

Hebben 5-HT₄ receptoragonisten nog toekomst?

Romain Lefebvre

Alumni; 19.9.2018

Addendum: Cisapride

Cisapride heeft een prokinetisch effect op gans de maagdartractus. Het wordt gebruikt om **gastro-oesofageale reflux** tegen te gaan, om de maagevacuatie te versnellen bij **gastroparesie** en ook bij bepaalde vormen van **constipatie** vooral pseudo-obstructie. Het wordt niet gebruikt als anti-emeticum.

Cisapride kan aanleiding geven tot diarree, krampen en borborygmi.

PREPULSID (Janssen Pharmaceutica)

cisapride

deelb. compr. 40 × 5 mg FV/ 517 F (b)

100 × 10 mg FV/ 1961 F (b)

druppels kind. 100 ml 1 mg/ml FV/ 284 F (b)

orale oploss. volw. 200 ml

5 mg/5 ml FV/ 557 F (b)

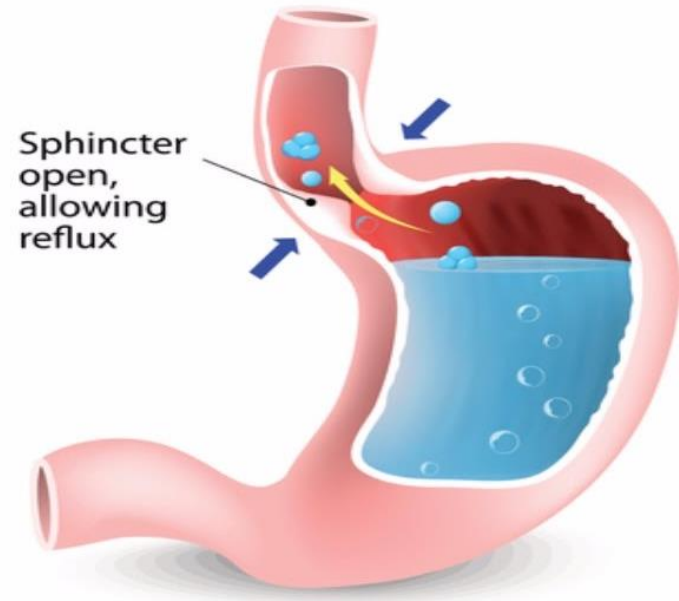
supp. 6 × 30 mg FV/ 433 F

Posol. volw.: 4 × per dag 5 à 10 mg

kind.: 4 × per dag 0,2 mg/kg

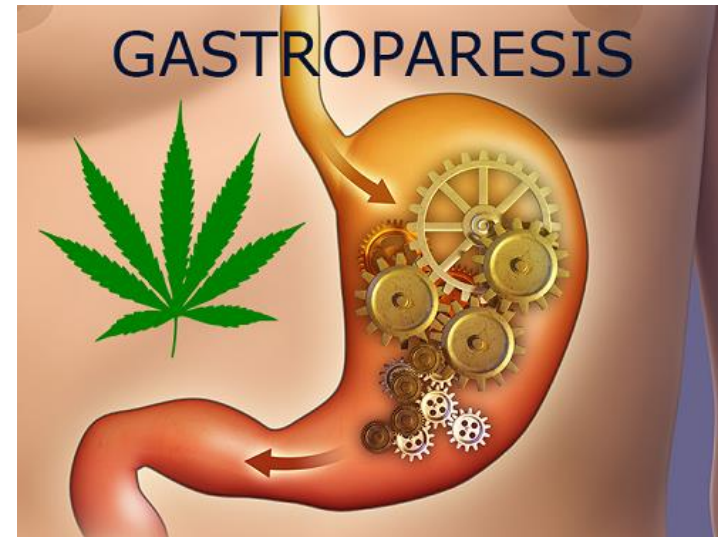


Gecommentarieerd
Geneesmiddelenrepertorium 1991



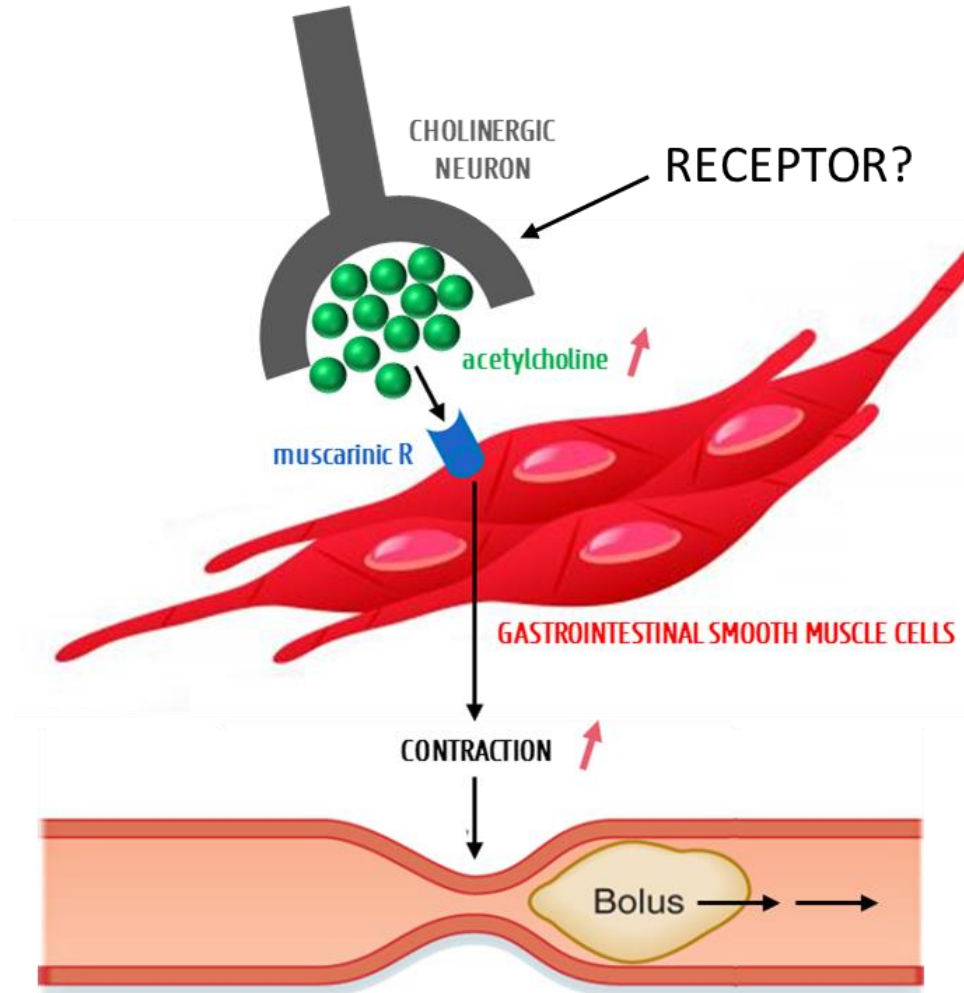
Sphincter open, allowing reflux

GERD



GASTROPARESIS

GASTROPROKINETIC = enhance GI motility



Bradley et al.
Neuropharmacology 1986
5-HT₁R 5-HT₂R 5-HT₃R

MOLECULAR PHARMACOLOGY, 34:880-887

A Nonclassical 5-Hydroxytryptamine Receptor Positively Coupled with Adenylate Cyclase in the Central Nervous System

ALINE DUMUIS, ROCHDI BOUHELAL,¹ MICHÈLE SEBBEN, ROBERT CORY, and JOËL BOCKAERT

Centre CNRS-INSERM de Pharmacologie-Endocrinologie, 34094 Montpellier Cedex 2, France

Received March 18, 1988; Accepted September 26, 1988

5-HT₄ R

Naunyn Schmiedebergs Arch Pharmacol. 1993 May;347(5):464-70.

Cisapride and a structural analogue, R 76,186, are 5-hydroxytryptamine₄ (5-HT₄) receptor agonists on the guinea-pig colon ascendens.

Briejer MR¹, Akkermans LM, Meulemans AL, Lefebvre RA, Schuurkes JA.

Neurogastroenterol Motil (2005) 17, 366–375

doi: 10.1111/j.1365-2982.2005.00621.x

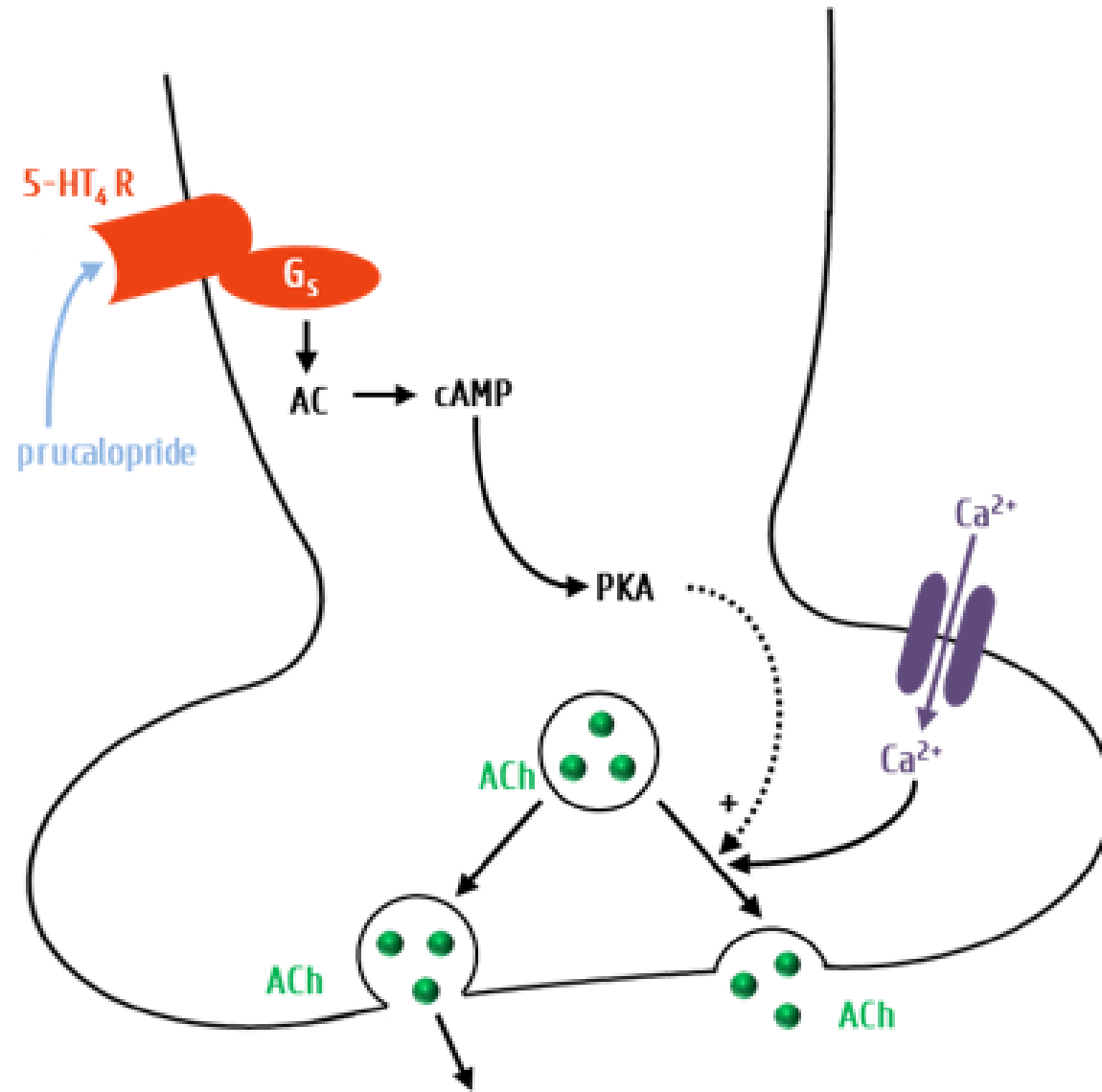
5-HT₄ receptors located on cholinergic nerves in human colon circular muscle

P. G. LECLERE,^{*,‡} N. H. PRINS,^{†,‡} J. A. J. SCHUURKES,[†] R. A. LEFEBVRE^{*}

^{*}Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium

[†]Department of Gastrointestinal Pharmacology, Johnson & Johnson Pharmaceutical Research & Development, A Division of Janssen Pharmaceutica N.V., Beerse, Belgium

POSTGANGLIONIC CHOLINERGIC NEURON





The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Volume 335:290-291 July 25, 1996 Number 4

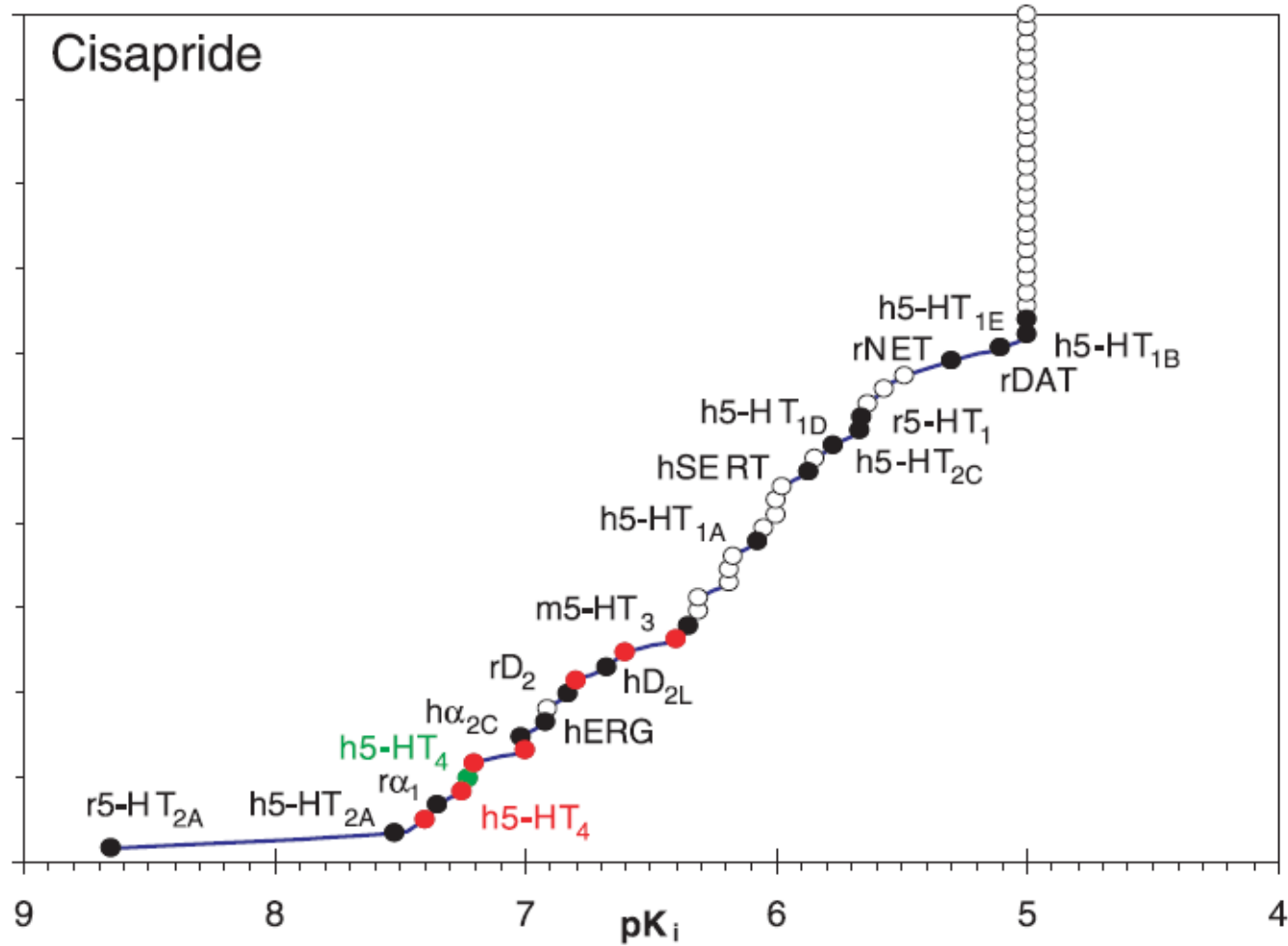
Cisapride and Fatal Arrhythmia

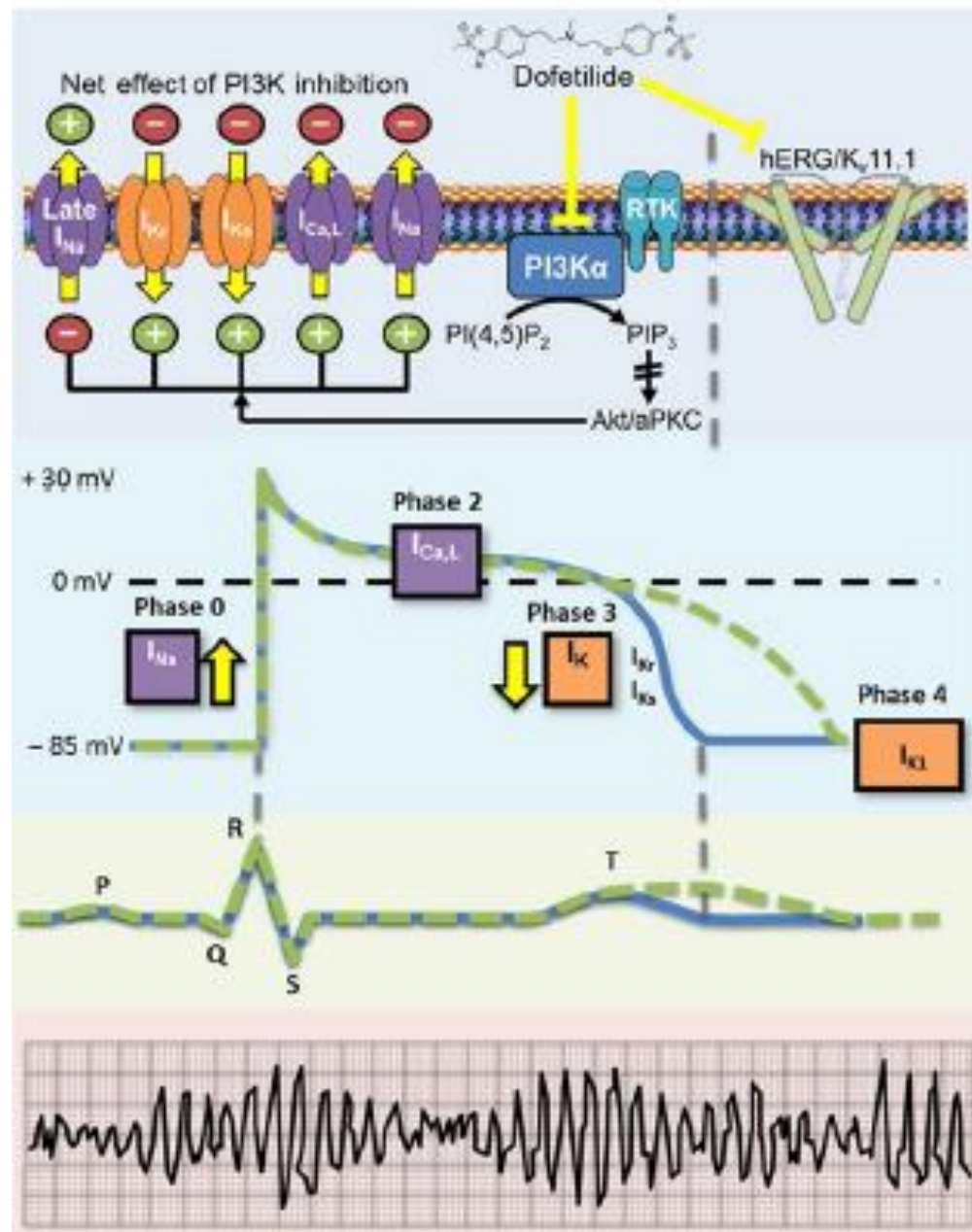
FDA 9.1993 – 4.1996

34 Torsade de pointes

23 QT-prolongation

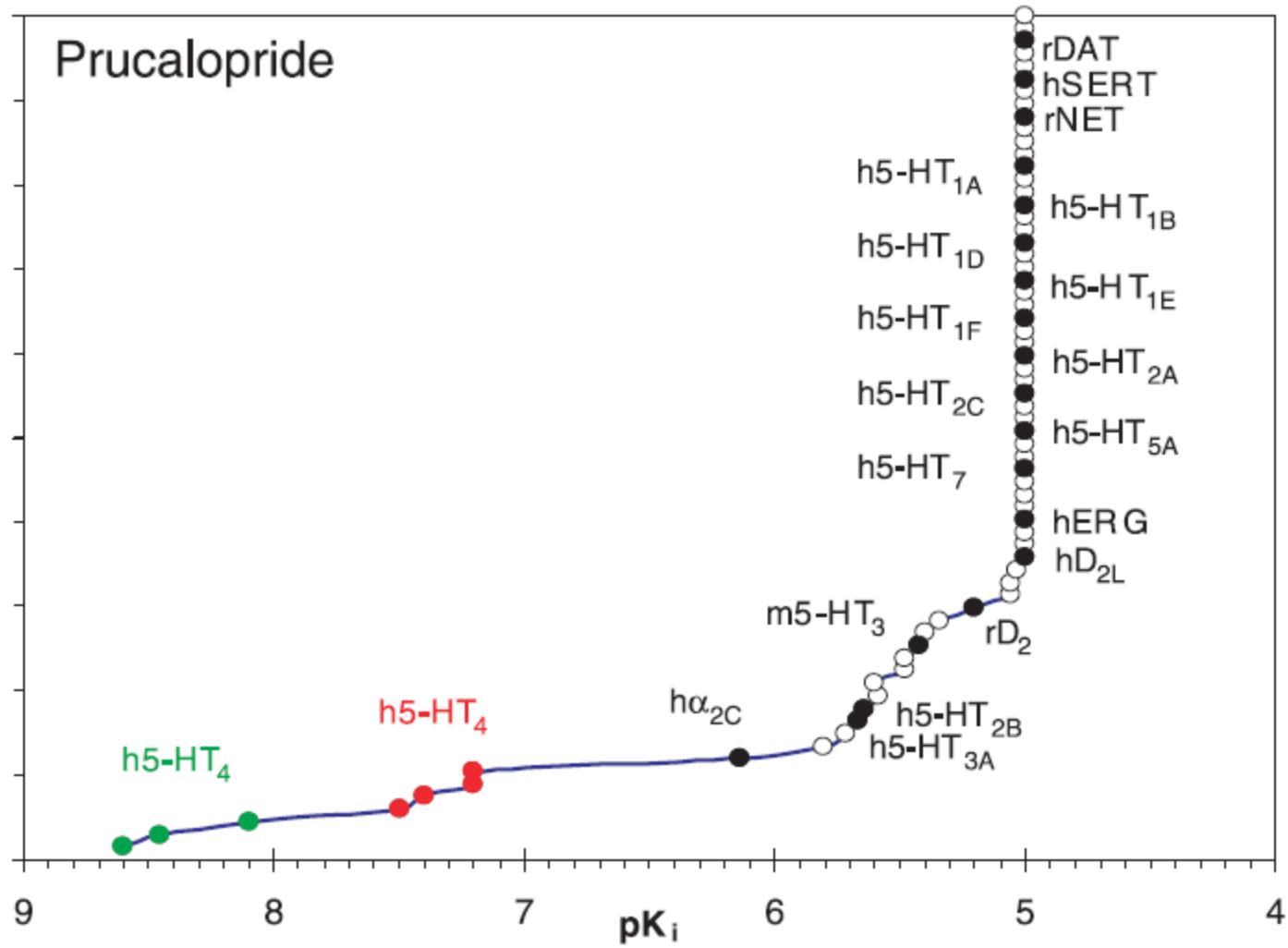
AFFINITY AT RECEPTORS AND CHANNELS



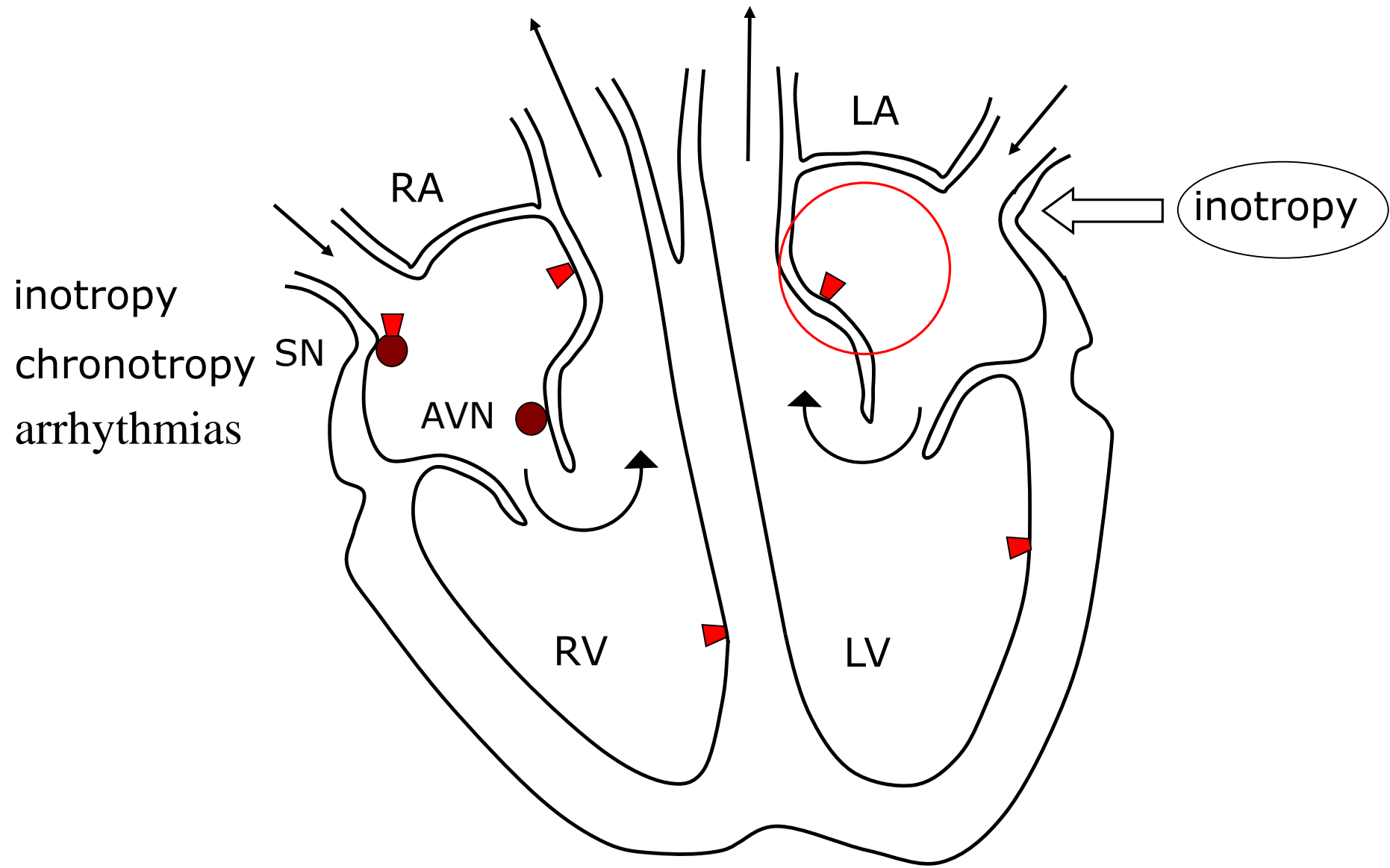


Giudicessi et al.; NGM 2018

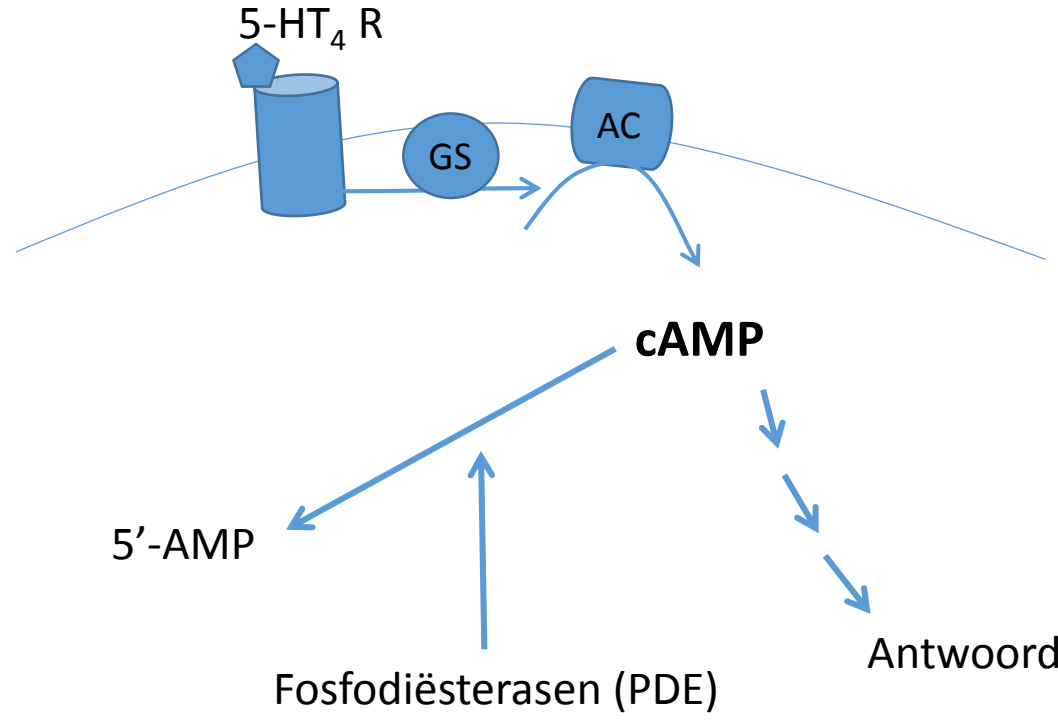
AFFINITY AT RECEPTORS AND CHANNELS



Localisation: heart



Controle van de cardiale 5-HT₄ receptor



De Maeyer et al.
Brit. J. Pharmacol. 2006

Mens

PDE 3

Afzal et al.

Brit. J. Pharmacol. 2008

Prucalopride (Resolor®)

Gecommentarieerd Geneesmiddelenrepertorium 2011

BIJZONDERE VOORZORGEN

- Gezien de chemische verwantschap met cisapride, waarvan het risico van verlenging van het QT-interval en “torsades de pointes” goed gekend is, is voorzichtigheid geboden bij patiënten met antecedenten van aritmie of bij gelijktijdige behandeling met andere geneesmiddelen die het QT-interval kunnen verlengen (zie “Ongewenste effecten” in inleiding).

Gecommentarieerd Geneesmiddelenrepertorium 2018

INDICATIES

- Chronische constipatie
- De juiste plaats van prucalopride is onduidelijk.

SELECTIVE 5-HT₄ RECEPTOR AGONISTS IN DEVELOPMENT

DA-6886
(Lee *et al.*, 2014)

phase 1, recruiting

constipation-predominant irritable bowel syndrome

velusetrag (TD-5108)
(Goldberg *et al.*, 2010; Manini
et al., 2010; Ahn *et al.*, 2015)

phase 2, completed

constipation, gastroparesis

naronapride (ATI-7505)
(Bowersox *et al.*, 2011)

phase 2, terminated

chronic idiopathic constipation

YKP10811
(Shin *et al.*, 2015)

phase 2, completed

constipation-predominant irritable bowel syndrome,
functional constipation

PF-00885706
(Komada *et al.*, 2009)

phase 2, terminated (on clinical hold
by the sponsor due to operational
reasons)

gastro-esophageal reflux disease

Theravance Biopharma Announces Positive Top-Line Results from **Phase 2b Study** of **Velusetrag** (TD-5108) in Patients with **Gastroparesis**

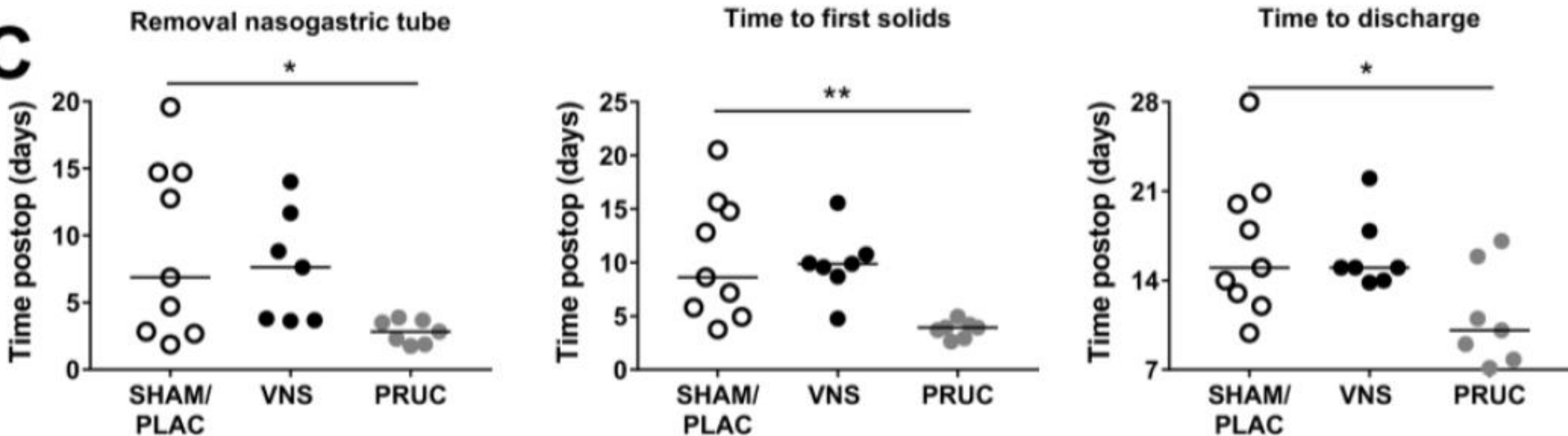
08/02/17

Improvements in Symptoms and Normalized Gastric Emptying Demonstrated in both Diabetic and Idiopathic Gastroparesis Patients

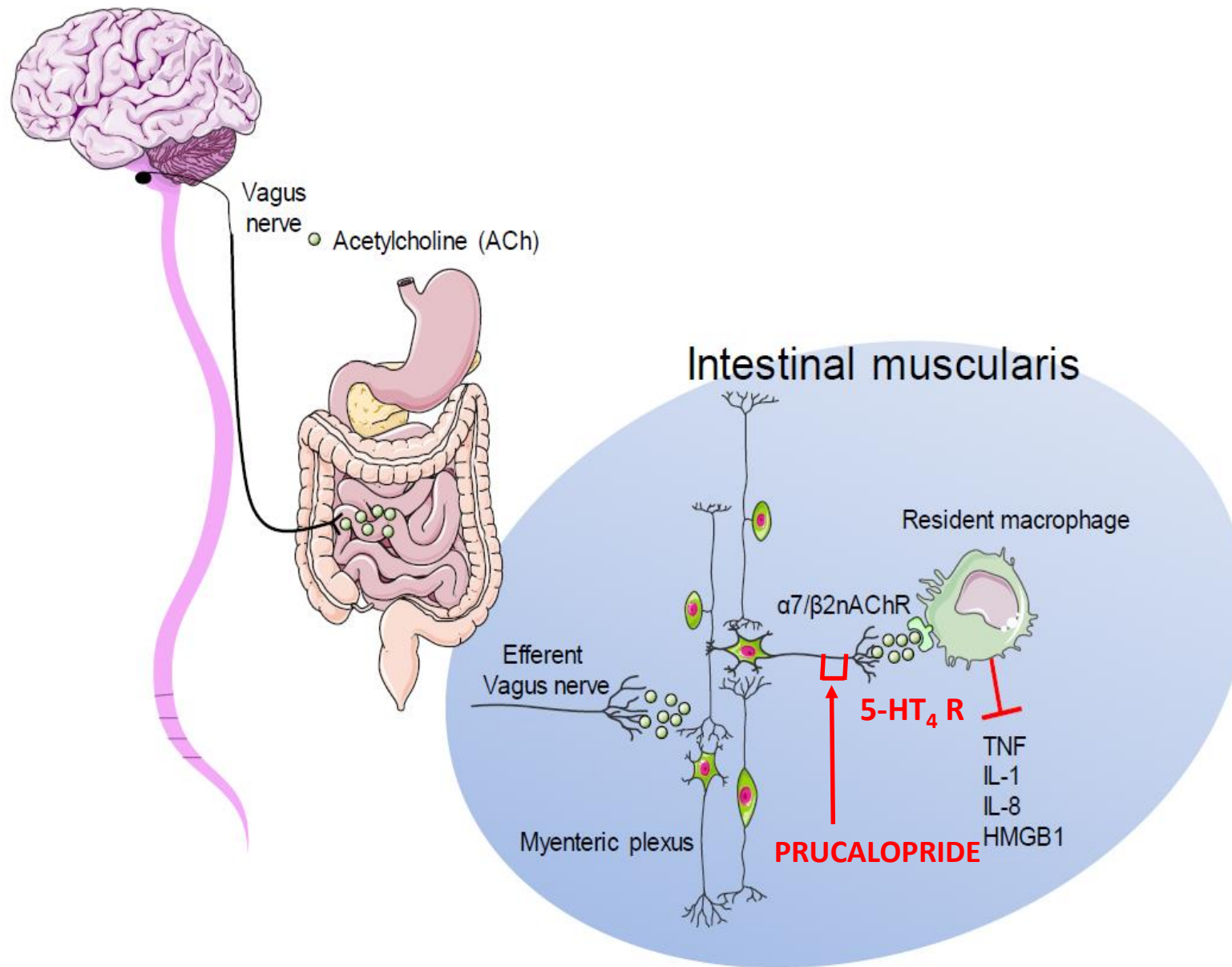
DUBLIN, Ireland, Aug. 2, 2017 /PRNewswire/ -- Theravance Biopharma, Inc. (NASDAQ: TBPH) ("Theravance Biopharma" or the "Company") today announced positive results from **a 12-week, Phase 2b study of velusetrag** (TD-5108), an oral investigational drug in development for the treatment of patients with diabetic and idiopathic gastroparesis. Top-line results from the study demonstrated statistically significant improvements in gastroparesis symptoms and gastric emptying **in patients receiving 5 mg of velusetrag as compared to placebo**. Additionally, velusetrag was shown to be generally well-tolerated, with 5 mg and placebo having comparable rates of adverse events (AEs) and serious adverse events (SAEs).

Prucalopride for postoperative ileus 2 mg at 16 and 2 h prior to surgery

C



Stakenborg N.; PhD, KUL 2018



Clinical Trials.gov

Prucalopride in postoperative ileus

Sponsor : University of Auckland, New Zealand

Double-blinded randomised placebo-controlled trial.

- Patients : 150, colonic surgery
- Treatment : 2 mg 2 – 3 h prior to surgery
2 mg/day postoperatively
- Status : Recruiting
- Estimated completion date : February 2019



5-Hydroxytryptamine (5-HT)₄ receptors in *post mortem* human brain tissue: distribution, pharmacology and effects of neurodegenerative diseases

G.P. Reynolds, S.L. Mason, A. Meldrum, S. De Keizer, *H. Parnes, †R.M. Eglen & ¹†E.H.F. Wong

Table 3 Levels of [³H]-GR 113808 binding in *post mortem* brain tissue in various neurodegenerative diseases

<i>Alzheimer's disease</i>	<i>Binding</i> (fmol mg ⁻¹ tissue)	<i>Ratio^a</i>	<i>Age</i> (yrs)	<i>Sex</i>	<i>Post mortem delay</i> (h)
Hippocampus					
Controls	2.34 ± 0.62	0.68 ± 0.25	75 ± 10	4F/4M	28 ± 11
Patients	0.78 ± 0.61***	0.64 ± 0.25	82 ± 8	6F/4M	33 ± 26

VRX-03011, a novel 5-HT₄ agonist, enhances memory and hippocampal acetylcholine efflux

Eric G. Mohler^{a,b,1}, Sharon Shacham^c, Silvia Noiman^c,
Frank Lezoualc'h^{d,e}, Sylvain Robert^{d,e}, Monique Gastineau^{d,e}, Joseph Rutkowski^c,
Yael Marantz^c, Aline Dumuis^f, Joel Bockaert^f, Paul E. Gold^{b,g}, Michael E. Ragozzino^{a,h,*}

Neurobiology of Aging 34 (2013) 1779–1789

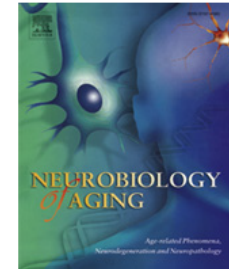


ELSEVIER

Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging



Chronic 5-HT₄ receptor activation decreases A β production and deposition in hAPP/PS1 mice

Ina Tesseur^{a,b,*}, Anna A. Pimenova^{a,b}, Adrian C. Lo^d, Marta Ciesielska^{a,b}, Stefan F. Lichtenthaler^c,
Joris H. De Maeyer^e, Jan A.J. Schuurkes^e, Rudi D'Hooge^d, Bart De Strooper^{a,b,*}

The potential for 5-HT₄ receptor agonists to offer clinical benefit for the treatment of AD, and other dementias, is supported by data from a small Phase 2 study in patients with mild to moderate AD with the selective 5-HT₄ receptor agonist, PRX-03140 (Megerian, 2008). PRX-03140 was associated with a statistically significant, 3.6 point improvement in the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) score of AD patients, versus a 0.9 point worsening for placebo, after only two weeks of therapy (Megerian, 2008).

Met dank aan

BEERSE

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TURNHOUT

Movetis/Shire-Movetis

Jan Schuurkes

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Pieter Janssen

GENT

Heymans Instituut

Pascal Leclere

Joris De Maeyer

Catherine Delesalle

Sabine Weninger

Filip de Vin

Sze Men Choi

Evelien Priem

Vicky Pauwelyn

Inge Van Colen

Els Van Deynse