VVZ-149

GlyT2 and 5HT2A receptor antagonist

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COI Disclosure

- None relevant

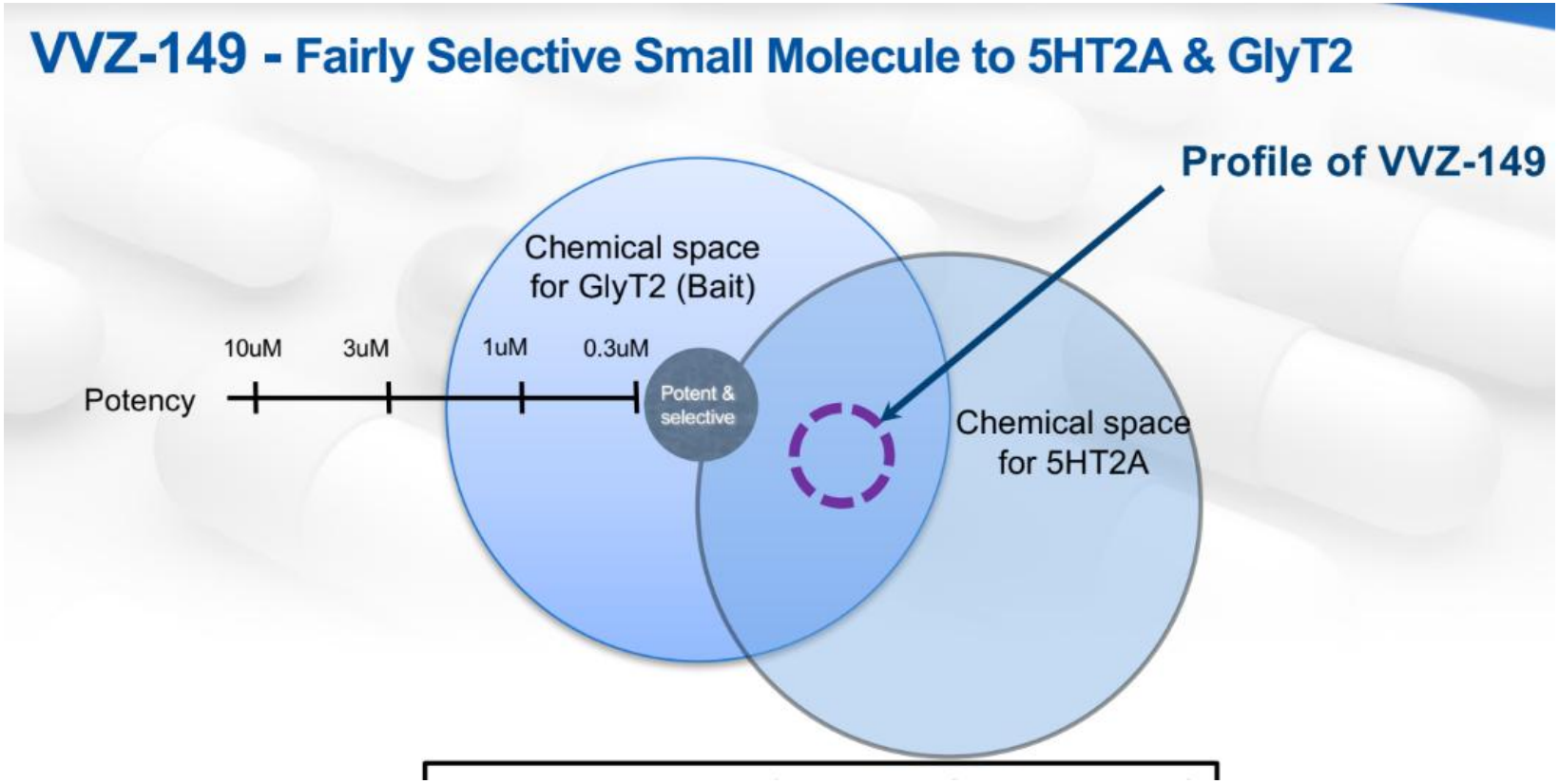
Overview

- Target small molecule drugs for CNS diseases, including pain
  - Specifically non-opioid, non-NSAID analgesics
- Unique drug identification process
  - Ex vivo screening technology
- Leading drug candidate – VVZ-149
  - Currently in Phase 2b & 3 Clinical Trials
    - Primary Target = Post-op Pain
- Fast Track Status granted by FDA
  - November, 2018

Unique Drug Development

- Historically single target approach
  - However, often failed in clinical tails with side effects
  - **Target potency/selectivity ≠ efficacy and safety**
- Most diseases result from the "malfunction" of the interactions among multiple related targets
- New approach
  - ***Target multiple receptors with less target potency/selectivity for each individual target but with more additive and synergetic effects that have more efficacy and less toxicity***

New Approach Targets Overlap



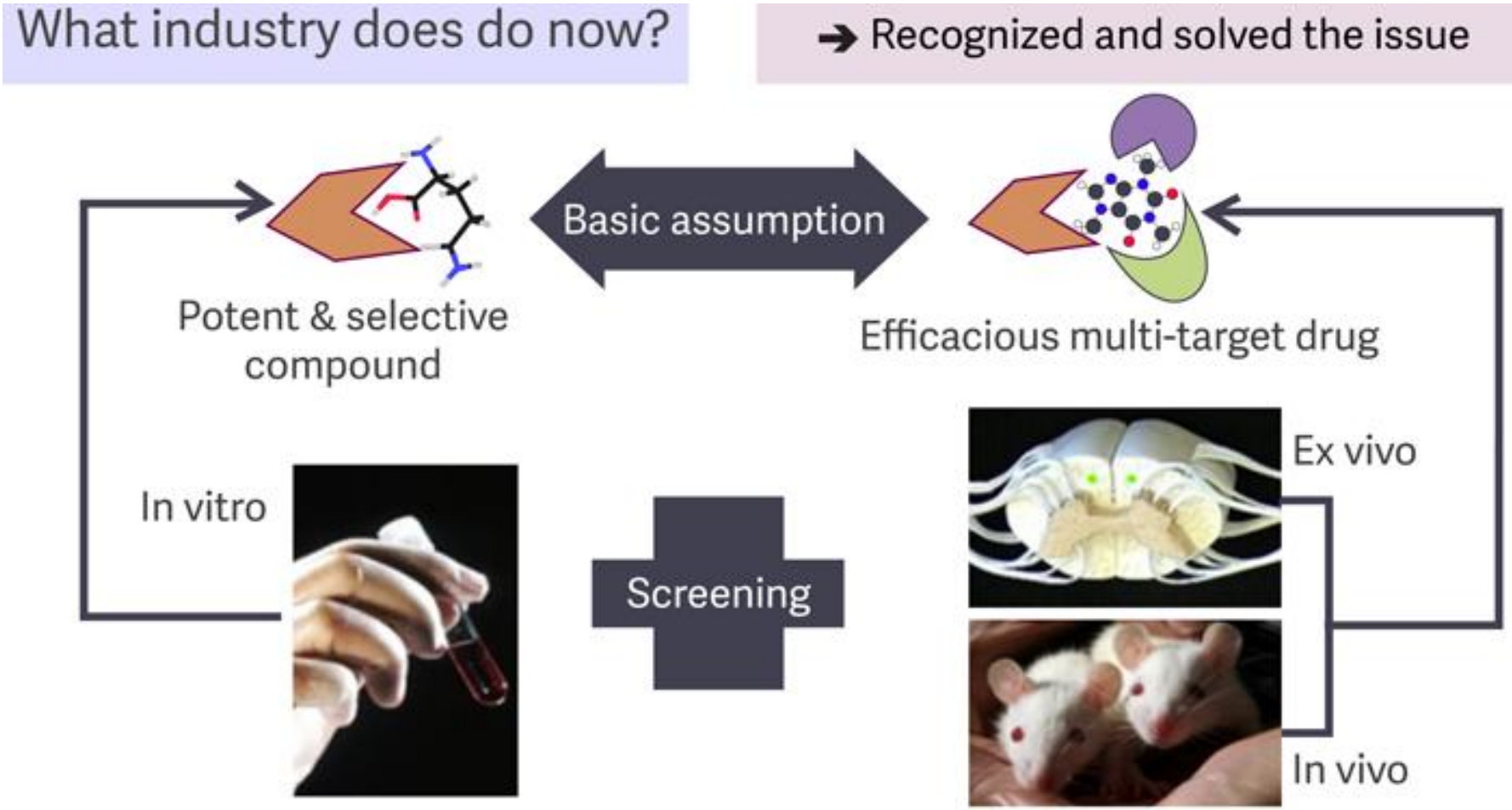
Not entirely novel idea…

Multi-Target CNS Drugs			
Brand Name	Companies	Sales	Targets
Seroquel	AstraZeneca	$ 5.8B (2011)	D1-4, 5HT2, a1/2, H1
Zyprexa	Lilly	$ 2.6B (2010)	5HT2, D2, GABAA
Effexor	Pfizer	$ 2.6B (2008)	SNRI
Risperdal	J&J	$ 4.5B (2007)	D2, 5HT2
Abillfy	Otsuka/BMS	$ 6.2B (2013)	D2 partial agonist, D3, 5HT2
Cymbalta	Lilly	$ 5.1B (2013)	SNRI
Effexor	Wyeth	$ 3.9B (2007)	SNRI

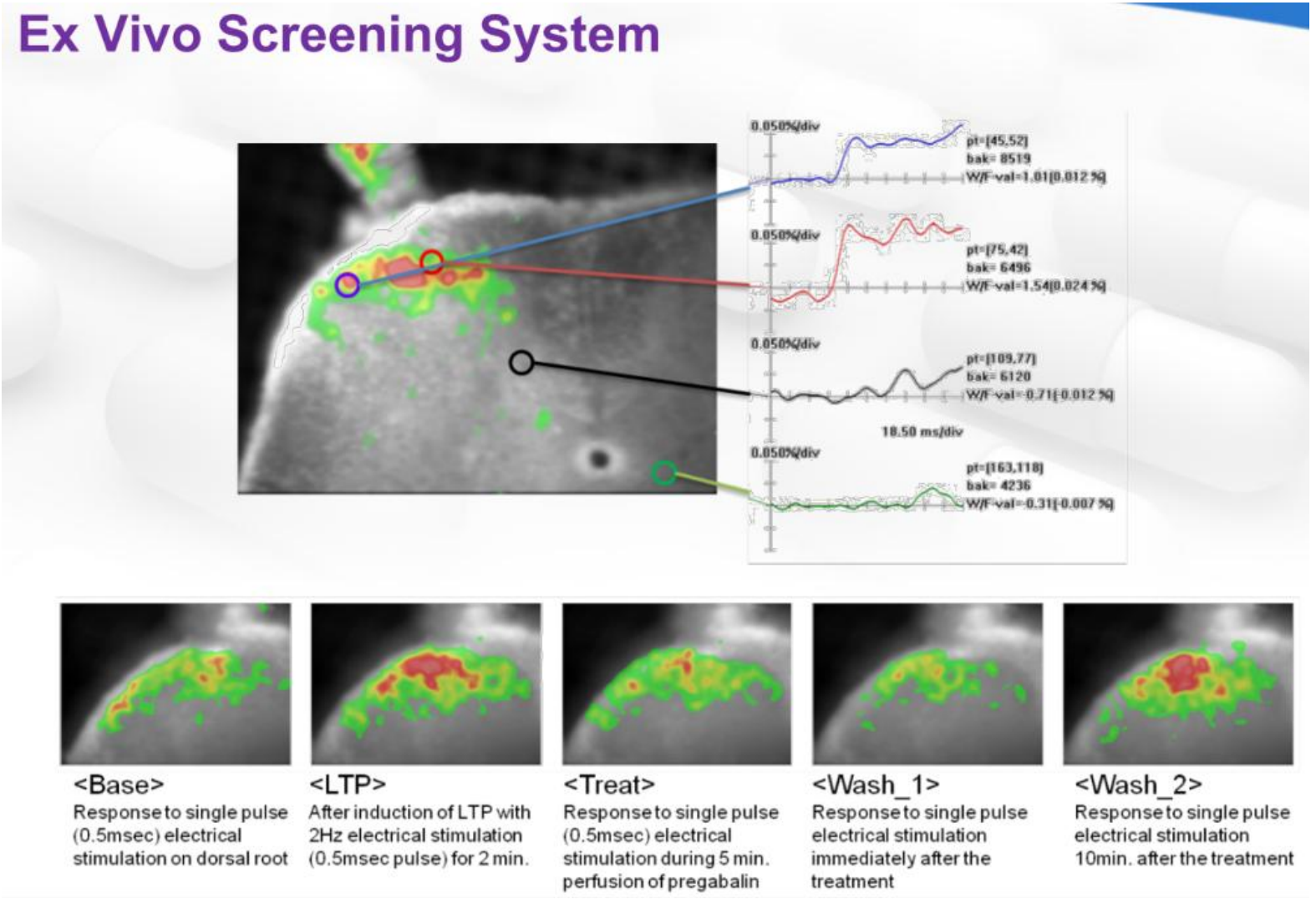
Types of testing…

- in vitro - test performed or taking place in a test tube, culture dish, or elsewhere outside a living organism.
- in vivo - test performed or taking place in a living organism.
- ex vivo – test performed or taking place in an organ, cells, or tissue taken from a living organism.

Ex Vivo Screen Technology



The change of optical signal stained with the voltage-sensitive dye



VVZ-149

- GlyT2 and 5HT2A receptor antagonist
- GlyT2 –blockage increases inhibitory synaptic transmission by glycine in the spinal cord, resulting in a reduction of pain transmissions to the brain ***(central effect)***
- 5HT2A - blockage decreases descending serotonergic facilitatory modulation on pain transmission by the brain and reduces nociceptor activation in peripheral nerves ***(central and peripheral effect)***

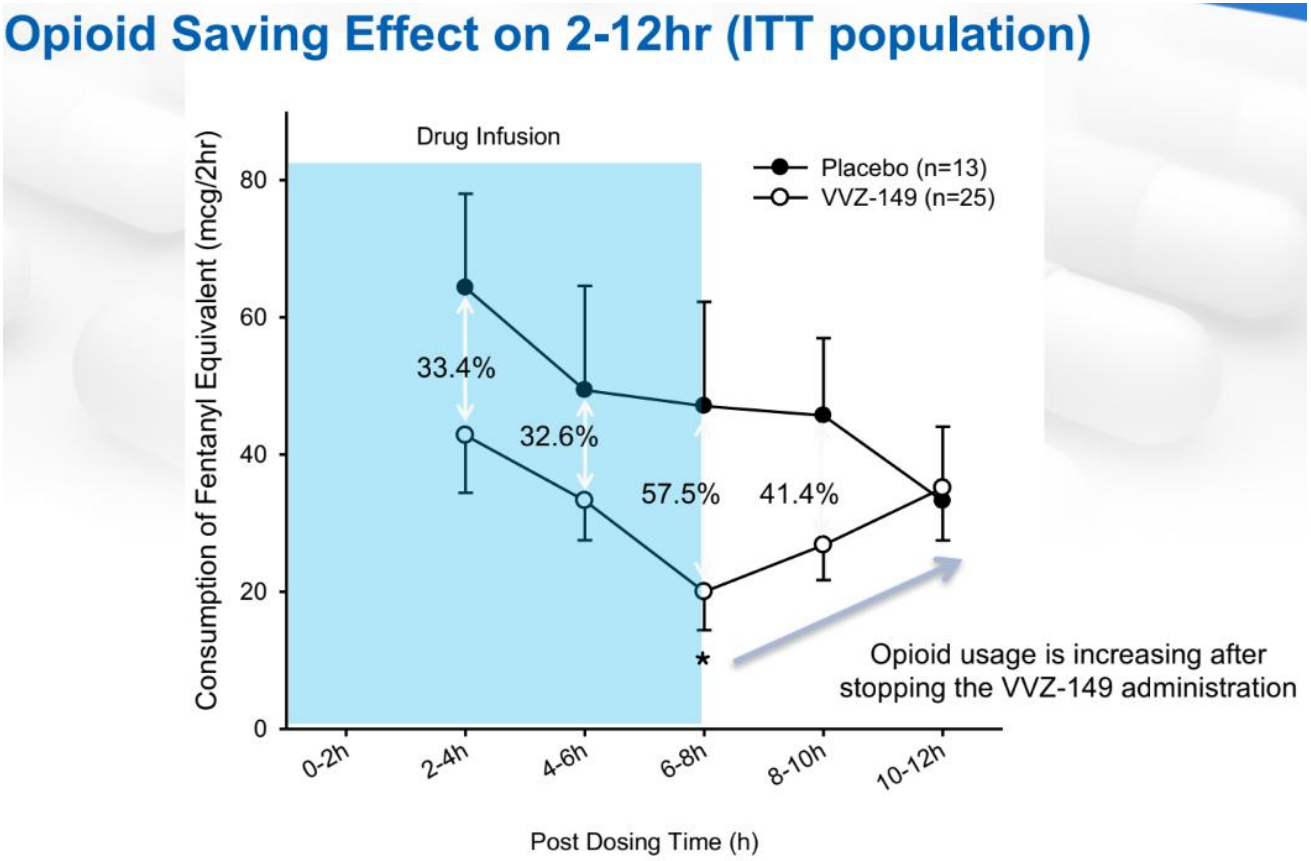
Trials

- **Pre-Clinical** – in rats, analgesic equivalent to morphine in post-op and formalin induced pain
- **Phase 1** – in healthy males – no clinically significant adverse effects
- **Phase 2** – completed or ongoing in Gastrectomy, Bunionectomy, Abdominoplasty, Hip Arthroplasty, Laparoscopic Colorectomy, Colorectal Surgery, Lumbar Radiculopathy
- **Phase 3 -** abdominal plastic surgery patients – completed in August 2019

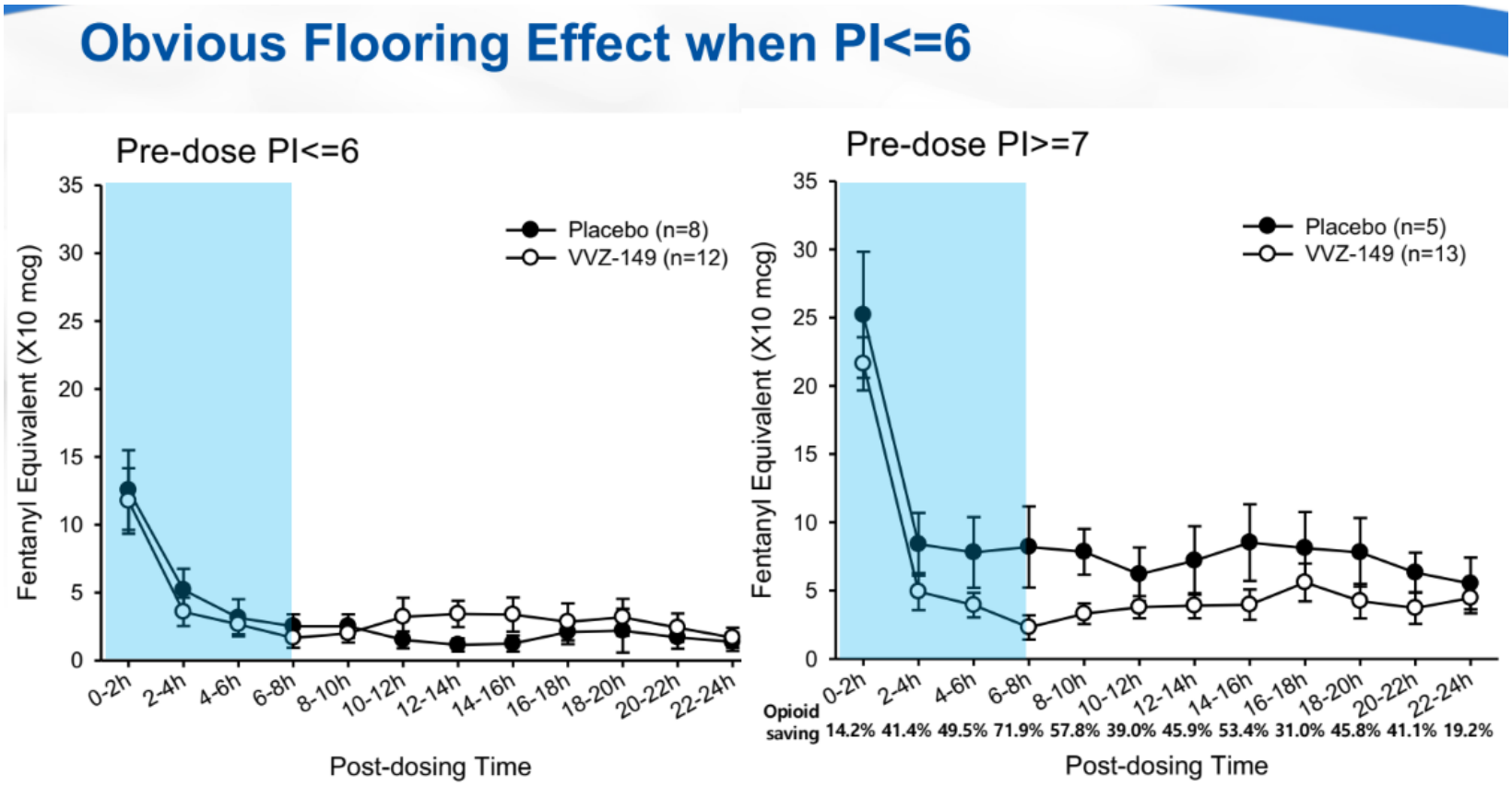
Phase 2 Study

- A Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Evaluate the Analgesic Efficacy and Safety of VVZ-149 Injection for Post-operative Pain following Laparoscopic-assisted Abdominal Gastrectomy in Early Gastric Cancer Patients
- Post-op pain score > or = to 5 for entry
- 2:1 Ratio - Loading dose 1.8mg/kg for 30 min followed by maintenance dose 1.3mg/kg/hr for 7.5hr vs Placebo
- Endpoint: Opioid Consumption of Fentanyl PCA with basal infusion 10mcg/hr (10mcg, 6 min lock-out) in 24 hr
- Endpoint: Pain Intensity in 24hr

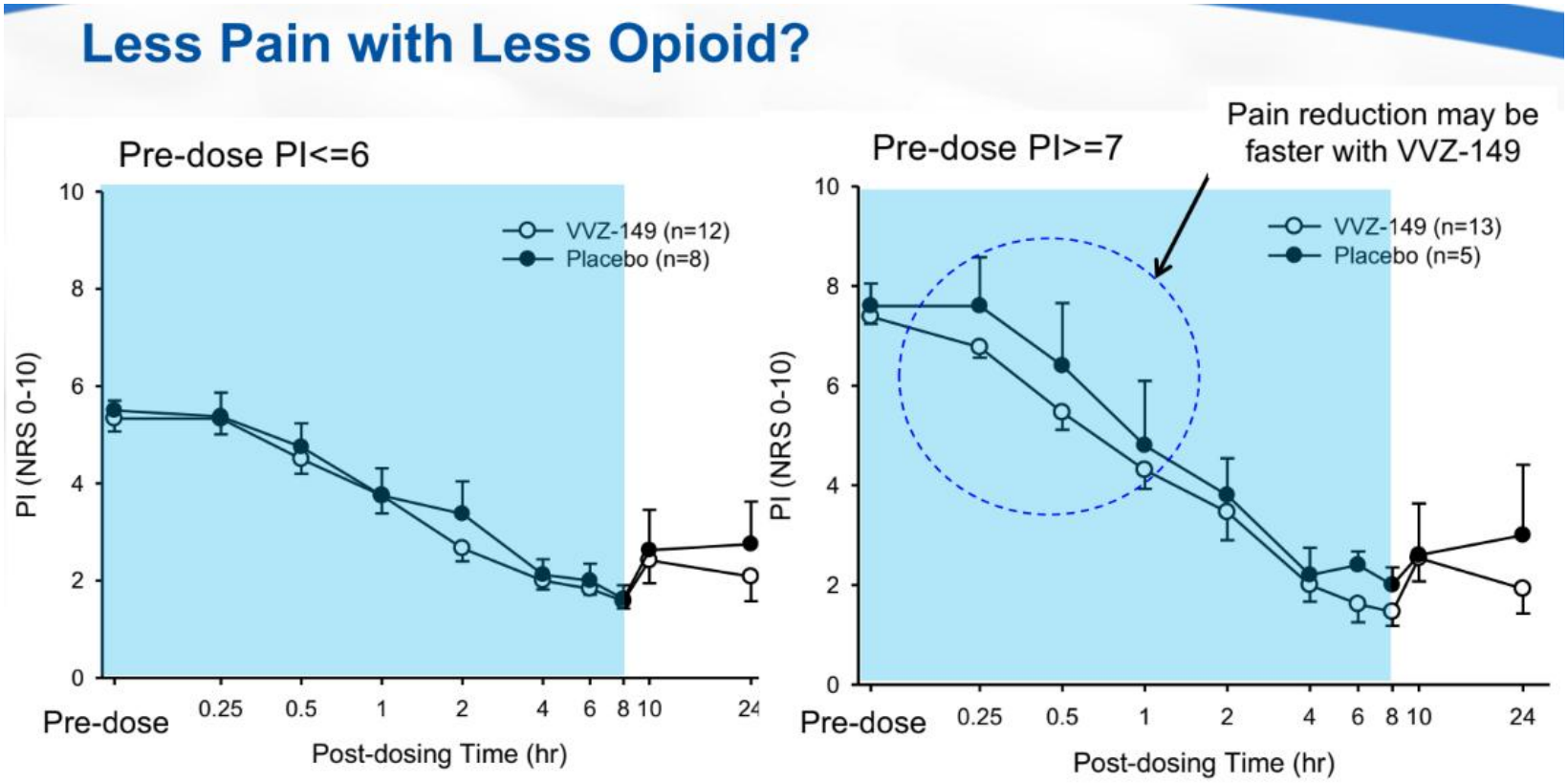
Opioid Sparing Effect



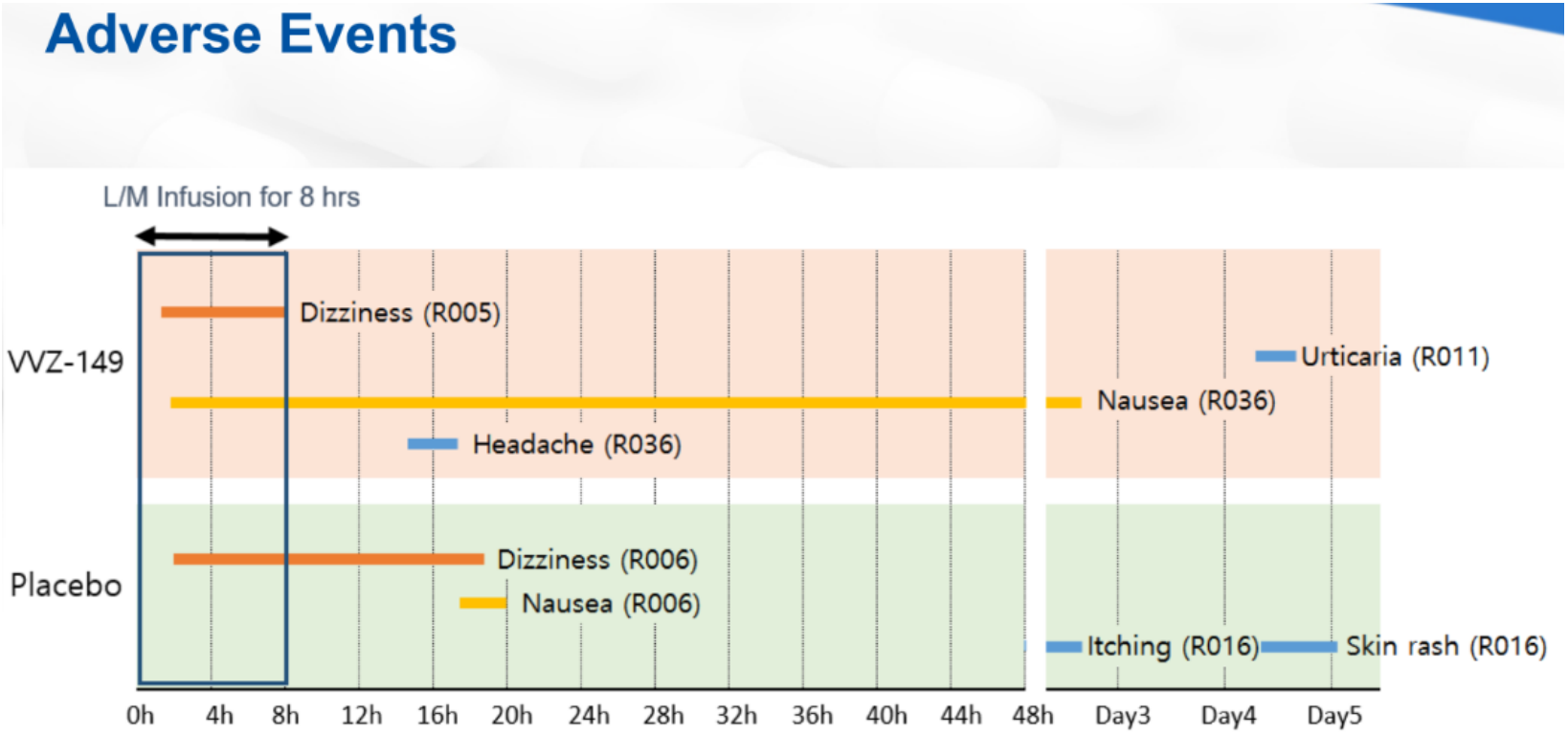
More Pain More Gain?



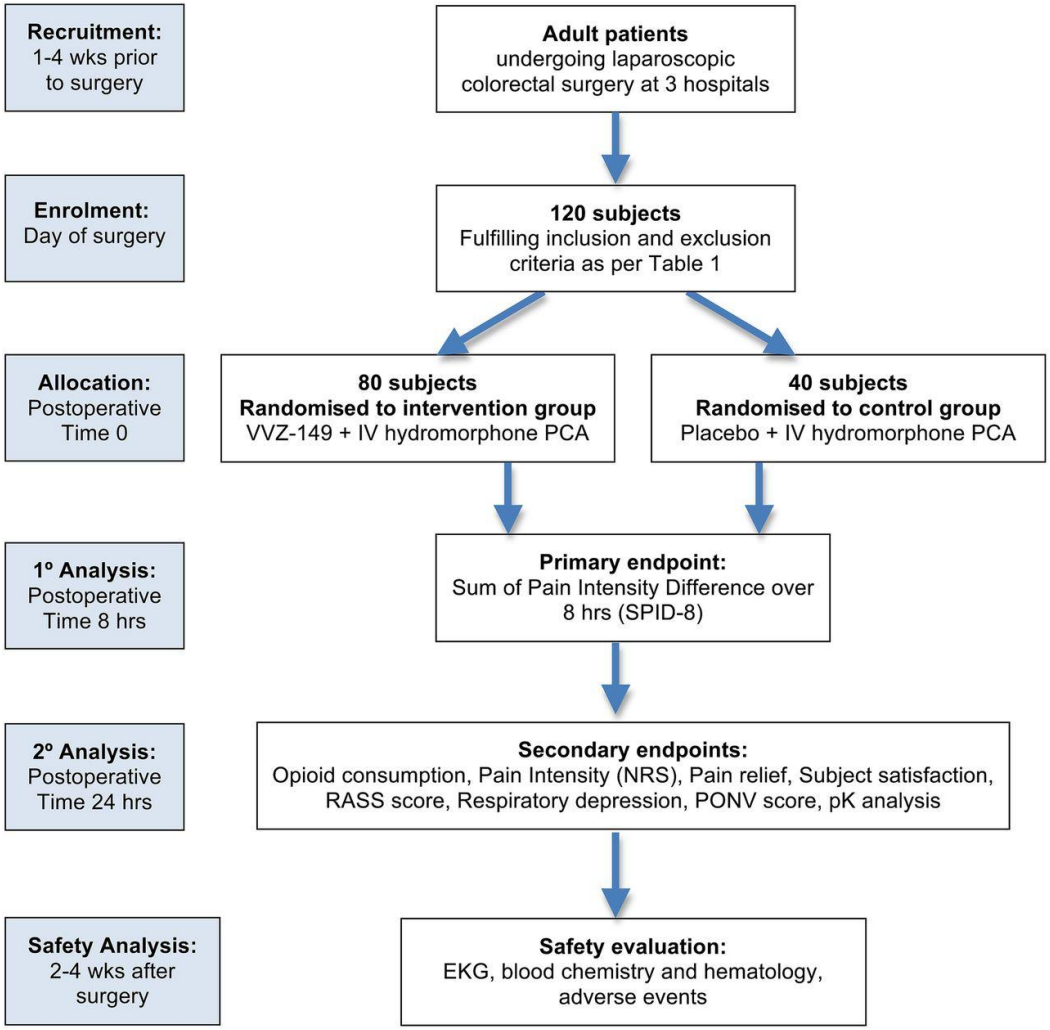
More Pain More Gain? Cont…



No Significant Adverse Effects



CONSORT diagram for VVZ-149 study flow.



Srdjan S Nedeljkovic et al. BMJ Open 2017;7:e011035

BMJ Open

Conclusion

- *No Phase 2 or Phase 3 data in peer-reviewed literature and minimal data in abstracts*
- Evidence of decreased opioid usage and decrease in pain scores while infusion is running
- Possible higher benefit in patients with higher baseline pain in immediate post-op period
- Unclear if there is any lasting effects once the infusion is stopped
- Good safety profile

References

- http://www.vivozon.com/
- https://www.clinicaltrials.gov/ct2/results?term=%22VVZ-149%22&rank=1#rowId0
- https://www.empr.com/home/news/drugs-in-the-pipeline/fda-grants-non-opioid-analgesic-vvz-149-fast-track-status/
- Lee_VVZ-149_Arrowhead Pain Summit 2016.pdf
- Oh J , Lee S , Kim A , Yoon J , Jang K , Lee DH , Cho S , Lee SR , Yu KS , Chung JY. Safety, Tolerability, and Pharmacokinetic Characteristics of a Novel Nonopioid Analgesic, VVZ-149 Injections in Healthy Volunteers: A First-in-Class, First-in-Human Study. J Clin Pharmacol. 2018 Jan;58(1):64-73. doi: 10.1002/jcph.973. Epub 2017 Aug 16.
- Nedeljkovic SS , Correll DJ , Bao X , Zamor N , Zeballos JL , Zhang Y , Young MJ , Ledley J , Sorace J , Eng K , Hamsher CP , Maniam R , Chin JW , Tsui B , Cho S , Lee DH . Randomised, double-blind, parallel group, placebo- controlled study to evaluate the analgesic efficacy and safety of VVZ-149 injections for postoperative pain following laparoscopic colorectal surgery. BMJ Open. 2017 Feb 17;7(2):e011035. doi: 10.1136/bmjopen-2016-011035.
- Pang MH1, Kim Y, Jung KW, Cho S, Lee DH. A series of case studies: practical methodology for identifying antinociceptive multi-target drugs. Drug Discov Today. 2012 May;17(9-10):425-34. doi: 10.1016/j.drudis.2012.01.003. Epub 2012 Jan 16.