GIDAC November 17, 2011

Evaluation of Cardiac Safety for Serotonin Receptor (5-HT_4) Agonists as GI Therapies

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Office of New Drugs III
Center for Drug Evaluation and Review
Food and Drug Administration

Outline

- **Introduction**
- **Guidance for Cardiac Assessment:**
  - ICH guidance S7A & S7B (nonclinical)
  - ICH guidance E 14 (clinical)
- **Other considerations:**
  - Drug-Drug Interactions: e.g. *in vitro/in vivo* cytochrome P450 evaluation
  - In vitro human platelet studies
- **Questions for GIDAC Advisory Committee**

Purpose

To provide recommendations to the Agency on the design and size of premarketing cardiovascular safety development programs necessary to support approval of products in the class of serotonin (5-hydroxytryptamine) receptor 4 (5-HT_4) agonists for the proposed indications of:

- chronic idiopathic (of unknown cause) constipation (CIC),
- constipation predominant irritable bowel syndrome (IBS-C),
- gastroparesis, and
- gastroesophageal reflux disease that does not respond to a proton pump inhibitor

Considerations for Developing GIDAC Agenda

- **New 5-HT_4 agonists are in the IND phase**
- **Advice applicable to all new 5-HT_4 agonist in development for GI indications**
- **Open AC**
  - FDA invited sponsors, those presenting have accepted the invitation
  - FDA has been permitted to present nonclinical and clinical data for ATI-7505 (naronapride).
- **Transparency regarding advice for CV risk assessment of new drugs in this class.**
  - Major Adverse Cardiac Events (MACE)
- **Review historical highlights of cardiovascular adverse events in this class**

Considerations for Cardiovascular Safety Evaluations in Non-Cardiac Drug Products

- Cardiovascular safety in the drug class
- Nonclinical and Phase 1&2 clinical evaluations
- Unmet medical need
- Population for which drug is being developed
  - context of use
- Assessment of efficacy and safety
  - Risk/Benefit Assessment

GI Experience with 5-HT4 Agonist Class

- **Cisapride (Propulsid – 1993-2000)**
  - Cardiac arrhythmias (QT prolongation) associated with Drug-Drug Interactions due to metabolic pathway (cytochrome P450)

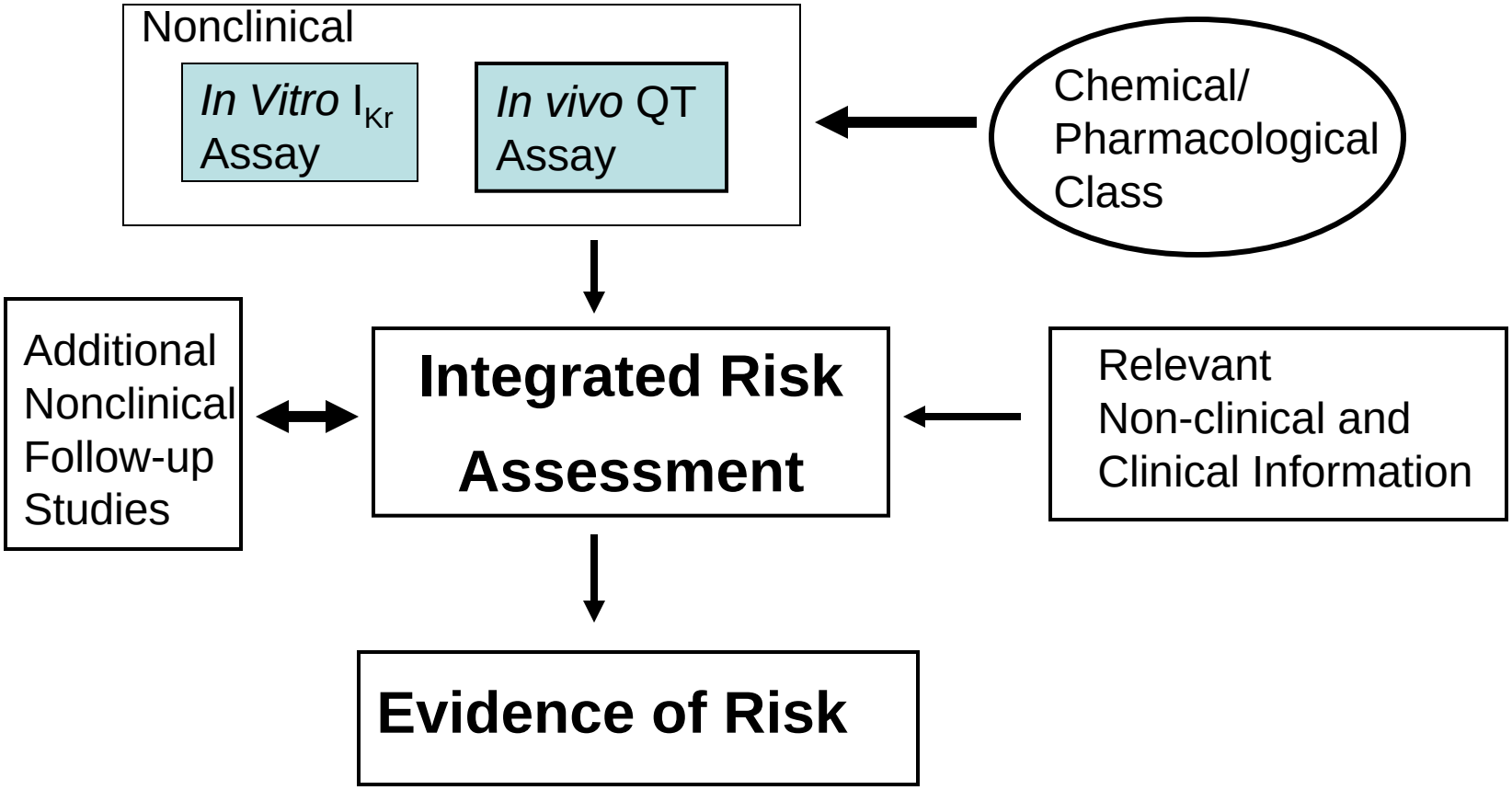
- **Tegaserod (Zelnorm - 2002-2007)**
  - Excess ischemic cardiovascular events

Both Drugs are no longer on the market in the U.S.

ICH Nonclinical Guidance: S7A & S7B

- **S7A:** evaluation of drug effects on the cardiovascular system (2001)
  - (e.g., cardiac output, ventricular contractility, vascular resistance, and effects of endogenous and/or exogenous substances on the cardiovascular responses).
- **S7B:** studies for the nonclinical evaluation of the potential for QT interval prolongation for drugs. (2005)
  - *In-vitro* Ikr assay (hERG) and *In-vivo* QT assay (ECG in canine)

Testing Strategy for CV effects



[1] Adapted from *Guidance for Industry: S7B*; October 2005

ICH Guidance E 14:

Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Oct 2005)

- Clinical studies to assess the potential of a drug to delay cardiac repolarization
  - Design, conduct, analysis, and interpretation of
- An adequate premarketing investigation of the safety of a new pharmaceutical agent should include rigorous characterization of its effects on the QT/QTc interval.
  - prolongation of the QT/QTc interval is the ECG finding associated with the increased susceptibility to these arrhythmias

Other Factors to Consider

- **Drug-Drug interactions:**
  - may result in significantly higher exposure to the parent compound and/or its metabolites potentially altering the safety profile.
  - Cytochrome P450 enzyme system
- **Additional clinical pharmacology studies for safety:**
  - Thorough QT (tQT) and
  - *in vitro* human platelet aggregation studies:
    - suggestive but not validated marker and its direct clinical application is unknown

Evidence of CV Risk During Drug Development

- Nonclinical study results
- Clinical pharmacology study results
  - ADME
  - Drug-drug interactions
  - Platelet studies
- Clinical Trials:
  - Phase 2&3 – underpowered to detect rare events

Clinical Cardiovascular Safety Assessments

- **Is a dedicated CV risk assessment warranted?**
- **Dedicated CV safety studies are impractical to perform on all drugs and for all indications**
  - the evidence implicating a drug or drug class must be carefully weighed prior to requiring studies before they are approved
- **if CV safety trials are considered to be necessary prior to approval, what level of CV risk should to be excluded?**

Statistical Considerations for Design of CV Safety Studies

- **Dedicated, randomized cardiovascular (CV) outcome trials**
  - Gold standard for determining the hazard ratio (HR)
  - Comparison of investigational treatment relative to a well understood control
  - typically designed as event-driven trials to rule out an excess risk measured by an upper bound of a 95% confidence interval for the hazard ratio
- **Non-enriched populations with a relatively low CV event rate require more patient years to be studied compared to enriched populations**
  - to observe the same number of CV events and
  - To achieve the same statistical power for a pre-specified hazard ratio margin

GIDAC Questions

November 17, 2011

1. For new products in the class, can nonclinical, clinical pharmacology, and clinical data, such as those presented for the newer 5-HT_4 agonists, dispel (i.e., alleviate the need for a “dedicated” safety study) the cardiovascular safety concerns (e.g., prolonged QT interval, ischemic events) raised by the clinical safety experience of the previously approved 5-HT_4 agonists?
   - If yes, specify on which data you are relying.

GIDAC Questions (cont'd)

November 17, 2011

2. Among the uses for which 5-HT_4 agonists are being developed, (chronic-idiopathic constipation, constipation predominant irritable bowel syndrome, gastroparesis, other functional motility disorders), is there an indication for which you would be unwilling to accept an increased cardiovascular risk?
   a. If yes, which ones and why?
   b. For those uses that you are willing to accept an increased risk, state the level of risk you would find unacceptable (e.g., Hazard Ratio)?

GIDAC Questions (cont'd)

(November 17, 2011)

3. Does the Committee recommend a "dedicated" cardiovascular safety trial (a trial in which the primary objective is to define cardiovascular risk) to demonstrate the safety of 5-HT_4 agonists?

GIDAC Questions (cont'd)

(November 17, 2011)

4. If you voted yes to Question #3, for each of the following populations, discuss whether you recommend that the trial be conducted prior to or post-approval?
   a. CIC (chronic-idiopathic constipation)
   b. IBS-C (constipation predominant irritable bowel syndrome)
   c. Gastroparesis
   d. Other functional motility diseases

GIDAC Questions (cont'd)

November 17, 2011

5. Discuss the characteristics which would define the "enriched population" for a "dedicated" cardiovascular study.

6. What elements to assess cardiovascular safety should be included in a standard phase 3 efficacy trial to assure accurate ascertainment of cardiovascular adverse events?

Background and Historical Overview

Aisha Peterson Johnson. MD, MPH, MBA
Division of Gastrointestinal and Inborn Error Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

Background and Historical Overview

Gastrointestinal Diseases Advisory Committee Meeting (GIDAC)

November 17, 2011

Aisha Peterson Johnson MD, MPH, MBA
Division of Gastroenterology Products

5-hydroxytryptamine (serotonin)

- Ubiquitous signaling molecule
- Largest amount of 5-HT (~90%) found in enteroendocrine cells of the GI mucosa
- Signaling molecule in the brain-gut axis
- Seven main receptor subtypes

5-HT Receptor Subtypes

Subtype	Location
5-HT_1	Blood vessels, CNS
5-HT_2	Blood Vessels , CNS , GI Tract Platelets, PNS , Smooth Muscle
5-HT_3	CNS, GI Tract, PNS
5-HT_4	CNS, GI Tract, PNS
5-HT_5	CNS
5-HT_6	CNS
5-HT_7	Blood Vessels , CNS , GI Tract

CNS = central nervous system; PNS = peripheral nervous system;
GI= Gastrointestinal

5-HT Receptor Subtypes and Vascular Function

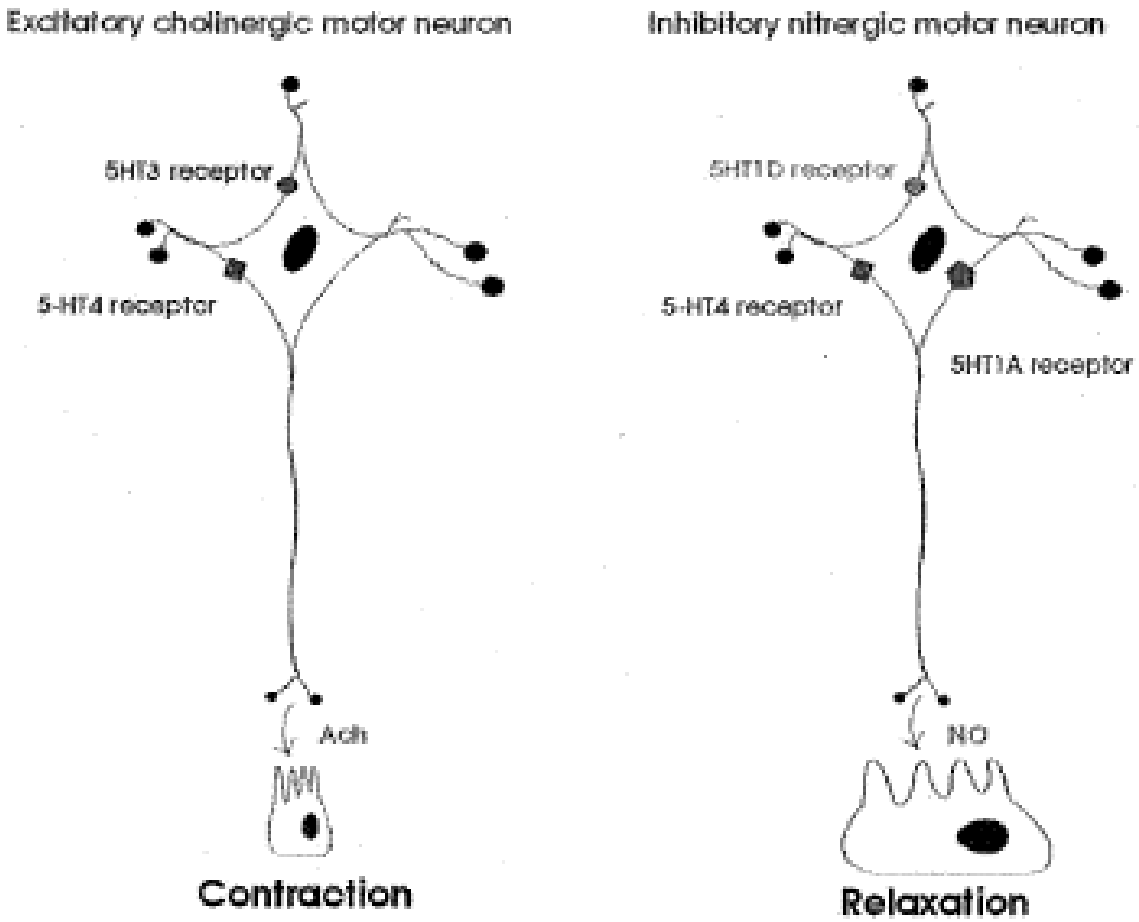
Artery		**Vein**	
Contraction	Relaxation	Contraction	Relaxation
5-HT_{1B} 5-HT_{2A}	5-HT_{1D} 5-HT_{7}	5-HT_{1B}	5-HT_{1D} 5-HT_{2B} 5-HT_{4} 5-HT_{7}

5-HT_4 Receptor Agonists

INCREASE GI MOTILITY

- Stimulate the peristaltic reflex
- Elicit contractile activity
- Stimulate release of inhibitory neuro transmitters that relax smooth muscle

Roles of 5-HT Receptors in the GI Tract



Sikander A, Rana S, Prasad K, Clinica Chemica Acta 403: 47-55", 2009

Potential 5-HT_4 agonist Uses

- CIC
- GERD, unresponsive to PPIs
- Postprandial distress syndrome
- Gastroparesis
- Functional dyspepsia
- Irritable bowel syndrome-constipation (IBS-C)
- Opioid induced constipation (OIC)

Limited Available Therapies

Condition	Approved Therapies
IBS-C	Lubiprostone (Amitiza®)
Chronic Idiopathic Constipation	Lactulose, Lubiprostone
Diabetic Gastroparesis	Metoclopramide (Reglan®)

Prevalence Estimates

GERD	FUNCTIONAL DYSPEPSIA
• $17B spent worldwide each year • Est. 10% of population experiences symptoms daily • Estimated 20-25% of patients (6.0-7.5M in US) do not obtain adequate relief from stomach acid-reducing treatments	• Est. 35-44M people (US) with symptoms • Major subtype is postprandial distress syndrome (PDS) defined by: ○ Postprandial fullness ○ Early satiety, or ○ Upper abdominal bloating
GASTROPARESIS	**LOWER GI INDICATIONS**
• Est. 5M people (US) with symptoms • High prevalence in diabetic patients • No existing therapies adequately meet this patient need	• Est. 36M people (US) with chronic constipation • Est. 5.5M adults (US) suffer from IBS with constipation • Est. 28M adults (US) suffer from IBS with intermittent constipation

Reproduced from Aryx Product fact sheet for Naronapride

History of 5-HT_4 Receptor Agonists and Cardiovascular Adverse Events

Cisapride

Indication: nocturnal heartburn due to GERD

Cardiac Safety Issue:
QT prolongation

Removed from U.S. market 7/14/2000

Non-selective: 5-HT_2 and 5-HT_3 antagonist
hERG channel blockade

Tegaserod (Zelnorm)

Indications: ♀ IBS-C (24-Jul-2002)
< 65 yrs old CIC (20-Aug-2004)

Cardiac Safety Issue:

Imbalance in ischemic cardiovascular events compared with placebo seen in meta-analysis of 29 post-marketing clinical trials

Zelnorm 13/11,614 = 0.11%

Placebo 1/7,031 = 0.01%

Removed from U.S. Market 3/30/2007

Order of Today's Presentations

Order of Presentations

- Johnson & Johnson
  - (Cisapride, [Propulsid])
- FDA
  - (Tegaserod, [Zelnorm])
- Theravance
  - (TD-5108/TD-8954)
- FDA
  - (ATI-7505, Naronapride)

Tegaserod
Nonclinical Studies

Gastrointestinal Drugs Advisory Committee Meeting

November 17, 2011

Ke Zhang, Ph.D.
Division of Gastroenterology and Inborn Errors Products

Tegaserod - Nonclinical Studies

- **Serotonin receptor selectivity studies**

- ***In vitro* cardiac studies**

  Effect on the hERG channel
  Effect on the action potentials
  Effect on the isolated coronary artery

- ***In vivo* cardiovascular safety pharmacology studies**

Serotonin Receptor Selectivity Studies

- Tegaserod (Zelnorm / HTF-919) is a 5-HT_4 partial agonist with moderate to high affinities for 5-HT_1 receptors

Binding Affinities for Different Serotonin Receptors

	5-HT_4	5-HT_{1A}	5-HT_{1C}	5-HT_{1D}	5-HT_2
	K_D (nM)	K_D (nM)	K_D (nM)	K_D (nM)	K_D (nM)
HTF 919	20	324	68	20	2512
Cisapride	60	1906	501	5495	7

Source: Pharmacology Review of NDA 21-200

K_D = dissociation constant

5-HT_1 and 5-HT_2 subtypes located in coronary artery, vasoconstriction

In vitro Cardiac Electrophysiology Studies

- **hERG channel in HEK293 cells**

IC_{50} for Tegaserod = 13 μM

IC_{50} for Cisapride = 0.044 μM

- **Guinea pig ventricular papillary muscle**

No effect on action potentials up to 1 μM

For Reference:

Human plasma level (Cmax) ~ 0.01 μM following 6 mg/BID

Isolated Coronary Artery Studies

- Tegaserod had no contractile activity on the isolated coronary arteries from pigs (30 μM), non-human primates (10 μM), and humans (30 μM)

- Tegaserod produced a small contractile response in canine coronary arteries at 5-10 μM

(Higgins et al, Naunyn-Schmiedeberg's *Arch Pharmacol*, September 8, 2011)

Isolated Coronary Artery Studies (Human)

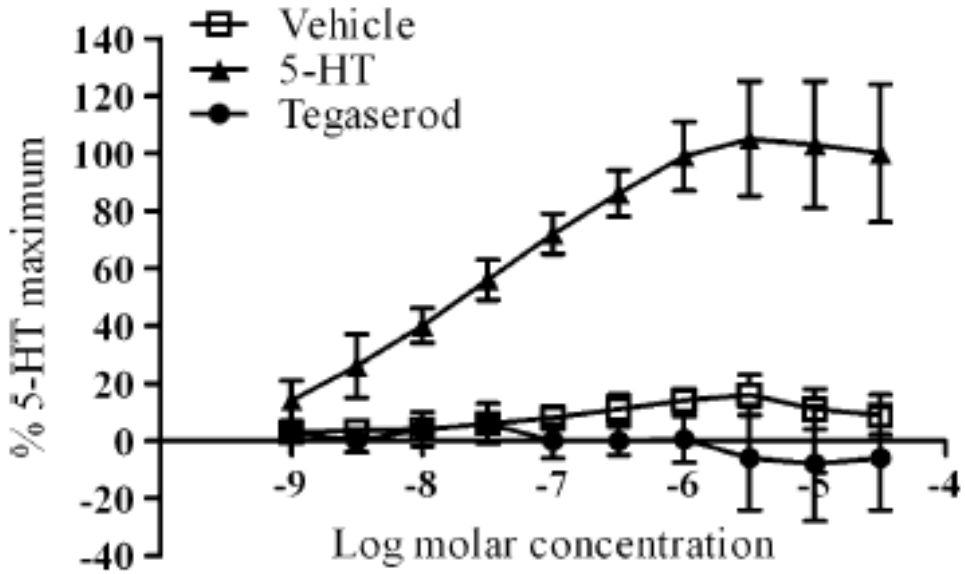
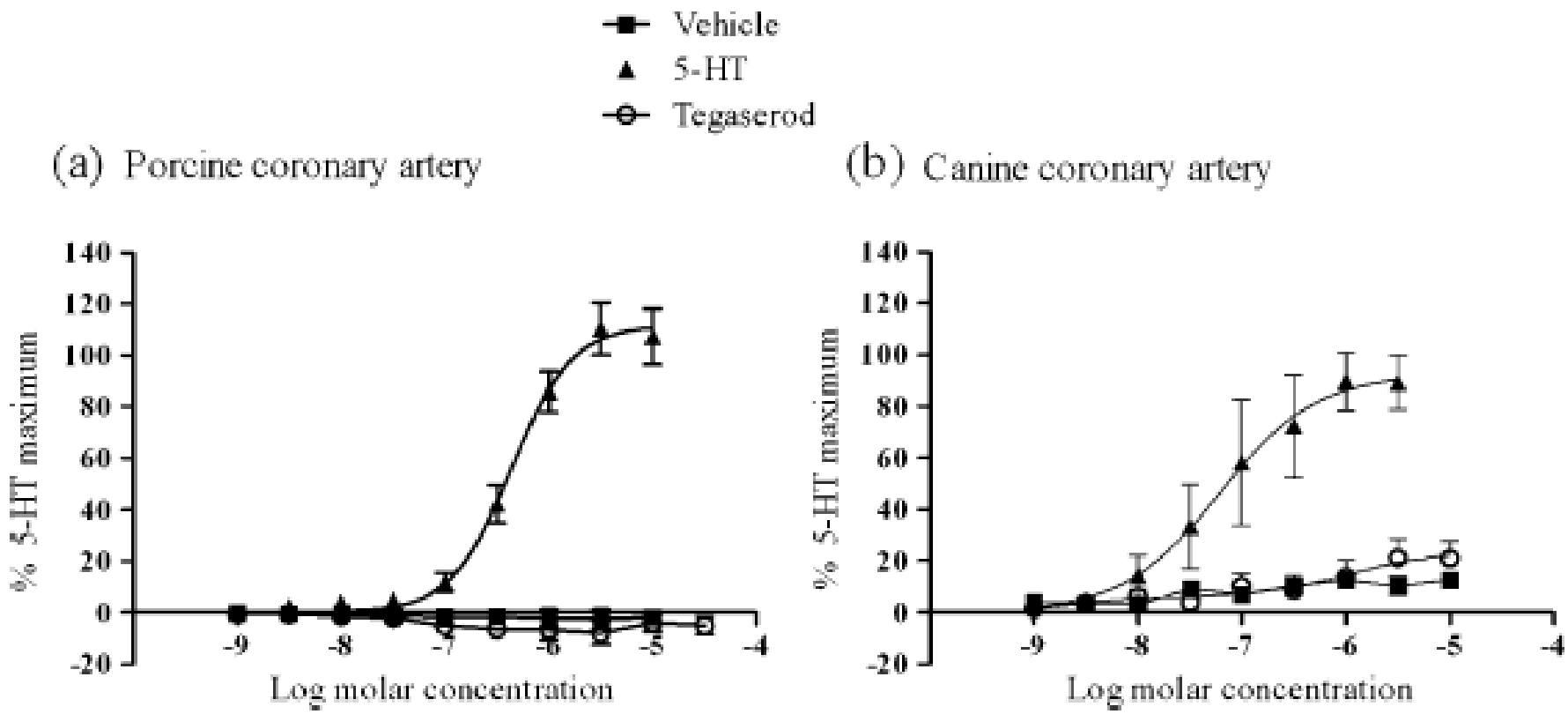


Fig. 1 Effects of 5-HT, tegaserod, and vehicle on resting tension of the human isolated coronary artery (n=4 or 5). Data are expressed as mean (±s.e. mean) percentages of the 5-HT-induced maximum contractile response

Higgins et al, Naunyn-Schmiedeberg's *Arch Pharmacol*, 2011

Isolated Coronary Artery Studies



Higgins et al, Naunyn-Schmiedeberg's *Arch Pharmacol*, 2011

In vivo Cardiovascular Safety Studies in dogs

- Study with intraduodenal doses up to 10 mg/kg
- Study with oral doses up to 10 mg/kg
- No effects on blood pressure, heart rate, cardiac output, ECG (QT interval)

For reference:
Dog Cmax: 401 ng/ml for males
277 ng/ml for females at 10 mg/kg
Human Cmax: ~ 6 ng/ml or 0.01 μM following 6 mg/BID

In vivo Cardiovascular Safety Studies (repeated dose toxicity studies in dogs)

- 2-week I.V. toxicity study at doses up to 1 mg/kg/day
- 26-week oral toxicity study at doses up to 60 mg/kg/day
- 52-week oral toxicity study at doses up to 70 mg/kg/day

No effect on ECG (heart rate and QT interval)

No histopathological changes in the heart

Clinical dose: 6 mg BID or 0.2 mg/kg/day (60 Kg body weight assumed)

Tegaserod: Nonclinical studies Summary

- 5-HT_4 receptor partial agonist with moderate to high affinity for 5-HT_1 receptor subtypes
- Tegaserod is a weak inhibitor of hERG potassium currents, but did not induce QT prolongation in *in vivo* studies in dogs
- Tegaserod did not induce contractions in the isolated coronary arteries from pigs, dogs, non-human primates, and humans at clinically relevant concentrations or doses

Tegaserod (Zelnorm®) Clinical pharmacology

Gastrointestinal Drugs Advisory Committee Meeting
November 17, 2011

Insook Kim, Ph.D.
Office of Clinical Pharmacology
CDER/FDA

Outline

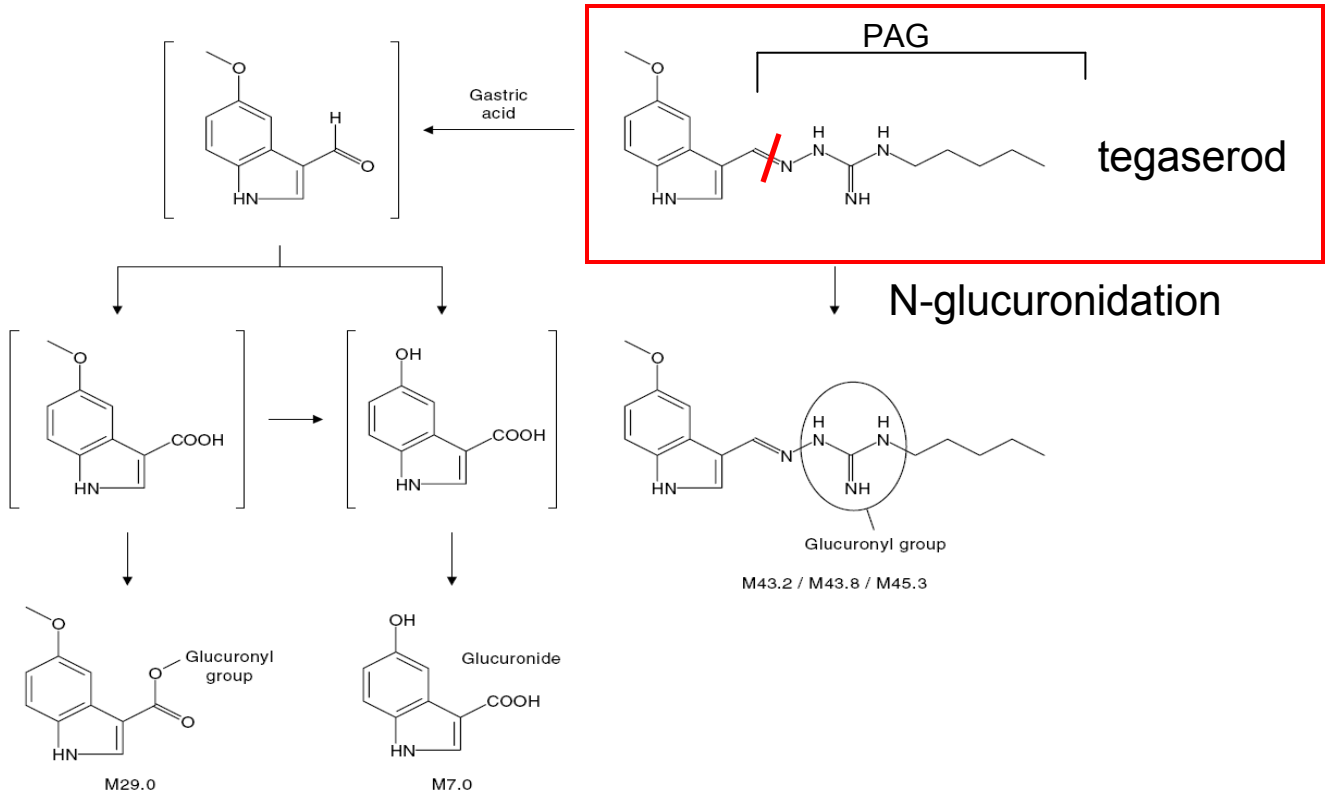
- Pharmacokinetics of Tegaserod
  - Metabolic pathway
- Drug interactions
- Effect of tegaserod on QT prolongation
- Effect of tegaserod on platelet aggregation

Tegaserod

- Approved dose: 6 mg twice daily
- Rapid absorption: Tmax ~ 1 hr
- Oral bioavailability is about 10%.
  - Eliminated mainly by metabolism
  - Unchanged tegaserod was undetectable in urine
- Metabolized mainly via two pathways
  - Acid hydrolysis in the stomach
  - Direct glucuronidation

Metabolic pathway

Pre-systemic in stomach



Major metabolite
M29

PAG: pentylaminoguanidine

Clin Pharmacokinet 2002; 41 (13): 1021-1042

Drug interactions

- In vivo drug interaction potential with concomitant CYP enzyme inhibitors appears to be low
  - Insignificant contribution of CYP enzymes in metabolism in human

- Concomitant P-gp inhibitor may increase systemic exposure of tegaserod
  - Tegaserod is a substrate of p-glycoprotein efflux transporter in vitro
  - Systemic exposure was increased by 74% with concomitant quinidine in human[1]

[1] The study was conducted after approval in the US.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000621/WC500058845.pdf

Effect of tegaserod on QT prolongation

- No thorough QT study was conducted
  - Guidance for TQT study published in 2005
- Evaluated in IBS-C patients during phase 3 trials[1,2]
  - Placebo, 2 mg or 6 mg tegaserod twice daily
  - Standard 12-lead ECG at 1.5-2.5 hours after the first and the last dose of tegaserod
- No clinically significant effect was noted
  - Change in QTc interval from baseline comparable among treatments
  - Similar rate of new or worsening QTc interval prolongation among treatments
  - No dose-dependent effect
  - No positive control

[1]Novartis (2000) Zelmac (tegaserod) Advisory Committee Briefing Document http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3627b1a.pdf

[2] NDA 21-200 Medical Review (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-200_Zelnorm.cfm)

Effect of Tegaserod on ECG

- In a small subgroup of patients >65 years the overall rate of ECG abnormalities (primarily ST-segment depression and/or T-wave alterations) was numerically higher in the tegaserod group than in the placebo group; however, evidence for ischemia is unclear given the small number of subjects in this subgroup[1]

[1]Novartis (2000) Zelmac (tegaserod) Advisory Committee Briefing Document

Effect on Platelet Aggregation In Vitro

- Two published studies (2010, 2011)
- Light Transmission Aggregometry for platelet aggregation
  - Light transmission through platelet rich plasma increases upon induction of platelet aggregation
  - Light transmission through platelet poor plasma sets a maximum
  - Determine % platelet aggregation with or without tegaserod

- Study design
  - Blood from healthy subjects
  - Pre-incubation of tegaserod in blood for 1 h
  - 10, 33, and 100 nM tegaserod
  - Platelet rich plasma was prepared and platelet aggregation was induced by agonist(s)

Increased platelet aggregation with tegaserod[1]

Agonist	Tegaserod concentration / Platelet Aggregation (%)				
	Vehicle	10 nM	33 nM	100 nM	Ref. Range
ADP 5 μM§	64.9 ±5 .4	74.8 ± 13.4*	75.4 ± 11.2*	79.3 ± 11.0*	60-82
ADP 20 μM§	74.7 ± 5.3	77.8 ± 6.7*	81.6 ± 7.8*	87.1 ± 7.6*	68-88
Collagen 1 μg/mL§	75.1 ± 5.2	77.1 ± 6.4	82.5 ± 6.9*	90.3 ± 7.3*	68-84
Collagen 5 μg/mL§	81.3 ± 7.0	84.9 ± 7.7	88.7 ± 8.3*	90.1 ± 8.6*	79-92
TRAP 20μM	88.3 ± 1.4	88.6 ± 1.9	89.0 ± 1.5	88.9 ± 3.2	78-93
Epinephrine 5 μM§	82.7 ± 6.9	85.6 ± 8.5	90.0 ± 6.6*	94.7 ± 7.2*	72-90
Serotonin 5 μM§	15.3 ± 4.4	21.6 ± 4.8*	22.0 ± 6.2*	26.7 ± 7.5*	10-18

Mean ± SD, § $p < 0.05$ (Overall) Friedman's Test, * $p < 0.05$ (Paired) Sign Test compared to vehicle

(n=20)

[1]Serebruany et al. (2010) *American Journal of Therapeutics*. 17, 543-552

Tegaserod potentiated platelet aggregation (Serebruany et al)

- Mild but statistically significant increase in platelet aggregation
  - Concentration-dependent increase
  - Average 9-15% higher with 100 nM tegaserod compared with vehicle

    (Human Cmax ~ 10 nM after 6 mg BID)
  - Consistent results with blood from IBS-C patients

Serebruany et al. (2010) *American Journal of Therapeutics*. 17, 543-552

Tegaserod showed no significant effect on platelet aggregation (Higgins et al.)

Platelet concentration	Agonist	% Platelet Aggregation (mean±SD)				p value (Friedman's test)
		Vehicle	Tegaserod (10 nM)	Tegaserod (33 nM)	Tegaserod (100 nM)	
250,000/μL	5 μM ADP	51.5±16.9	54.4±15.4	51.3±16.8	54.1±18.2	0.9777
	1 μM ADP/5 μM 5-HT	34.1±14.8	25.7±12.3	29.7±12.0	28.4±11.8	0.3667
350,000/μL	5 μM ADP	62.0±13.9	60.2±18.0	59.3±16.4	58.6±18.4	0.9197
	1 μM ADP/5 μM 5-HT	41.5±14.3	30.1±13.0	36.9±14.6	36.8±18.5	0.0794

(n=10)

Higgins et al. (2011) Naunyn-Schmiedeberg's *Archive of Pharmacology*, Published online: 08 September 2011)

Summary

- In vivo drug interaction potential with CYP enzyme inhibitors is low
- Systemic exposure can be increased by concomitant P-gp inhibitor(s)
- No thorough QT study
  - No significant effect of tegaserod on QT prolongation during phase 3 trials
- Effect of tegaserod on platelet aggregation is inconsistent
  - Mild potentiation vs. no effect on platelet aggregation
  - Effect of the major metabolite M29 was not studied
  - Interpretation of platelet aggregation study results in predicting cardiovascular events is challenging

Tegaserod (Zelnorm®) Clinical

Gastrointestinal Drugs Advisory Committee Meeting
November 17, 2011

Aisha Peterson Johnson MD, MPH, MBA
Division of Gastroenterology Products

Tegaserod (Zelnorm)

Regulatory History

2002

Approved for women with constipation predominant irritable bowel syndrome (IBS-C)

2004

Approved for Chronic Idiopathic constipation (CIC) in patients less than 65 years old

Tegaserod (Zelnorm)

2004

Tegaserod labeling updated to warn about possible side effects including diarrhea and ischemic colitis

2006

Swissmedic requested meta-analysis of any ischemic events

2007 (March 9)

Novartis submitted full safety report to FDA showing imbalance in ischemic events in patients taking Tegaserod compared to placebo

2007 (March 30)

Zelnorm withdrawn from US market

Tegaserod Meta-Analysis

- Retrospective
- 29 placebo-controlled trials
- External Adjudication of CV Events

Event	Tegaserod	Placebo
MI	4	0
Strokes	3	0
Unstable Angina	6	0
TIA	0	1
Event Rate	**13/11,614 (0.11%)**	**1/7,031 (0.01%)**

Tegaserod Availability
(after market withdrawal)

Novartis Treatment IND

- ✓ 6 mg twice daily
- ✓ No major CV ischemic events reported
- ✓ Closed in 2008

Now available on a limited basis through emergency IND

Thank you!

Naronapride – Cardiac Safety

November 17, 2011

GIDAC

Sushanta Chakder, Ph.D.
Division of Gastroenterology and Inborn Errors Products

Naronapride (ATI-7505)

- 5-HT_4 receptor agonist and a structural analog of cisapride
- A more potent and more selective 5-HT_4 receptor agonist than cisapride
- Hydrolyzed to an active metabolite, ATI-7500, by plasma and tissue esterases

Binding Affinity for 5-HT and Dopamine Receptor Subtypes

Agent	5-HT_4 Receptor (G.pig Striatum)	5-HT_3 Receptor (HEK-293 Cells)	5-HT_{2B} Receptor (CHO Cells)	Dopamine D_{2L} Receptor (CHO Cells)	Dopamine D_{2S} Receptor (CHO Cells)
ATI-7505	1.39 nM	>6,757 nM	804 nM	205 nM	68 nM
ATI-7500	>500 nM	>6,757 nM	6,810 nM	N/A	13,860 nM
Cisapride	150 nM	1,340 nM	74 nM	N/A	N/A
Norcisapride	N/A	150 nM	N/A	N/A	N/A

Data presented as Ki Values; N/A = data not available

Binding Potencies for Different Cardiac Ion Channels

Target	% Inhibition at 10 μM		
	ATI-7505	ATI-7500	Cisapride
Calcium channel L-type, benzodiazepine	15	9	91
Calcium channel L-type, dihydropyridine	13	-11	66
Calcium channel L-type, phenylalkylamine	38	4	94
Potassium channel KA	5	0	35
Sodium channel site 2	17	2	110

Source: *Sponsor's IND submission*

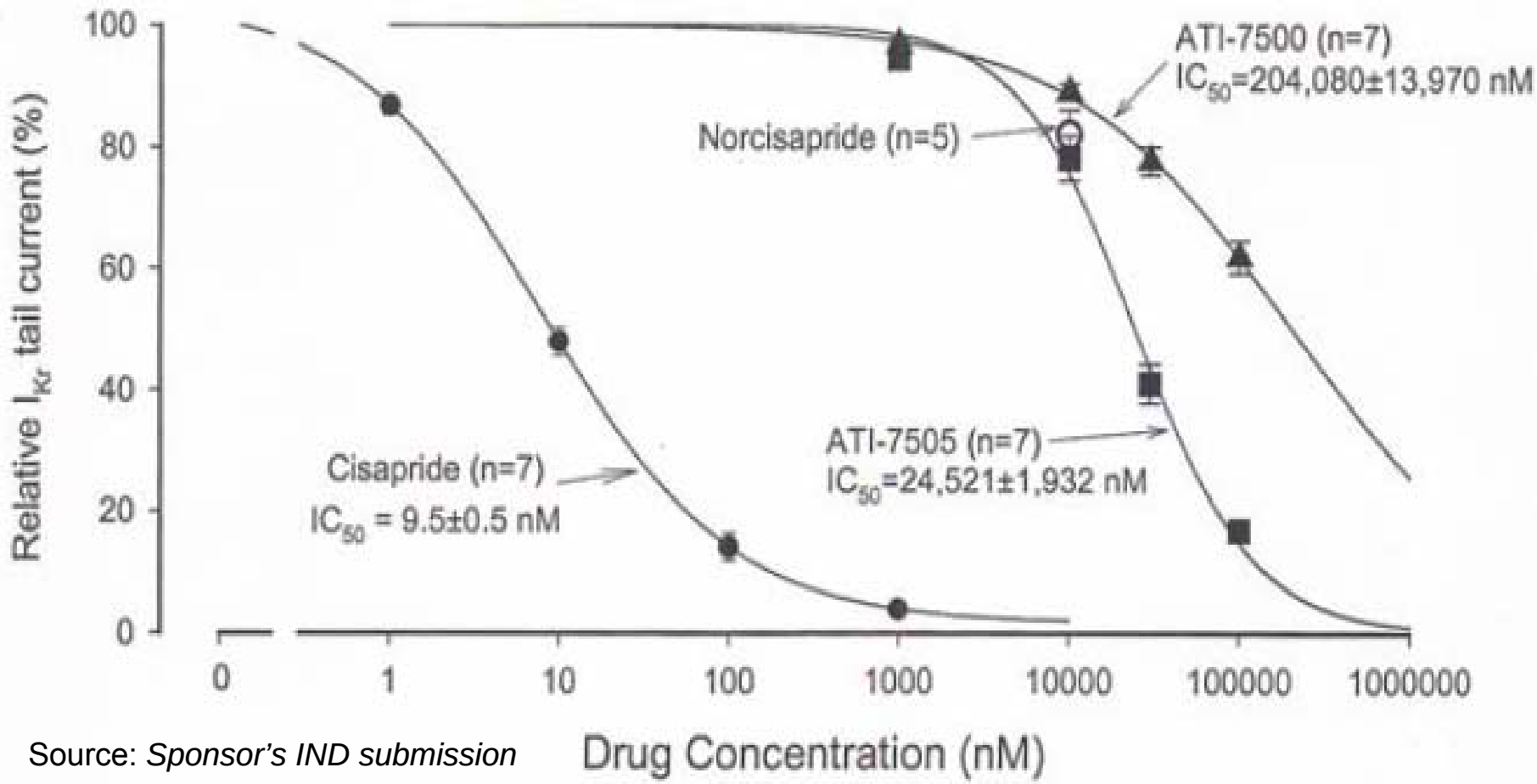
Summary of Binding Selectivity of ATI-7505

- High binding affinity for 5-HT_4 receptors
  - ATI-7500 has low or minimal affinity
- Moderate affinity for 5-HT_{2B} receptors
- Very low affinity for 5-HT_3 receptors
- ATI-7505 and ATI-7500 had low or no binding affinities for L-type calcium, potassium, or sodium channels

Cardiovascular Safety Pharmacology Studies

- hERG potassium channels (IKr inhibition delays cardiac repolarization and causes QT prolongation)
- Non-IKr channels in guinea pig cardiac myocytes
- Electrophysiological studies in isolated guinea pig hearts
- Action Potential Duration (APD) in rabbit Purkinje fibers (prolongation of APD is associated with IKr inhibition)
- Cardiac safety study in anesthetized dogs
- Cardiac safety study in anesthetized guinea pigs

Concentration-response Curve for the hERG Channel Inhibition



Source: *Sponsor's IND submission*

Inhibition of hERG Potassium Channels

Compound	IC_{50} (nM)
ATI-7505	24,521 ± 1,932
ATI-7500	204,080 ± 13,970
Cisapride	9.5 ± 0.5
Norcisapride	> 10,000

The vehicle, DMSO had minimal effect on tail I_{kr} (96.6 ± 0.5%)

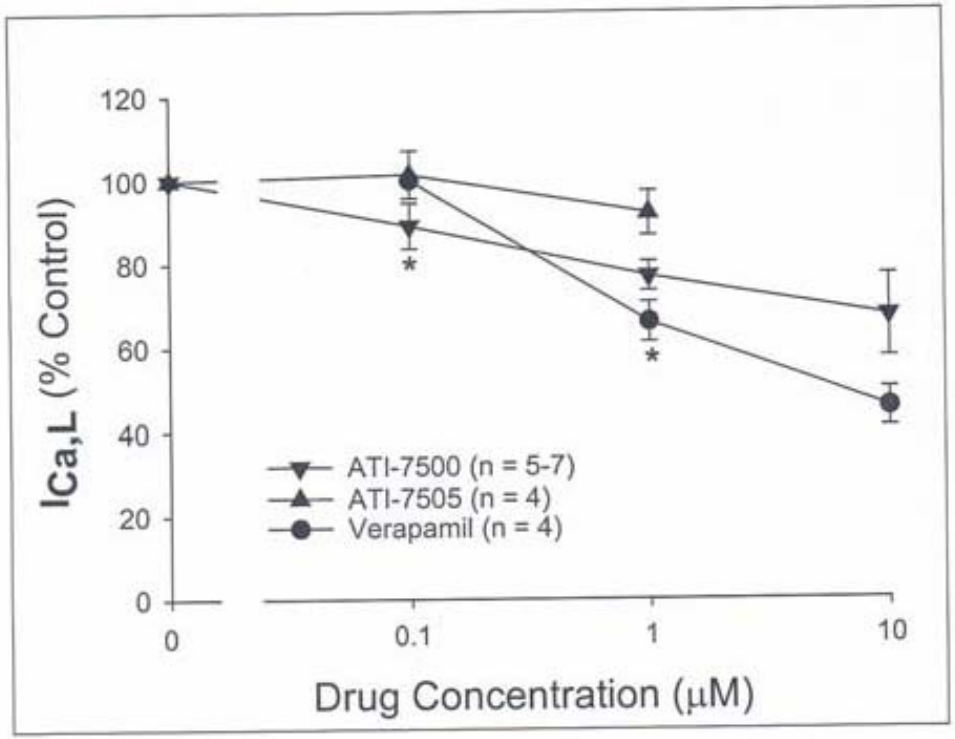
Inhibition of hERG Potassium Channels

- ATI-7505 and ATI-7500 caused concentration-dependent inhibition of hERG channels
- ATI-7505 was ~2600-fold less potent than cisapride
- ATI-7500 was ~21,000-fold less potent than cisapride

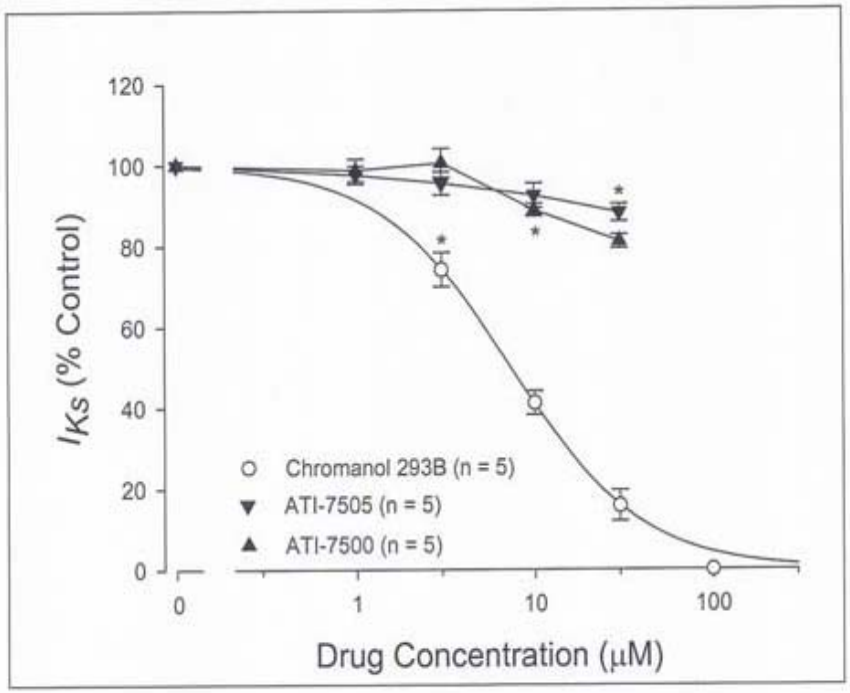
Effects on Cardiac Non-IKr Ion Channels

Ion-Channel Current	ATI-7505 IC_{50} (nM)	ATI-7500 IC_{50} (nM)	Cisapride IC_{50} (nM)
Early I_{Na}	>30,000	>30,000	11,400
Late I_{Na}	>1,000	>1,000	Not Tested
I_{Ca}, L	>1,000	>10,000	Not Tested
I_{Ks}	>30,000	>10,000	Not Tested
I_{Kl}	>30,000	>30,000	>30,000

Effects on Non-IKr Channels



Shown is the mean ± SEM of a number (n) of patch clamp experiments in guinea pig ventricular myocytes expressing native $I_{Ca,L}$. Data is expressed as % vehicle control early $I_{Ca,L}$.
*, drug threshold concentration, $P < 0.05$ versus vehicle controls
Note: Vehicle (DMSO, 0.01%$_{v/v}$) had no effect on $I_{Ca,L}$ (<4% of values in the absence of DMSO, n = 7).



Shown is the mean ± SEM of a number (n) of patch clamp experiments in guinea pig ventricular myocytes expressing native I_{Ks}. Data is expressed as % vehicle control I_{Ks}.
The IC_{50}, value of chromanol 293B to inhibit early I_{Ks} was 7.4±0.1 μM.
*, drug threshold concentration, $P < 0.05$ versus vehicle controls
Note: Vehicle (DMSO, 0.01%$_{v/v}$) had no effect on I_{Ks} (<3% inhibition relative to values in the absence of DMSO, n = 5).

Source: *Sponsor's IND submission*

Electrophysiological Effects in Guinea Pig Hearts

Parameters	1,000 nM (Mean % Increase)			10,000 nM (Mean % Increase)		
	Cisapride	ATI-7505	ATI-7500	Cisapride	ATI-7505	ATI-7500
QT Interval	**9.6%**	1.1%	0%	**11.1%**	**6.2%**	0%
SA Interval	23.8%	13.1%	3.1%	95.8%	17.5%	2.3%
QRS Interval	7.5%	0%	0.5%	110.6%	0%	0%
AH Interval	19.0%	1.0%	2.3%	120.7%	7.2%	3.1%
$MAPD_{90}$	10.7%	0%	0.5%	15.9%	6.1%	1.1%
HV Interval	8.9%	20.0%	5.3%	230.3%	45.0%	6.7%

SA interval, atrial recording time; AH interval, atrioventricular nodal conduction time; MAPD, monophasic action potential duration; HV interval, His Purkinke conduction time

Action Potential Duration in Rabbit Purkinje Fibers (ms)

90% Repolarization					
	Vehicle	**ATI-7505**			
		10 nM	**100 nM**	**1000 nM**	**Sotalol (10 µM)**
1 Hz 20 min	234	243	248	253	283
1 Hz 30 min	237	246	251	262	302
0.2 Hz	264	290	311	315	469
		ATI-7500			
1 Hz 20 min	269	279	276	283	312
1 Hz 30 min	283	281	281	287	328
0.2 Hz	341	351	331	369	440
		Cisapride (10 nM)	**Cisapride (100 nM)**		
1 Hz 20 min	260	271	315		367
1 Hz 30 min	260	276	335		391
0.2 Hz	333	345	406		502

Summary of In Vitro Cardiac Electrophysiology Findings

- ATI-7505 and ATI-7500 had no effect on early and late Na currents
- ATI-7505 had no effect on L-type Ca channels, and ATI-7500 caused a small Inhibition at high concentrations
- Both ATI-7505 and ATI-7500 had weak inhibitory effects on I_{KS}.
- In isolated guinea pig hearts, ATI-7505 caused a slight increase in QT intervals
- In Rabbit Purkinje fibers, ATI-7505 prolonged APD_{90} at 0.2 Hz stimulation

Cardiovascular Effects in Anesthetized Dogs

Treatment	QTc (msec)	QTc Change (msec)
ATI-7505 (1 mg/kg)		
0 min Post-Dose	264 ± 6	--
5 min Post-Dose	279 ± 11	+15
10 min Post-Dose	271 ± 8	+ 7
30 min Post-Dose	258 ± 6	-6
ATI-7505 (2 mg/kg)		
0 min Post-Dose	265 ± 9	--
5 min Post-Dose	280 ± 12	+15
10 min Post-Dose	280 ± 12	+15
30 min Post-Dose	270 ± 13	+5

Effects on QTc in Anesthetized Guinea Pigs

Treatment	Baseline (ms)	Δ, 1 min.	Δ, 3 min.	Δ, 5 min.	Δ, 10 min.	Δ, 20 min.
Vehicle	254.3	+3.0	+2.0	+2.7	+0.7	-1.7
Cisapride						
0.3 mg/kg	276.3	+0.3	+1.3	-0.7	-0.7	-1.7
1.0 mg/kg	250.7	**+14.3**	**+24.3**	**+21.3**	**+17.7**	**+16.3**
ATI-7505						
0.3 mg/kg	250.7	+5.0	+4.3	+2.7	-0.7	-4.3
1.0 mg/kg	231.0	+6.0	+3.0	+1.7	+0.7	+2.0
3.0 mg/kg	263.0	+4.5	**+22.0**	+8.7	-1.7	-6.7
ATI-7500						
3.0 mg/kg	258.7	+4.3	+4.3	+3.7	-0.3	-1.3

Summary and Conclusion

- ATI-7505 is a selective 5-HT_4 receptor agonist with moderate to low affinities for 5-HT_3 and 5-HT_{2B} receptors
- Caused an inhibition of hERG potassium currents; ATI-7505 was ~2600-fold less potent than cisapride
- In isolated guinea pig hearts, ATI-7505 caused a slight increase in QT intervals
- In rabbit Purkinje fibers, it caused a slight increase in action potential duration
- In anesthetized dogs and guinea pigs, intravenous ATI-7505 caused a small transient increase in QTc
- No QT prolongation was observed in the 9-month chronic toxicity study in dogs at 3 and 10 mg/kg/day doses

Naronapride (ATI-7505) Clinical pharmacology

Gastrointestinal Drugs Advisory Committee Meeting
November 17, 2011

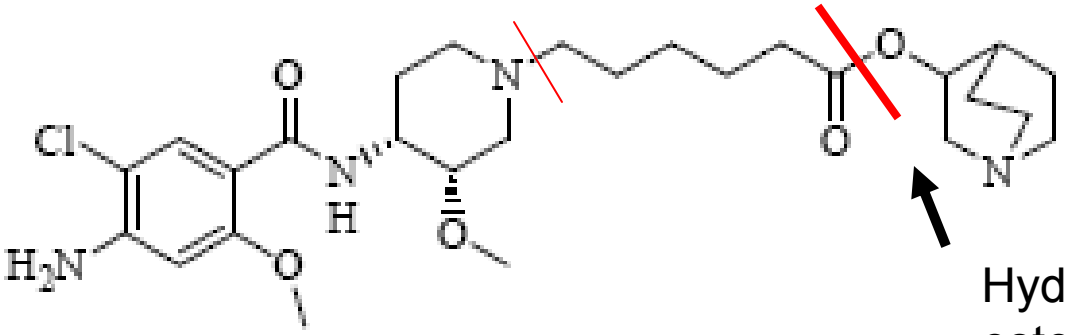
Insook Kim, Ph.D.
Office of Clinical Pharmacology
CDER/FDA

Outline

- Pharmacokinetics of Naronapride
  - Metabolic pathway of Naronapride
- Effect of Naronapride on QT prolongation in the thorough QT study
- Effect of Naronapride on platelet aggregation in vitro

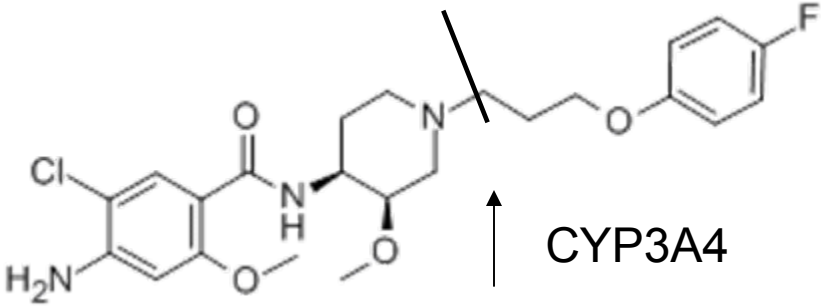
Naronapride (ATI-7505)

Naronapride



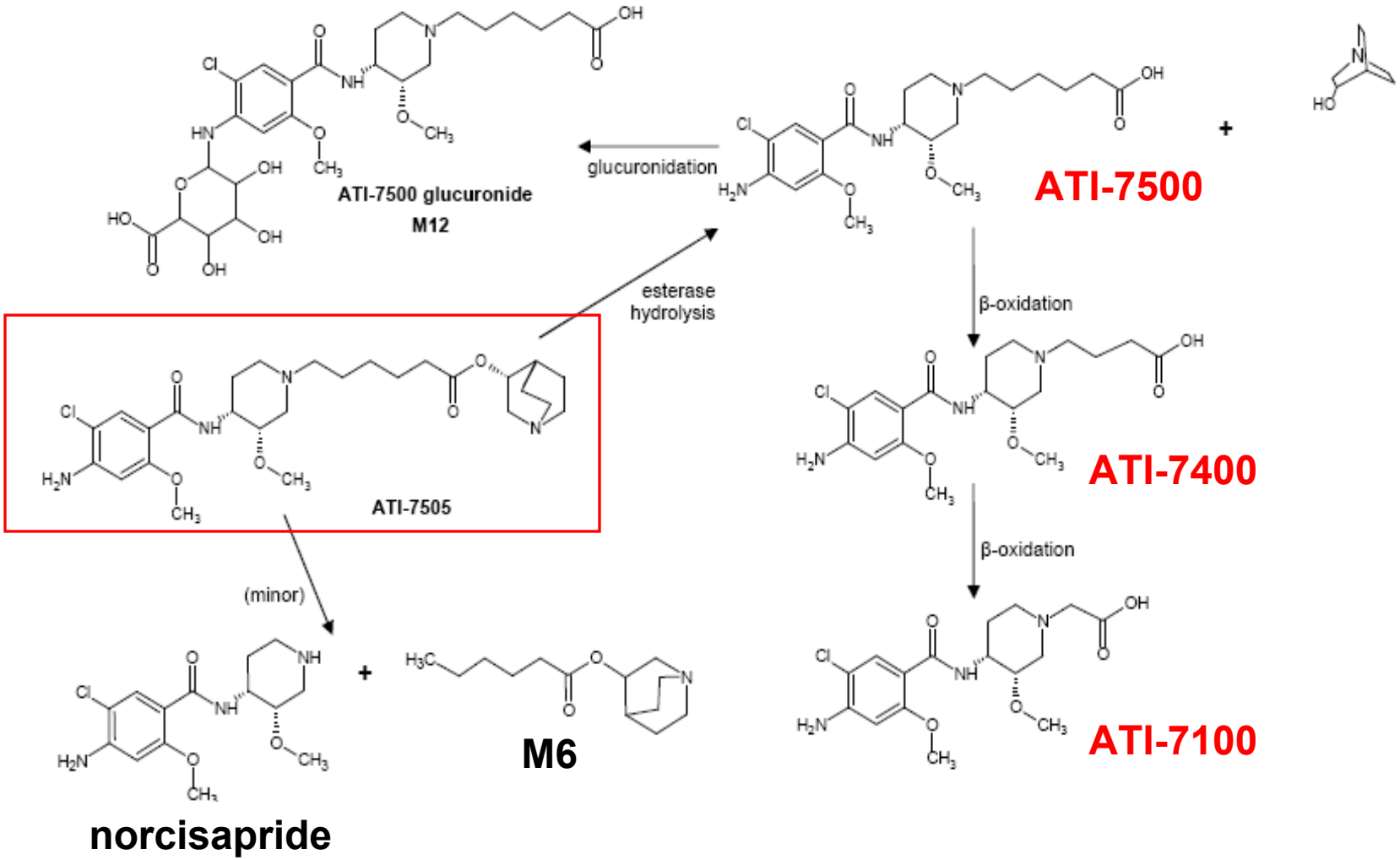
Hydrolysis esterase(s)

Cisapride

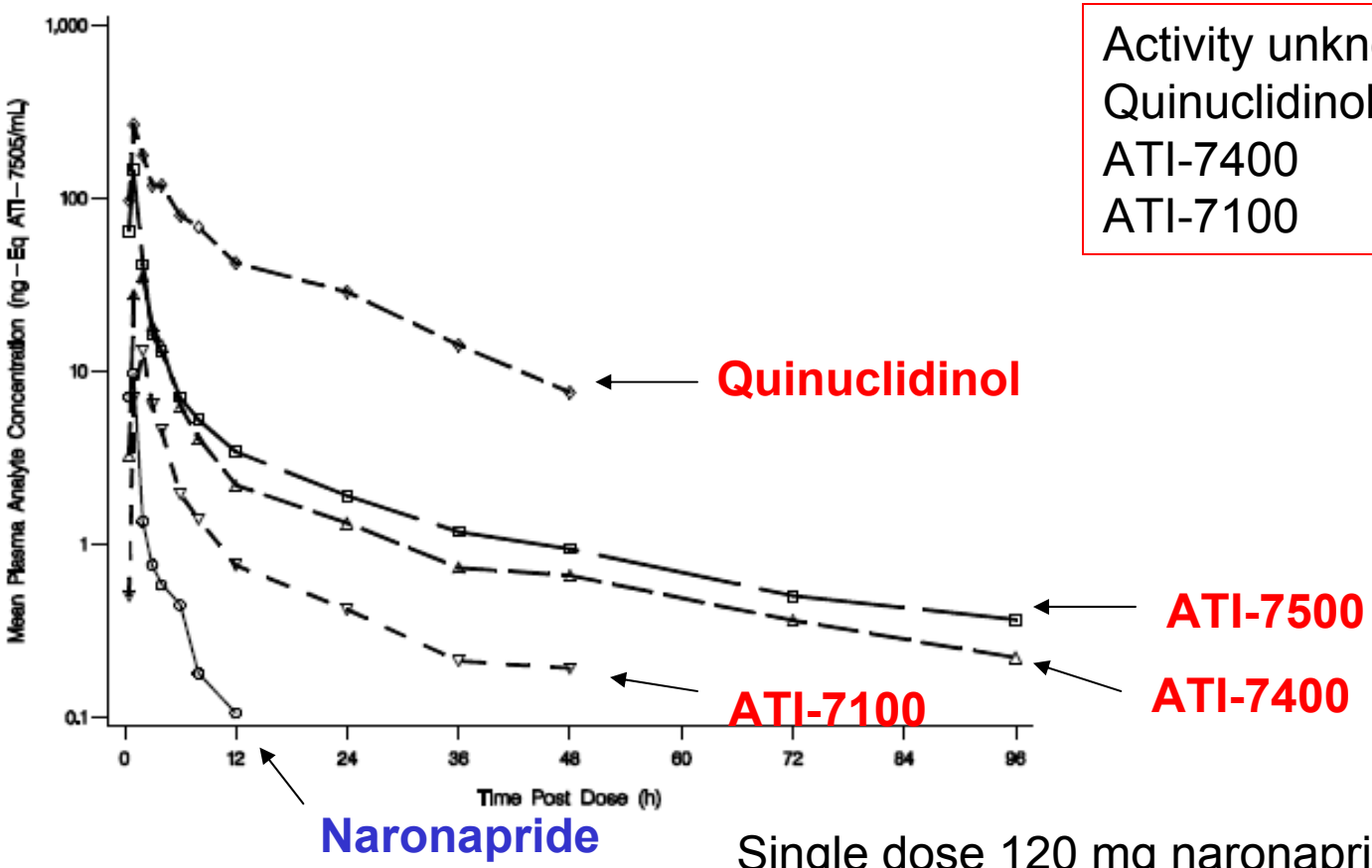


CYP3A4

Proposed metabolic pathway



Higher systemic exposure to metabolites than naronapride



Activity unknown for
Quinuclidinol
ATI-7400
ATI-7100

Single dose 120 mg naronapride

Source: Sponsor's IND *Mass Balance study ATI-7505 CLN-714*

Drug disposition characteristics

- Rapid absorption: Tmax: 1-2 h
- Nonlinear PK
  - 2x ↑ in dose ⇒ 4x ↑ in systemic exposure
- Eliminated mainly through metabolism
  - Major: Ester hydrolysis
    - Higher systemic exposure to major metabolites than naronapride
  - Minor: CYP enzymes
    - Metabolites formed by CYP enzymes, including norcisapride, are only detectable in urine
- Naronapride appears to be a substrate of P-gp in vitro

Factors that may affect naronapride PK

- In vivo DDI studies have not been conducted
  - CYP-mediated drug interaction potential appears to be low
  - Naronapride exposure may increase with concomitant P-gp inhibitor such as quinidine

- PK in patients with organ impairment has not been studied
  - Naronapride exposure may increase in patients with organ impairment such as hepatic impairment

Thorough QT study

- ATI-7505 CLN-713: Single-center, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study in healthy male and female volunteers

- Treatment
  - Single dose Moxifloxacin 400 mg
  - Multiple doses every 6 hours for 7 days
    - Placebo
    - **40 mg** Naronapride
    - **200 mg** Naronapride

Reviewed by FDA IRT-QT team

No significant QT prolongation effect in the TQT study

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
ATI-7505 40 mg	4.00	3.1	(-1.2 , 7.3)
ATI-7505 200 mg	0.00	5.5	(1.5 , 9.5)
Moxifloxacin 400 mg*	1.75	11.4	(7.1 , 15.8)

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 3 time points is 6 ms.

- 90% CI for ΔΔQTcI
  - Moxifloxacin: Largest lower bound **> 5 ms**
  - Naronapride : Largest upper bound **< 10ms**

The tQT study covers the exposure expected with the proposed dosing regimen of 80 mg BID

Mean Cmax (ng/ml; range) at steady-state following Q6h dosing

Dose	40 mg	200 mg	80 mg[1]
Naronapride Cmax	5.88 (0.89-18.7)	66.2 (17.9-154)	11.9 ± 5.9

- The mean Cmax of the supratherapeutic dose i.e. 200 mg is 3-5 fold higher than that for the proposed 80 mg BID regimen

[1] PK obtained from a different study

No Effect of Naronapride on Platelet Aggregation In Vitro

- Light Transmission Aggregometry
  - Blood from healthy volunteers
  - 10, 30, and 100 ng/ml naronapride
  - Esterase inhibitor to prevent hydrolysis
  - Agonist: collagen to 2 μM final conc.

- Naronapride did not induce or inhibit platelet aggregation

- Effect of metabolites was not addressed

Summary-PK

- Non-linear PK over 40-200 mg
- Hydrolysis by esterases is a major metabolic pathway
  - Higher systemic exposure to major metabolites than naronapride
  - Activity is unknown for metabolites, ATI-7400, ATI-7100, and quinuclidinol
- Drug-drug interaction potential
  - Concomitant p-gp inhibitor(s)

Summary-Cardiac safety studies

- No evidence of QT prolongation by naronapride up to 200 mg Q6h
  - Proposed dosage regimen for phase 3 trials: up to 80 mg twice daily
- No effects of naronapride on platelet aggregation in vitro up to 100 ng/ml
  - Effect of the major metabolites was not addressed

Thank you

Naronapride
Review of Clinical Information

Gastrointestinal Diseases Advisory Committee Meeting (GIDAC)
November 17, 2011

Aisha Peterson Johnson MD, MPH, MBA
Division of Gastroenterology Products

Naronapride Completed Clinical Studies

Completed Phase 2 Clinical Studies (Naronapride)

Protocol	ATI-7505-CLN-711
Design	P2, R, DB, PC, 5-arm study
Arms	Placebo, 20, 40, 80, 120 mg
Enrolled	212
Indication	CIC

Naronapride Phase 2 Efficacy Results

Primary Endpoint:

Total number of Spontaneous Bowel Movements (SBMs) during Week 1

Primary Efficacy Result:

Only the 80 mg BID group achieved a statistically significant increase in the number of SBMs compared to placebo for the first week of treatment

Naronapride Phase 2 Safety Results

- No Deaths
- No CV Adverse Events
- No Bowel Perforation

Naronapride Phase 2 Safety Results

	Naronapride	Placebo
Any Adverse Event	27.8% (47/169)	22.0% (9/41)
Gastrointestinal Disorders	11.2% (19/169)	12.2% (5/41)
Nausea	3.6% (6/169)	7.3% (3/41)
Abdominal Pain	3.6% (6/169)	0%
Nervous System Disorders	6.5% (11/169)	4.9% (2/41)
Headache	4.7% (8/169)	4.9% (2/41)

Naronapride Proposed Phase 3 Clinical Studies

Proposed Protocol ATI-7505-CLN-720

Indication	CIC
Number of Patients	600 (200 per arm)
Arms	Placebo Naronapride 40 mg bid Naronapride 80 mg bid
Treatment Duration	12 weeks

Protocol ATI-7505-CLN-720

Study Objective	To assess the efficacy and safety of naronapride in the treatment of patients with chronic idiopathic constipation and to establish an optimal dose regimen.
Primary Efficacy Endpoint	Complete spontaneous bowel movement (CSBM) overall responder analysis

CV Exclusion Criteria

Excluded:

Patients with significant CV risk such as the presence or suspected presence of unstable coronary artery disease, myocardial infarction, stroke, or transient ischemic attack within six months of screening

Prohibited Concomitant Meds

- Laxatives (prescription, over-the-counter, or herbal), other than the supplied rescue medication (bisacodyl tablets or suppositories)
- Medications which might impair bowel transit or which might be the cause of the patient's constipation:
  - Antidiarrheals and antispasmodics
  - Antipsychotic agents
  - Tricyclic antidepressants
  - Verapamil
  - Opiates, except for labeled doses given for two days or less after the first week of study drug administration
  - Antacids containing aluminum hydroxide or magnesium hydroxide

Proposed CV Safety Assessments Protocol 720

Assessment	Timing
Blood pressure, pulse	Screening Days 1, 15, 29, 43, 71, 99
Complete Physical exam	Screening Day 99
12-lead ECG	Screening Days 15, 43, 71, 99

CV Adjudication Committee

- Establish diagnostic criteria
- Blindly review all available clinical data
- Only adjudicated events will be included in safety reporting and stats
- Comprised of Cardiologists, Neurologists, and other physicians experienced in adjudication of CV endpoints

Cardiovascular events with planned adjudication

- Non-fatal myocardial infarction
- Non-fatal ischemic stroke
- Cardiovascular death, including sudden death
- Acute coronary syndrome
- Angina pectoris not leading to hospitalization
- Transient ischemic attack
- Hospitalization for coronary revascularization

Additional Cardiac Risk Assessment Proposals from Aryx

(if required by the FDA)

Timing of Options

Post-Approval (if required by FDA)

- Prospective observational cohort study
- Prospective patient registry

Pre-Approval (if required by FDA)

- Controlled CV Safety study in 1,000 patients ≥65 years old

Post-Approval

- Prospective, observational cohort study using health care or insurance databases to compare the CV risk of naronapride to a matched comparator group

OR

- Prospective patient registry with investigators chosen from a variety of practice types

Controlled CV Safety Study in Patients ≥ 65 years old

- Randomized, double-blind, placebo-controlled, parallel design in pts ≥65 years
- Approximately 1000 patients
- Drug dose: 80 mg BID vs Placebo
- Efficacy assessments q 3 months, at least 1 year, same endpoints as Study 720
- All CV events adjudicated by blinded committee

Controlled CV Safety Study

- Safety Measurements
  - Routine chemistry and hematology, VS, ECG, and adverse events
  - Ascertainment, characterization, and follow-up of all cardiovascular events
  - All reported cardiovascular events will be adjudicated by a blinded committee
  - A DMC would review safety data periodically for patient welfare

Summary

Naronapride Cardiovascular Safety

- Selective, high-affinity 5-HT_4 receptor agonist
- Negative TQT Study
- Negative Platelet Aggregation Study
- Metabolism via esterase activity, not P450 pathway like cisapride
- ~2000 fold less potent hERG inhibition than cisapride
- Less binding and inhibition of other ion channels compared to cisapride

Naronapride Summary

<u>Completed/Planned Studies</u>

- Approximately 950 subjects exposed
  - No deaths
  - No CV events
  - Most common AEs: nausea, diarrhea, headache
- Study 720 (proposed phase 3 trial)
  - Planned
  - Routine cardiac monitoring
  - Exclusion of patients with significant CV risk
  - Adjudication of CV events

Thank you!

Summary & Next Steps: Cardiovascular Risk of 5-HT_4 Agonists

Gastrointestinal Diseases Advisory Committee Meeting (GIDAC)

November 17, 2011

Robert P. Fiorentino, MD, MPH

Division of Gastroenterology & Inborn Errors Products

What we know: Cisapride

- **Cisapride**
  - Drug-drug interactions were important to its safety profile
  - Caused QT prolongation

➢ *Lessons learned:*
  - We incorporate *in vitro* and clinical DDI studies into drug development programs
  - Thorough QT studies are now mandated

What we know: Tegaserod

- **Tegaserod** (Zelnorm)
  - Rare CV ischemic events of unclear etiology
  - Clinical trial ECG data were collected
    - No significant QT effects
    - ST segment changes (elderly)
  - Nonclinical studies did not suggest a clear CV safety concern (small contractile effects on canine coronary arteries at high doses)
  - Off target receptor binding (5-HT_1); +/- platelet aggregation studies
  - P-gp substrate but not of CYP450

➢ *Lessons Learned:*
  - Safety signals may not be detected in modestly sized clinical trials under controlled conditions
  - Analysis of voluntary postmarket AE reports is not an ideal means to evaluate cardiovascular safety: *confounding & lack of control arm*
  - Nonclinical studies do not assure human safety
  - Pathophysiologic etiologies of ischemic events can be unclear

What we know: TD-5108 (velusetrag) & TD-8954

- *In early stages of drug development*
- **TD-5108 (velusetrag)**
  - Weak inhibitor of hERG
  - No electrophysiologic effects were observed in dog
  - Did not induce contractions in isolated coronary arteries (pigs, dogs, and humans)
  - Metabolism: *substrate of CYP3A4 and P-gp*
  - Platelet aggregation study: *Absence of an effect*
  - 2 published studies: *Unclear CV effects in early phase study*
- **TD-8954**
  - Some CV effects in dogs at high doses (unclear relevance)
  - Single clinical trial reported in literature

What we know: **Naronapride**

- ***In vitro* studies:**
  - *Selective 5-HT_4 agonist*
  - *Metabolite receptor binding not fully characterized*
  - *5-HT_{1B} & 5-HT_{2A} binding studies?*
- **Animal Studies:**
  - *In Vitro* Cardiac Electrophysiology Studies: *Variable effects*
  - *In Vivo* Cardiac Safety Pharmacology Studies: *Weak CV effects*
- **Drug-drug Interaction**
  - *P-gp substrate; low CYP metabolism*
- **Platelet Aggregation Study:** *No effect observed*
- **Thorough QT Study:** *Negative (at proposed doses)*
- **Clinical:** *No deaths or CV events reported to date*

Lingering Concerns

- Although we understand the underlying cause of cisapride's safety profile, for tegaserod we don't
  - Where do we look for a signal?
- A *closer look* for cardiovascular adverse events in clinical studies would be prompted by:
  - Significant off-target receptor binding
  - Effects on platelet aggregation
  - Nonclinical findings in supplemental CV studies
- Nonclinical studies provide *some* but not complete assurance of human safety
  - A negative nonclinical program does not necessarily rule out a risk in humans
- Completed early phase clinical studies provide limited CV safety data

Moving Forward

- Is there evidence that further evaluation of CV ischemic events is needed?
- How should we determine whether 5-HT_4 agonists increase CV risk in patients?
  - *CV adverse event monitoring in phase 3 efficacy trials?*
  - *Dedicated prospective clinical CV safety study designed to answer that question?*
- Is a dedicated prospective study warranted, given the available data on the risk of CV ischemia?
  - CV safety trials can be large and resource-intensive

Dedicated Cardiovascular Safety Studies

If done, should be designed to rule out an increased CV risk that would be deemed *unacceptable* in the population with the disease.

- *What level of risk is unacceptable?*
- *How do we capture enough CV events in a GI disease population?*
- *Conduct before or after approval?*

Dedicated Cardiovascular Safety Studies

Further discussion on study design, power and sample size issues relevant to the clinical evaluation of CV events…

Thank You

Power and Sample Size Considerations for a Dedicated Cardiovascular Safety Trial to Rule Out a Pre-specified Cardiovascular Risk

November 17, 2011

Eugenio Andraca-Carrera, Ph.D.

Office of Biostatistics. Division of Biometrics 7
Center for Drug Evaluation and Research
Food and Drug Administration

Background

- **Event-driven trial:** a trial that is powered by the total number of events observed at the time of analysis
- **Hazard:** probability of an event happening in a short interval of time (instantaneous)
- **Hazard ratio (HR):** proportion of the hazards in two treatment groups. The proportion is assumed to be constant through time (also known as proportional hazards assumption)
- **Patient years:** number of patients x number of years in the trial

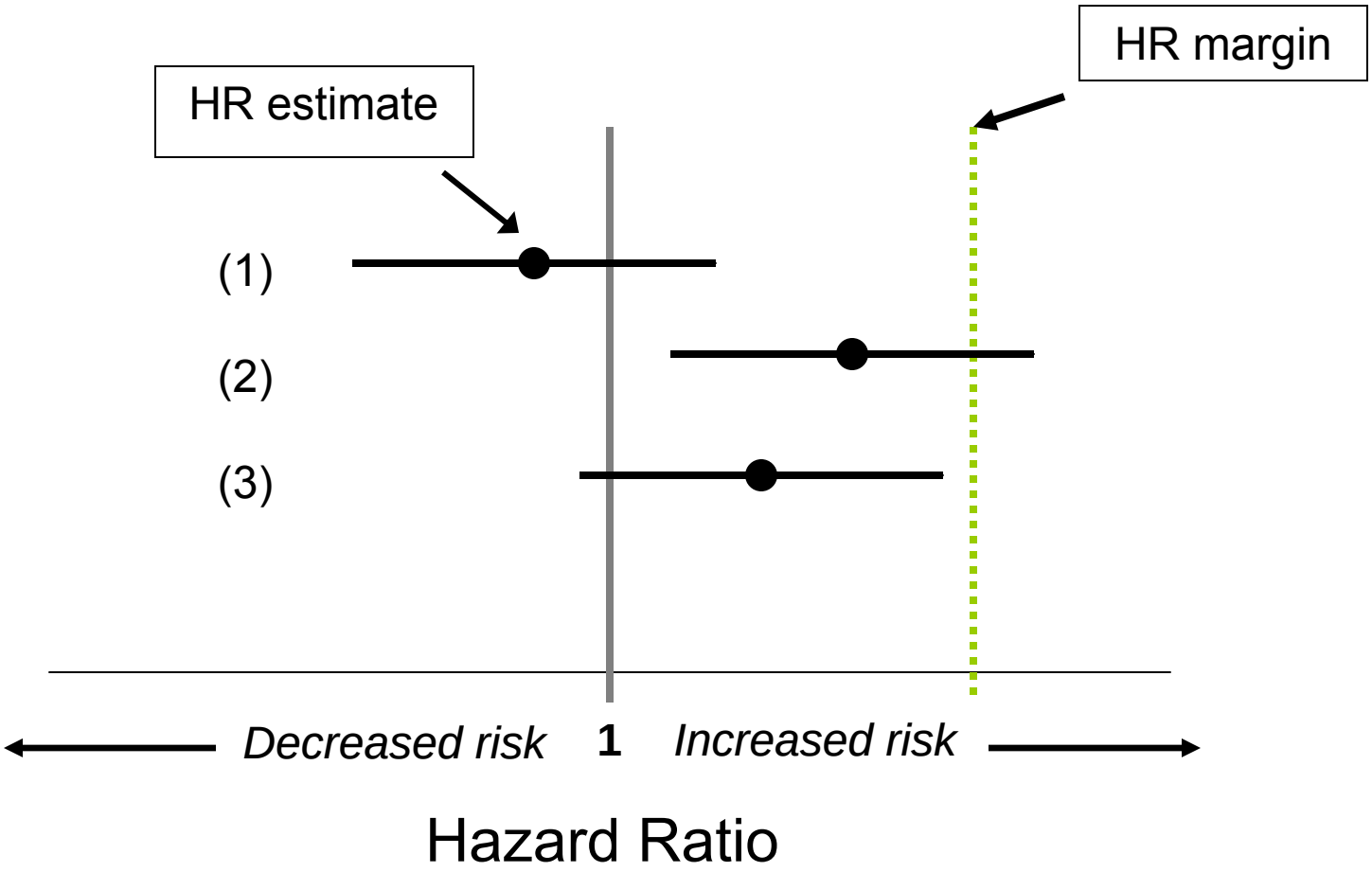
CV Safety Trial Considerations

- **CV safety outcome of interest:** CV safety trials commonly use major adverse cardiovascular events, “MACE”, composed of cardiovascular death, myocardial infarction and non-fatal stroke

- **Hazard ratio margin or excess risk to rule out:** excess risk is typically expressed in the form of relative risk or a hazard ratio and is set as the upper bound of a 95% confidence interval

- **Population of interest:** the power of a CV safety trial is determined by the number of events. It is common to study a high risk or “enriched” population in order to reduce the number of patient years needed to observe these events

Illustration of Trial Objective



Total Events Needed to Power a CV Safety Trial

	Hazard Ratio Margin (Treatment / Control)					
	1.5	**2.0**	**2.5**	**3.0**	**3.5**	**4.0**
80% Power	191	66	38	27	21	17
90% Power	256	88	51	35	27	22

Assuming the baseline underlying HR = 1 and two-sided α=0.05

Maximum estimated HR to rule out an excess risk

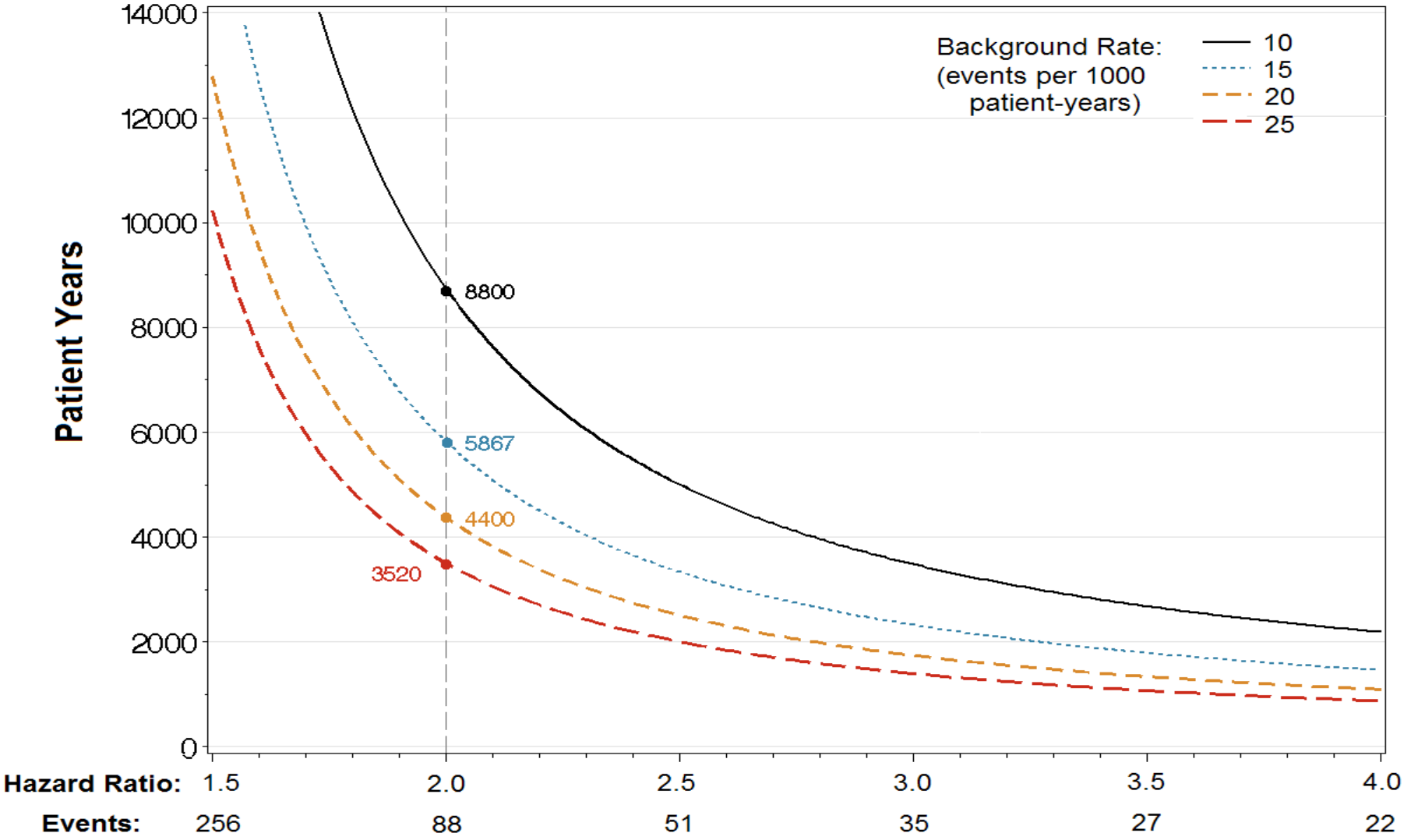
	Hazard Ratio Margin (Treatment / Control)					
	1.5	**2.0**	**2.5**	**3.0**	**3.5**	**4.0**
80% Power, events:	191	66	38	27	21	17
maximum HR estimate:	**1.13**	**1.23**	**1.32**	**1.41**	**1.49**	**1.55**
90% Power, events:	256	88	51	35	27	22
maximum HR estimate:	**1.17**	**1.32**	**1.44**	**1.55**	**1.65**	**1.73**

Sample Size Assumptions

- The number of patients or patient years required to observe a defined number of events depends on the background risk.
  - **Non-enriched population:** observational study of Tegaserod (Zelnorm) suggests the rate of CV events (MI or stroke) is between **1 and 3 per 1000** patient years[1] in a population with 80% women and 75% under 55 years old
  - **Enriched population:** population with CV risk factors and an estimated rate of CV events between **10 and 20 per 1000** patient years

[1] Loughlin J, Quinn S, Rivero E, et al. Tegaserod and the risk of cardiovascular ischemic events: An observational cohort study. J Cardiovasc Pharm Ther., 2010;15(2):151-157.

Sample Size Scenarios with 90% Power in an **Enriched Population**



Total Patient Years Needed to Power a CV Safety Trial

	Hazard Ratio Margin (Treatment / Control)					
	1.5	2.0	2.5	3.0	3.5	4.0
Total events needed for 80% Power	**191**	**66**	**38**	**27**	**21**	**17**
Background rate = 3 per 1000	**63667**	**22000**	**12667**	**9000**	**7000**	**5667**
Background rate = 20 per 1000	**9550**	**3300**	**1900**	**1350**	**1050**	**850**
Total events needed for 90% Power	**256**	**88**	**51**	**35**	**27**	**22**
Background rate = 3 per 1000	**85333**	**29333**	**17000**	**11667**	**9000**	**7333**
Background rate = 20 per 1000	**12800**	**4400**	**2550**	**1750**	**1350**	**1100**

BR = Background Rate

***Non-enriched population**

***Enriched population**

Conclusions

- A trial with a smaller Hazard Ratio margin requires more observed events to be adequately powered
- The background rate of events determines the number of expected patient years needed to observe a defined number of events
- An enriched population has a higher background rate and therefore requires fewer patient years to observe the same number of events and achieve the same power as a non-enriched population