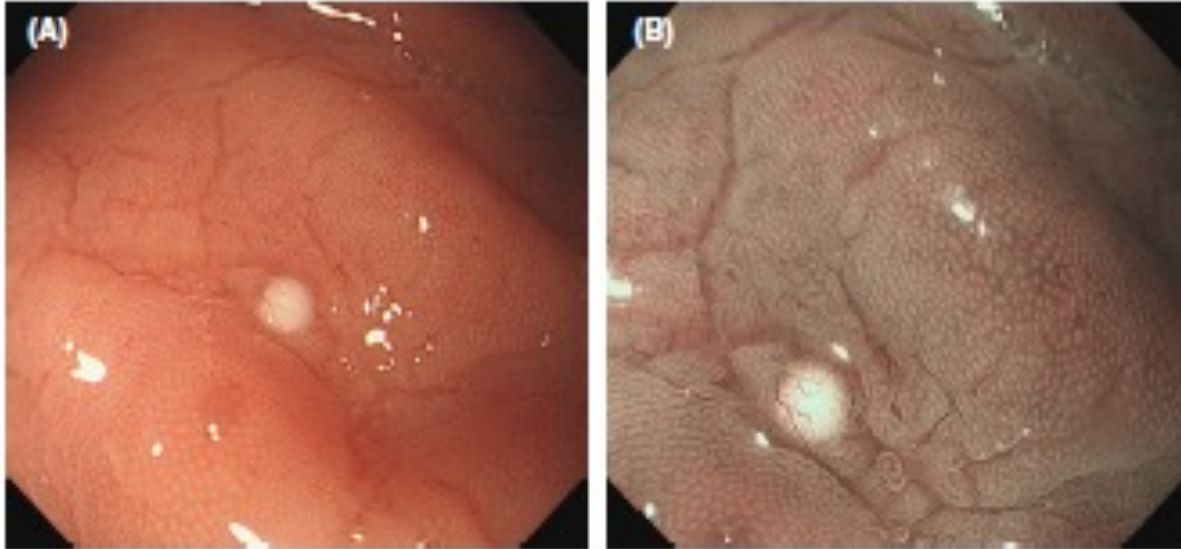
| | Vonoprazan (n = 155) | Lansoprazole (n = 67) |
|---------------------------------------|-------------------------|--------------------------|
| Serious drug-related AEs | 2.2% | 0 |
| AEs leading to discontinuation | 3.0% | 0 |
| Fatal AEs | 0 | 0 |
| Gastric polyps | 36% | 40% |
| Diarrhea | 6.7% | 6.0% |

C. difficile infection

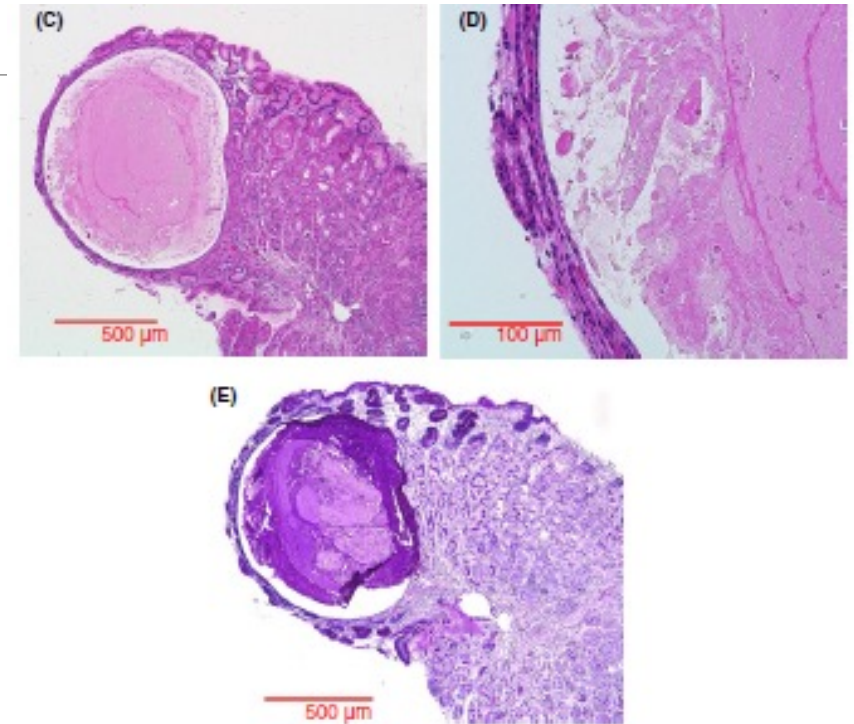
| | CDI patients (N = 4,466) | Controls (N = 13,220) | OR (95% CI) |
|-------------------|-----------------------------|--------------------------|----------------------------|
| PPIs | 45.0% | 38.0% | 1.3 (1.2 – 1.4) |
| Vonoprazan | 6.4% | 5.3% | 1.4 (1.2 – 1.7) |

With PPI use as reference standard,
no increased risk with vonoprazan:
OR = 1.07 (0.91 – 1.26)

“Stardust” gastric mucosa



Point prevalence 4.9% at 4 years (N = 2516)



Mucus pool within dilated duct
Flattening of glandular epithelium

Summary

Vonoprazan offers some advantages over PPIs in EE

- Faster healing
- Superiority in LA grades C/D
- Lower relapse rates during maintenance
- Efficacy unrelated to CYP2C19 status
- Can be taken regardless of food intake

Results from phase 3 EE trial in US and Europe awaited

No current safety concerns

- Ongoing studies of gastrin levels and gastric histology

Planned US phase 2 placebo-controlled trial in NERD