Zelnorm™ (tegaserod)

Presentation to the Gastrointestinal Drugs Advisory Committee

October 17, 2018

US WorldMeds (US Agent for Sloan Pharma)

Zelnorm History and Program Introduction

Kristen Gullo
VP, Development & Regulatory Affairs
US WorldMeds

Outline

- Regulatory history of Zelnorm
- Unmet medical need in IBS-C
- Approaches to ensuring favorable benefit-risk

Zelnorm Reintroduction

- US WorldMeds acquired Zelnorm to bring an effective treatment for IBS-C back to market
  - Response to prescription treatments varies
  - Some patients dissatisfied with current options
- Reintroduction efforts focused on defining appropriate populations for Zelnorm in whom benefits outweigh risks

Zelnorm Approval History

- 5-HT_4 receptor agonist
- Original development program (N>8,000)
  - 7 studies in IBS-C
  - 6 studies in CIC
- US Approvals for IBS-C in women (2002) and CIC in men and women (2004)
- Previously approved in 56 countries
- Currently marketed in Mexico, Ecuador, and Brazil
- US availability through expanded access program

Zelnorm Market Withdrawal (2007)

- SwissMedic study data inquiry led to expanded analysis across pooled database of all controlled trials in multiple indications
  - 29 controlled trials
  - N >18,000
- Imbalance reported in ischemic cardiovascular events:
  - 13 (0.11%) vs. 1 (0.01%) in active and placebo treatment groups, respectively
- Withdrawn promptly to enable more thorough case evaluation and follow-up investigation

Rationale for IBS-C Focus

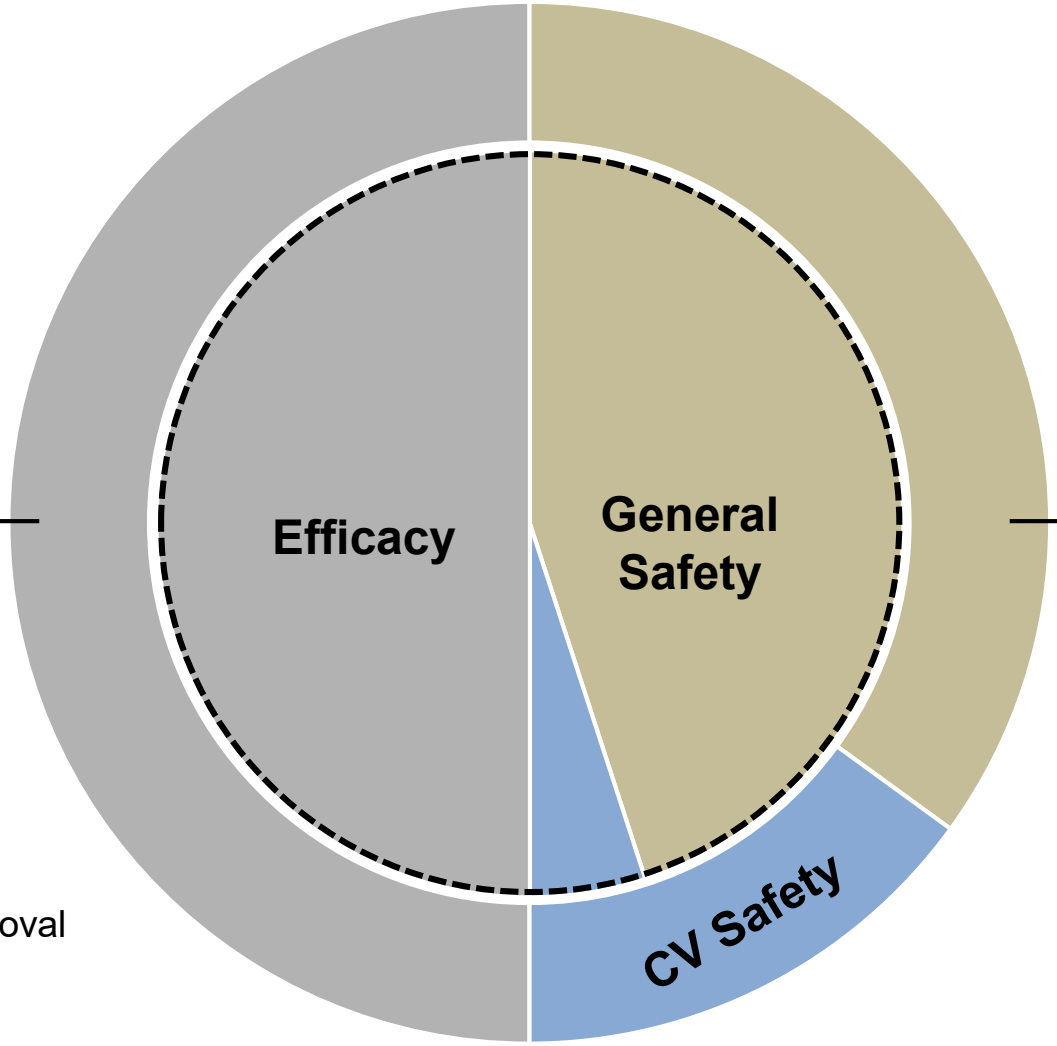
- High unmet medical need
- IBS-C is chronic GI condition characterized by constipation and abdominal pain
  - Diagnosed through Rome Foundation criteria
  - Full symptom complex includes constipation, abdominal pain/discomfort, bloating, flatulence
  - Waxing and waning symptoms over many years
- 5-8% of US adults (12-20M) are affected by IBS-C
- Predominantly young women
- Both physicians and patients perceive a need for additional treatment options
  - 79% of HCPs not satisfied with available treatments
  - 63% of surveyed patients not satisfied with available treatments as a result of either insufficient efficacy or side effects

Quigley; Eamonn, M. 2018. Adv Ther.

IBS-C Reintroduction Efforts

- Characterize imbalance from controlled trials to assess any potential contribution of Zelnorm
- Weigh informed risk assessment in the context of benefit

Expanded Body of Efficacy and Safety Data

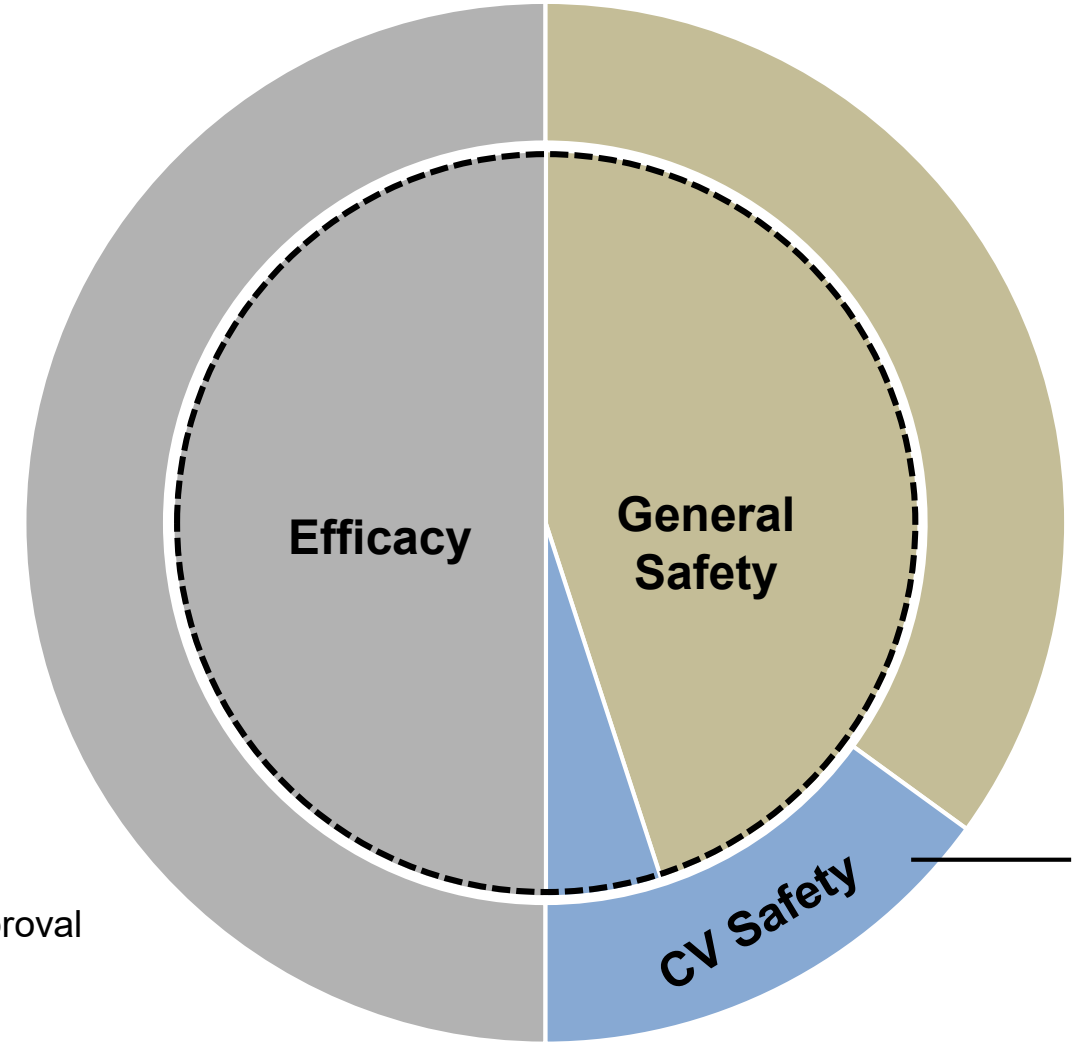


- 2x IBS-C RCTs post-approval (N=3,321)

- Additional analysis of pooled RCTs
- 1.6M patient years post marketing experience
- Expanded access safety reporting

---- Original approval

Expanded Body of Efficacy and Safety Data



- Detailed CV event case evaluations
- Clinical CV parameter analyses across 29 RCTs
- Epidemiology studies
- Mechanistic evaluations

---- Original approval

Reintroduction Approaches

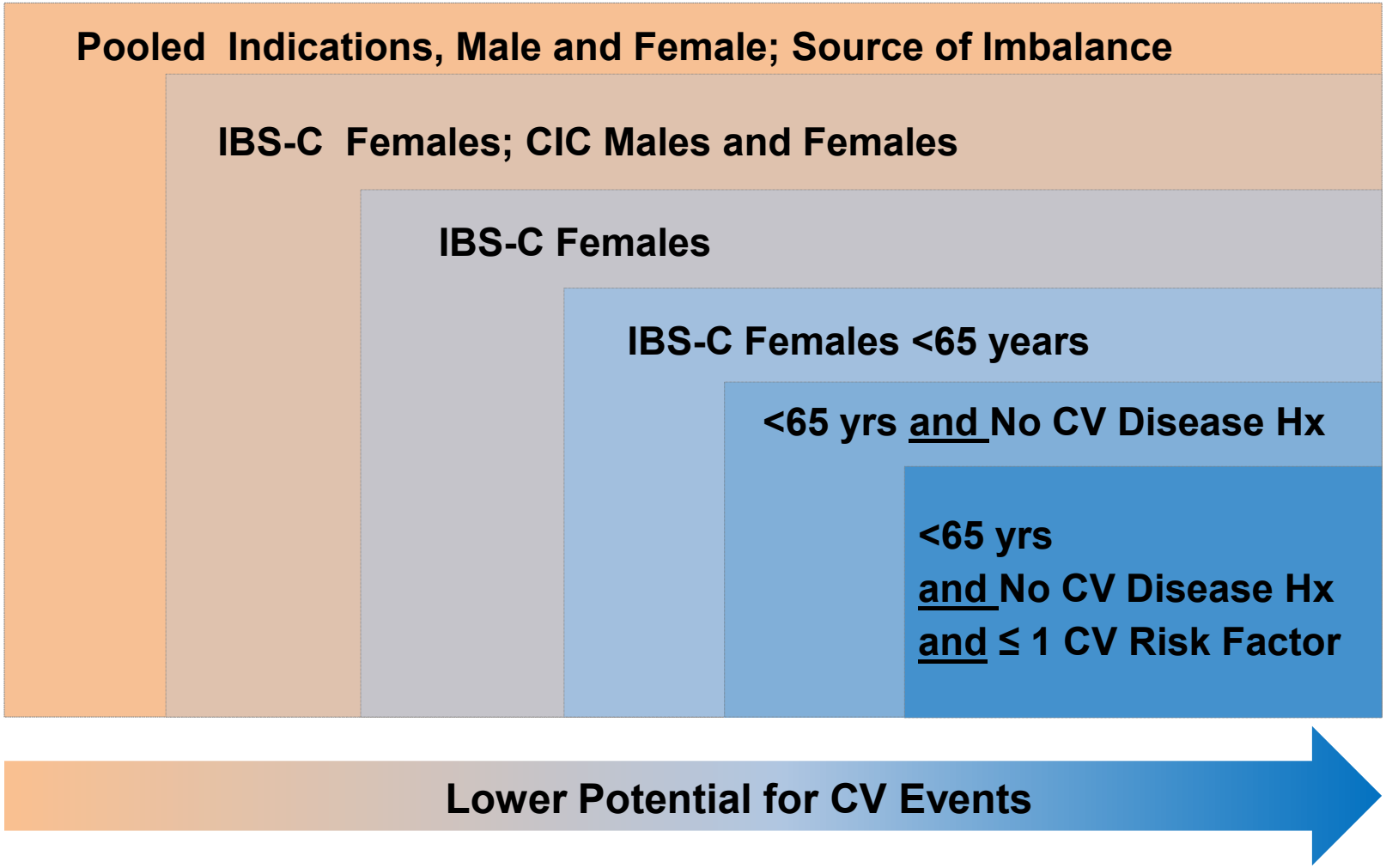
- Two possible approaches for ensuring favorable benefit risk in IBS-C patients

Population with lower background risk for CV events

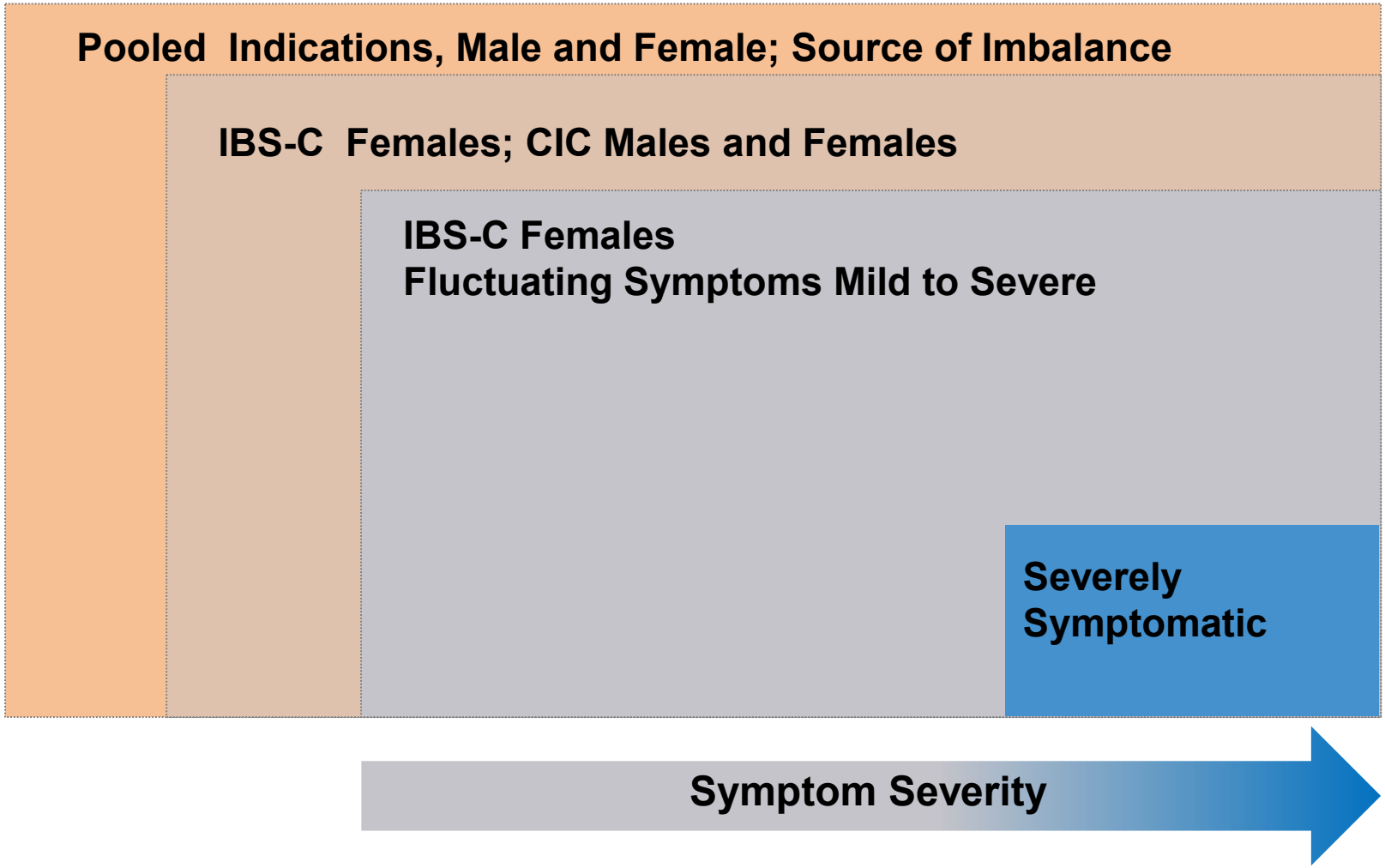
OR

Population with severe symptoms

Populations Across CV Risk Spectrum



Populations Defined By Symptom Severity



Sponsor's Proposal

- Female IBS-C patients at low CV risk
- Defined as:
  - Age <65
  - No history of ischemic CV disease

Agenda

Zelnorm History and Program Introduction	**Kristen Gullo** *VP, Development & Regulatory Affairs* *US WorldMeds*
CV Safety Evaluation	**Philip Sager, MD, FACC, FAHA** *Adjunct Professor of Medicine* *Stanford University School of Medicine*
General Safety and Efficacy Overview	**Rachael Gerlach, PhD** *Zelnorm Program Lead* *US WorldMeds*
Medical Landscape and Benefit Risk	**Colin Howden, MD** *Chief, Division of Gastroenterology* *University of Tennessee Health Science Center*
Closing Remarks	**Kristen Gullo** *VP, Development & Regulatory Affairs* *US WorldMeds*

Cardiovascular Safety Evaluation

Philip Sager, MD
Adjunct Professor of Medicine
Stanford University School of Medicine

Assessment of Zelnorm CV Safety

- Initial CV signal and subsequent adjudication from controlled clinical database
- Epidemiological studies focused on CV events
- Nonclinical data and clinical evaluation of QTc, BP, and heart rate across the clinical trials
- Platelet, receptor, and arterial vasoconstriction mechanistic studies

Safety Databases

Database	Description	Number of Patients Mean Duration of Exposure ± SD	
		Zelnorm	Placebo
DB15	29 double-blind, placebo-controlled trials in both males and females, multiple GI indications; treatment duration between 4 and 12 weeks	N = 11,614 57 ± 29 days	N = 7,031 58 ± 28 days
DB14	7 open label, long-term trials in both males and females, multiple GI indications; treatment duration between 6 and 13 months	N = 3,289 227 ± 133 days	NA

Adjudication of Clinical Trial Data

- Reasons to adjudicate CV events
  - Improve diagnostic accuracy
  - Ensure events are appropriately collected and classified
- Potential limitations of retrospective review of trials not designed to evaluate CV safety

Adjudications

DB15 (N=18,645)

24 cases identified for adjudication

Zelnorm: 20; Placebo: 4

304 cases identified for adjudication

Zelnorm: 198; Placebo: 106

Internal Adjudication
(Novartis, Feb 2007)

- Limited source documentation

First External Adjudication
(Mt. Sinai, March 2007)

- Additional source documentation

Second External Adjudication
(Duke Clinical Research Institute, May-Oct 2007)

- Extensive source documentation
- Pre-defined event definitions
- Prospective MACE evaluation*
- Independent voting

MACE: Myocardial infarction, non-fatal stroke, CV death

Seltzer, et al.; Am Heart J 2015;169:197-204

Adjudication Results

	Internal Adjudication (Novartis)			First External Adjudication (Mt. Sinai)		Second External Adjudication (Duke)	
	CVI[a] Cases	Major Cases[b]	MACE	CVI[a] Cases	MACE	CVI[a] Cases	MACE
Zelnorm (N=11,614)	18 (0.15%)	11 (0.09%)	-	13 (0.11%)	7 (0.06%)	7 (0.06%)	4 (0.03%)
Placebo (N=7,031)	2 (0.03%)	1 (0.01%)	-	1 (0.01%)	0	1 (0.01%)	0
Percent Delta Difference (95% CI)	0.13% (0.02%, 0.22%)	0.08% (-0.01%, 0.16%)		0.10% (0.02%, 0.18%)	0.06% (-0.003%, 0.12%)	0.05% (-0.03%, 0.11%)	0.03% (-0.02%, 0.09%)

a. CV Ischemic Events: Cardiac death, MI, unstable angina, CVA, TIA
b. Cardiac death, MI, unstable angina, CVA

Number of Events in Target Population

Number of Confirmed Adjudicated CV and MACE Cases Identified in the First and Second External Adjudication Datasets

		DB15		Females <65 with No History of CV Ischemic Disease	
		Zelnorm (N=11,614)	Placebo (N=7,031)	Zelnorm (N=9,548)	Placebo (N=5,748)
First Adjudication (Mt Sinai)	CV Ischemic Events	13 (0.11%)	1 (0.01%)	5 (0.05%)	0
	MACE Events	7 (0.06%)	0	3 (0.03%)	0
Second Adjudication (Duke Clinical Research)	CV Ischemic Events	7 (0.06%)	1 (0.01%)	2 (0.02%)	0
	MACE Events	4 (0.03%)	0	1 (0.01%)	0

Long Term Studies: CV Ischemic Events

Adjudicator's Assessment	Zelnorm N = 3,289 n (%)
All Patients	4
Total CV ischemic events	4 (0.12)
Unstable angina	3 (0.09)
Stroke	1 (0.03)

DB14; As adjudicated by Second External Adjudication (Duke)

Epidemiological Evaluation
Loughlin Study

- Ingenix Research Database; patient healthcare claims (real world use)
- New Zelnorm initiators matched with non-initiators (n=52,229 pts. each); followed for 6 months
  - Covered all healthcare, maximizing case attainment
  - New user parallel cohort design
- Use of propensity score matching to reduce potential confounding bias
  - >200 factors, including CV co-morbidities and CV risk factors
- CV events identified in claims database confirmed by medical record review
- Planned power >80% to detect a 1.7 fold increase in ischemic events compared to a matched control cohort

Loughlin, et al. J. Cardiovasc. Pharmacol. Ther. 2010.

Loughlin Study Findings: Medical Record-Confirmed Events

Events	Initiators	Number of Events (n= 52,229 per group)	Hazard Ratio (95% CI)
Cardiac Events[a]	**Zelnorm Initiators**	107	0.95 (0.73-1.23)
	Non-Initiators	115	
Stroke	**Zelnorm Initiators**	16	0.90 (0.46-1.77)
	Non-Initiators	18	

a. Cardiac events includes acute coronary syndrome, myocardial infarction and coronary revascularization
Loughlin, et al. J. Cardiovasc. Pharmacol. Ther. 2010.

Loughlin Study Findings: Incidence Rates

Events	Initiators	Number of Events (n= 52,229 per group)	Person-Years	Incidence Rate per 1000 Person-Years
Cardiac Events[a]	**Zelnorm Initiators**	107	22,160	4.83
	Non-Initiators	115	22,182	5.18
Stroke	**Zelnorm Initiators**	16	22,181	0.72
	Non-Initiators	18	22,205	0.81

a. Cardiac events includes acute coronary syndrome, myocardial infarction and coronary revascularization: medical chart confirmed cases

Loughlin, et al. J. Cardiovasc. Pharmacol. Ther. 2010.

Epidemiological Evaluation
Anderson Study

- Independently designed, executed, and analyzed
- Database: Intermountain Healthcare database
- Zelnorm treated patients (n = 2,603) were matched 1:6 with untreated (n = 15,618) patients based on age, sex, and date of Zelnorm initiation
- Mean duration of therapy 4 months
- Followed for a mean of 2.5 years
- In order to evaluate short term effects, the data were also analyzed after 3 months of therapy

Anderson, et al. J. Cardiovasc. Pharmacol. 2009.

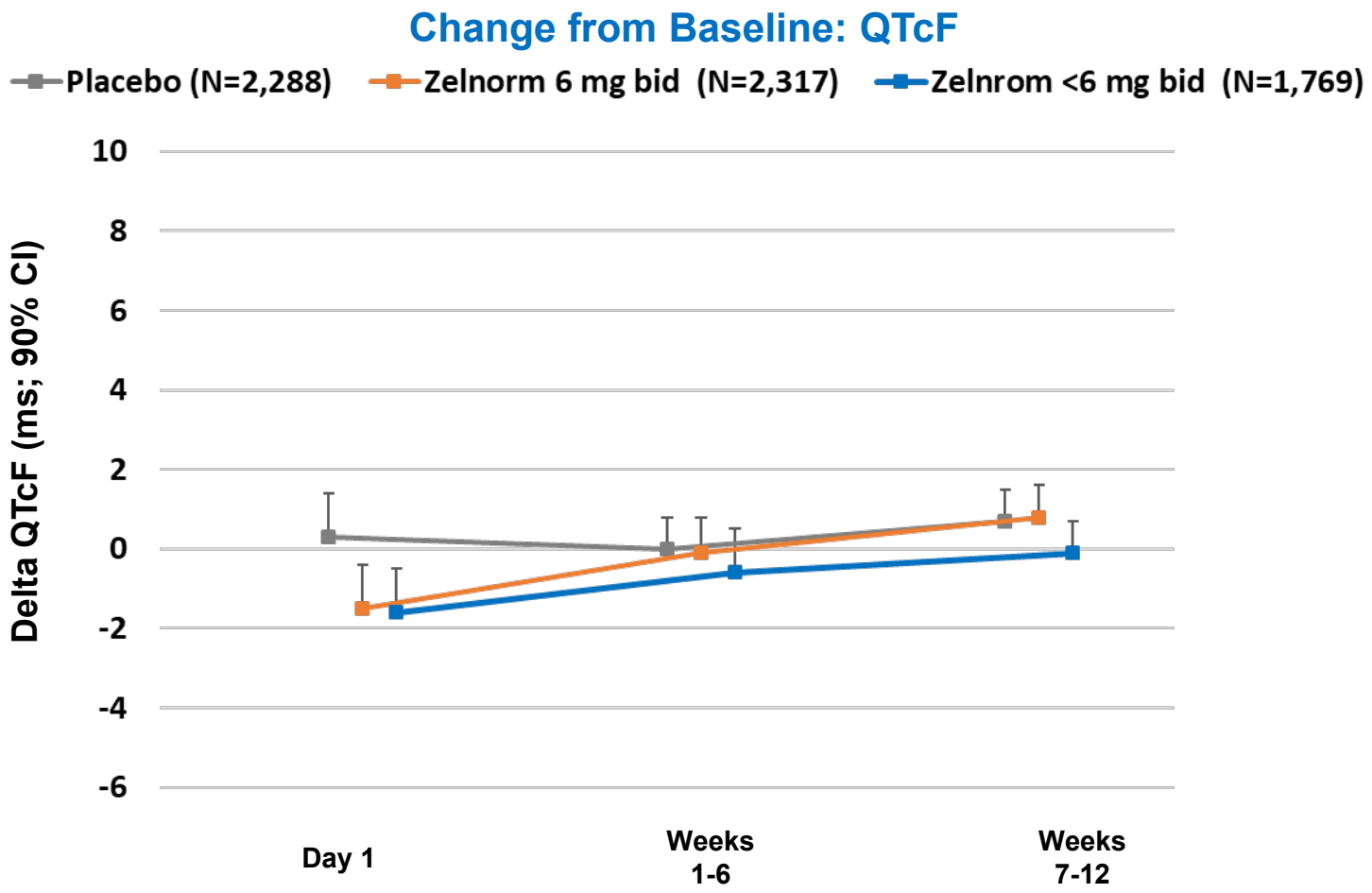
Anderson Study Results

- CV event rates:
  - Overall
    - OR = 1.26 (0.62-2.58), p = 0.53
  - After adjusting for CV risk factors
    - OR= 1.06 (0.56-2.02), p= 0.85
  - No differences between the groups after 3 months of therapy
    - Zelnorm: 0 events vs. comparator: 7 events (0.04%), p=0.60

Cardiac Electrophysiology/Arrhythmia Evaluation

- Nonclinical evaluation
  - HERG liability (IC_{50}:C_{max} margin >1300x)
  - Canine CV safety study showed no ECG effects
    - No histopathological changes in the heart
  - Ventricular Repolarization: Langendorff-perfused rabbit heart and guinea pig papillary fibers
  - Action potentials of isolated human atrial myocytes
- Clinical evaluation
  - Human ECG parameters (QTcF, heart rate, PR or QRS)
  - Centrally analyzed ECGs performed
  - Overall no meaningful effects on ECG parameters

Core Lab Analysis of QTcF: Change from Baseline in DB15 Patients



Adjudicated Arrhythmias (DB15)

	Placebo-Controlled (DB15)	
	Zelnorm (N = 11,614)	**Placebo** (N = 7,031)
Events	n (%)	n (%)
Any Event	**11 (0.09%)**	**5 (0.07%)**
Atrial Fibrillation	5 (0.04%)	1 (0.01%)
Ventricular Fibrillation*	1 (0.01%)	0
Ventricular Tachycardia	1 (0.01%)	0
Other Supraventricular Tachycardia	2 (0.02%)	1 (0.01%)
Sinus Bradycardia, Tachycardia, 2nd degree AV Block, or, Other	2 (0.03%)	3 (0.04%)

Source: Second External Adjudication (Duke)

Patients with atrial fibrillation receiving Zelnorm

- Two patients had a prior history of atrial fibrillation
- Significant risk factors for atrial fibrillation
  - In all, age >60 yo, multiple CV risk factors or CAD

* Associated with an acute MI; another subject had VF during CABG surgery

Blood Pressure

- Canine CV Safety study
  - No effect on BP up to ~113 human C_{max}
- Clinical studies
  - Measured BP at multiple time points
  - No effect observed with the maximal clinical dose (6 mg bid)
  - At supratherapeutic doses, a clinically non-significant increase in systolic BP of 1-1.9 mmHg was noted
  - Increases in diastolic BP were not observed

Platelet Binding and Aggregation

- Zelnorm does not bind to platelets
- *In vitro* platelet aggregation
  - Higgins, et al., 2012; Beattie, et al., 2013; Conlon, et al., 2018
    - Zelnorm had no effect on platelet aggregation
  - Serebruany, et al., 2010
    - Small increase in aggregation was observed for some agonists, primarily at supratherapeutic exposures
- A platelet aggregation study of the primary metabolite M29, showed minor increases in aggregation. However, interpretability of the data is limited since samples for aggregometry were associated with platelet activation

Serebruany, et al. American journal of therapeutics. 2010; Higgins, et al. Naunyn-Schmiedeberg's archives of pharmacology. 2012; Beattie, et al. Vascul Pharmacol. 2013.; Conlon, et al. J Pharmacol Exp Ther. 2018.

Vasomotor Activity

- Three serotonergic receptors whose stimulation could potentially elicit arterial vasoconstriction include:
  - 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2B}
- Zelnorm is an antagonist at these receptors
- *In vitro* and *in vivo* studies show that Zelnorm does not affect arterial vasomotor activity
  - No effect on healthy or diseased human coronary arteries
  - No meaningful vasoconstrictor effects on human mesenteric arteries and non-human primate coronary arteries
    - Zelnorm blocks vasoconstrictor effect of 5-HT and 5-HT_{1B} agonists

Beattie, et al. Vascul Pharmacol. 2013; Cortijo, et al. Br J Pharmacol. 1997; Ullmer, et al. FEBS Lett. 1995

CV Safety Conclusions

- Small numerical imbalance in CV events from clinical trial database
- No clinically meaningful QTc or BP/HR effects at clinical doses
- No indication of a ventricular arrhythmic effect
- Nonclinical studies have shown no mechanistic link to CV ischemic effects
  - Platelet aggregation
  - Arterial vasoconstriction
  - Receptor binding
- Epidemiological studies showed no difference in rates of ischemic events in Zelnorm-treated patients vs. comparator groups

Efficacy and General Safety Overview

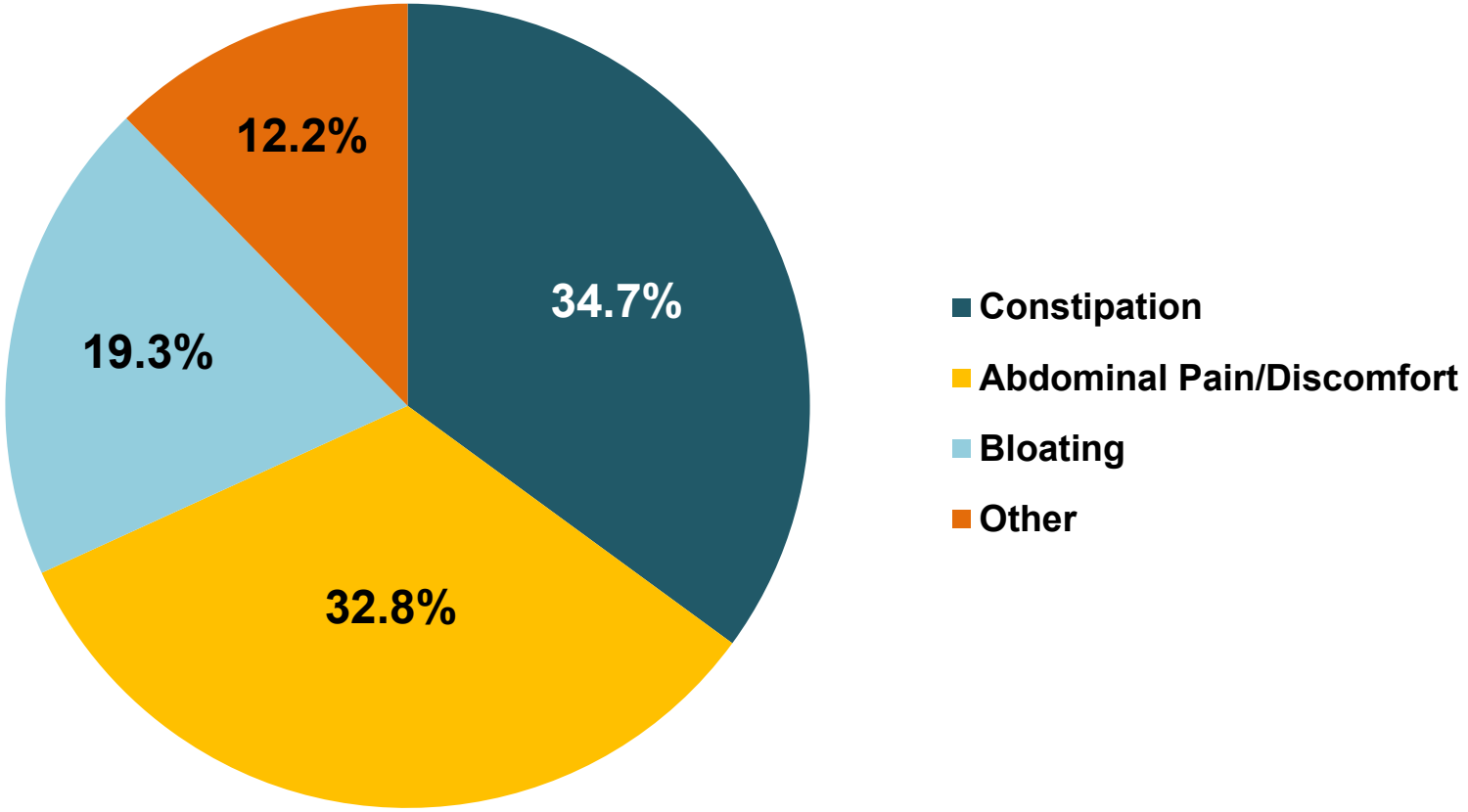
Rachael Gerlach, PhD
Zelnorm Program Lead
US WorldMeds

Outline

- Mechanism of action
- Overview of clinical efficacy program
  - Symptom improvement
  - Efficacy results using current standards
  - Efficacy in proposed population for reintroduction

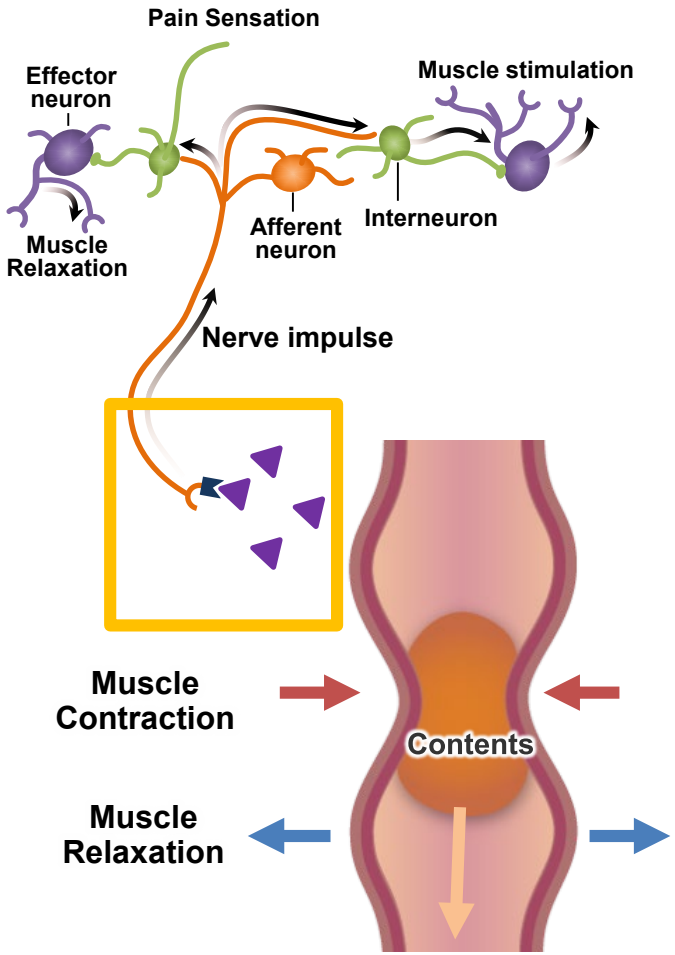
Overview of IBS-C Symptoms

Patients' Most Bothersome IBS-C Symptom (N=2,660)



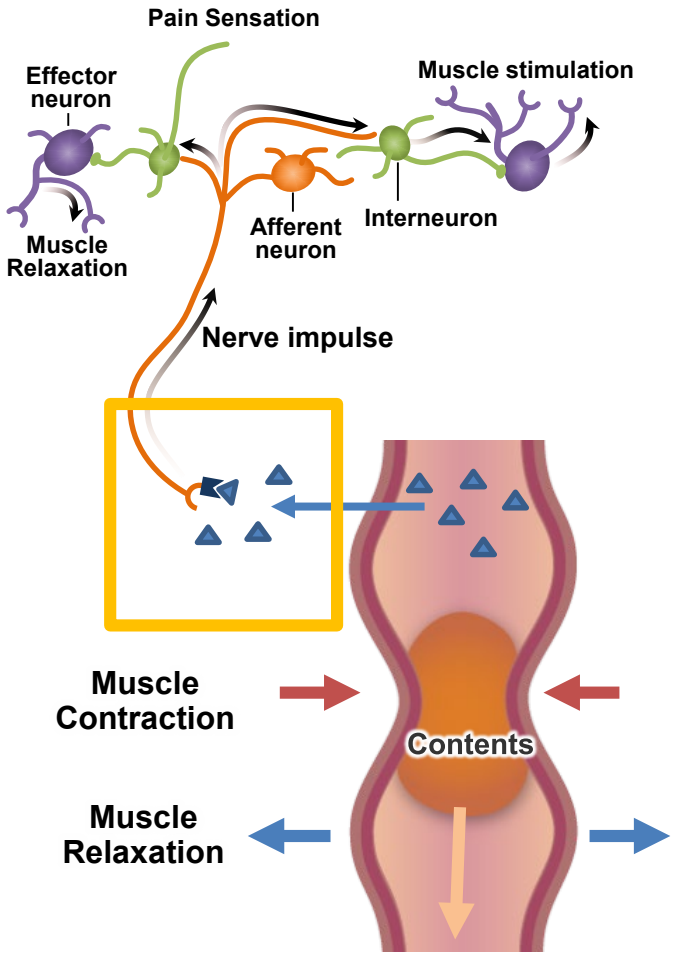
Tack et al. *Gut.* 2005.

Pharmacologic Mechanism



- 5-HT (serotonin) signaling in GI tract important to normal bowel function
- Impaired 5-HT signaling may result in constipation, bloating, and abdominal pain
- Zelnorm targets 5-HT_4 receptors at multiple neurons (sensory, motor, secretory motor) and smooth muscle cells in GI tract to:
  - **Induce both contraction and relaxation**
  - **Decrease pain signaling**
- Zelnorm targets enterocytes to:
  - **Increase luminal H_2O and Cl^- secretion**

Pharmacologic Mechanism



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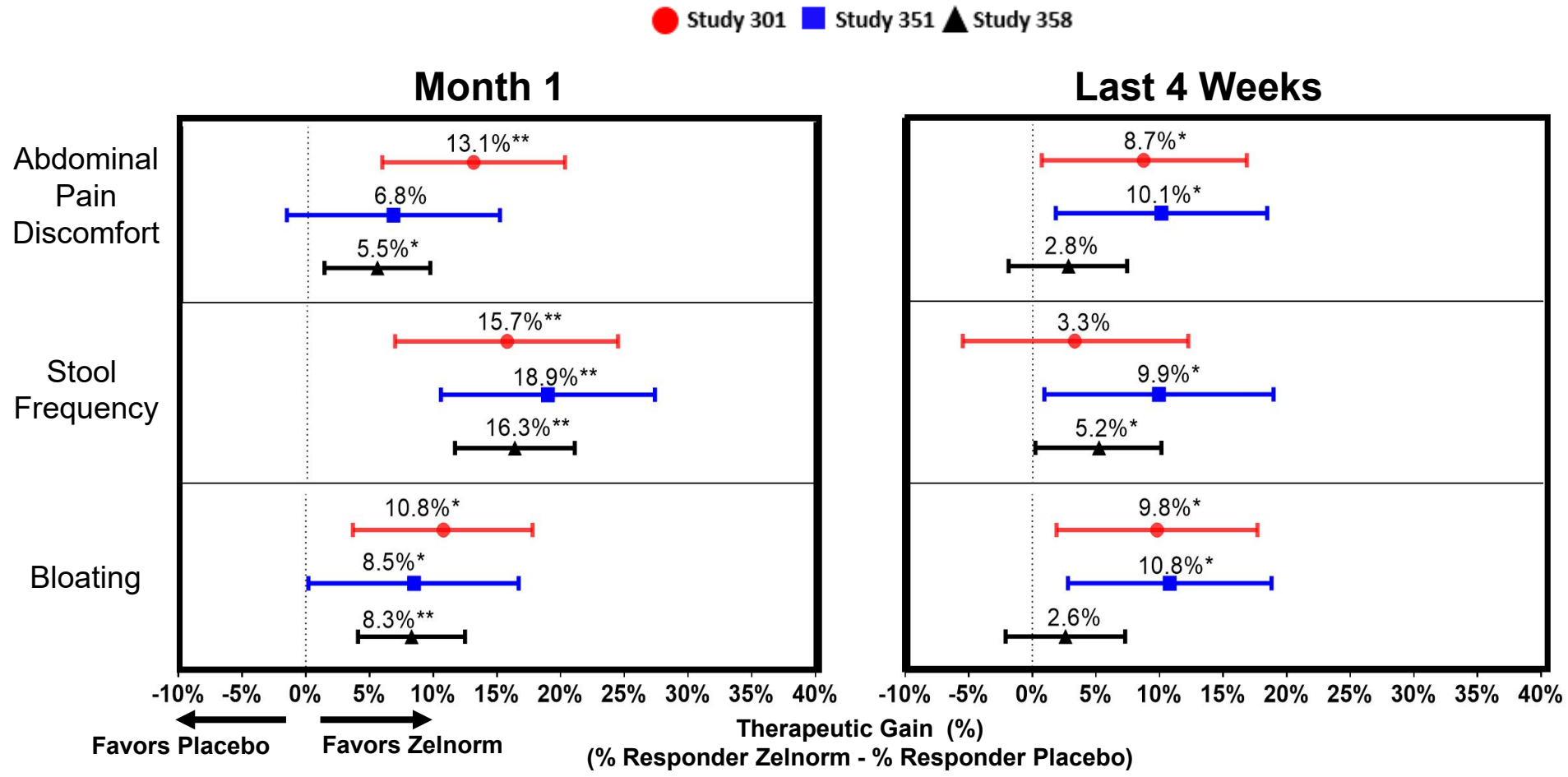
Clinical Efficacy Program for Zelnorm™ in IBS-C Placebo-Controlled Trials

Study No.	N	Patient Population	Treatment Duration	Assessments
B301	881	Men & Women (IBS-C)	12 weeks-fixed	• Overall relief • Abdominal pain & discomfort • Stool frequency • Stool consistency • Bloating
B351	799	Men & Women (IBS-C)	12 weeks-fixed	
B358	1,519	Women (IBS-C)	12 weeks-fixed	
B307	845	Men & Women (IBS-C)	12 weeks-titration	
A2306	2,660	Women *18-65* (IBS-C)	4 weeks-retreat	
A2417	661	Women *18-65* (IBS-C; IBS-M)	4 weeks	

Endpoint Definitions for Symptom Assessments

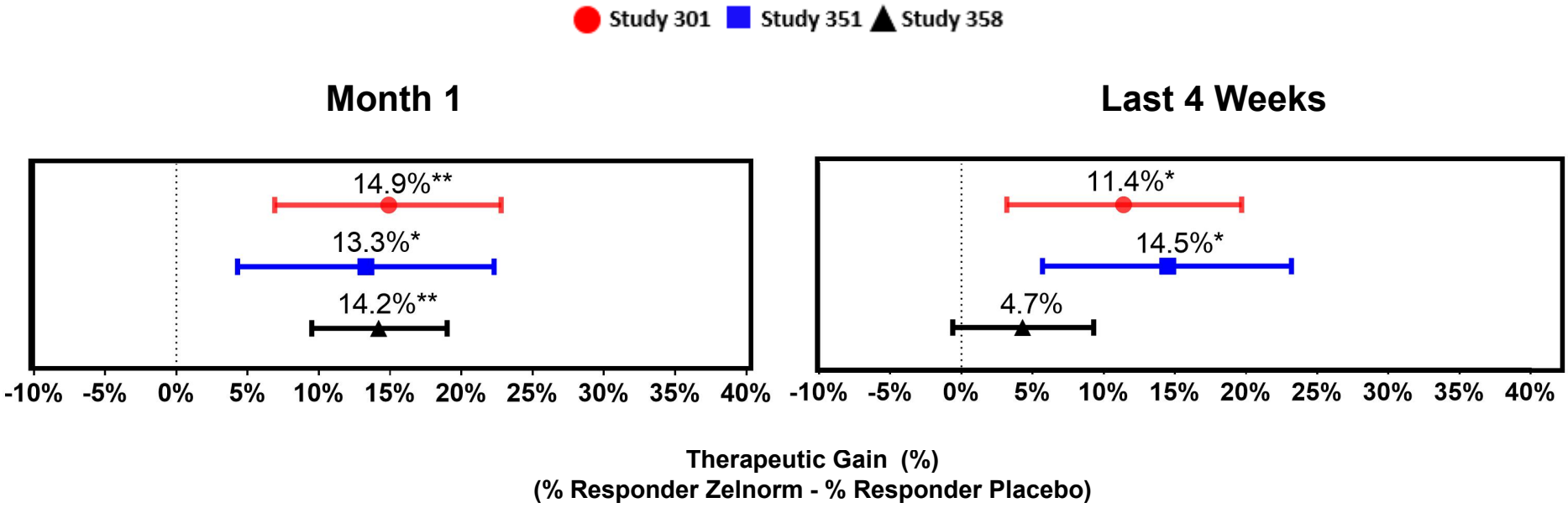
- Abdominal pain and discomfort
  - ≥1 improvement in abdominal pain and discomfort severity scale for 50%
- Stool frequency
  - ≥1 BM increase for 50%
- Bloating
  - ≥1 improvement in bloating severity scale for 50%

Zelnorm Demonstrates Improvement in Key Symptoms Across Studies and Time



* p<0.05
** p<0.001

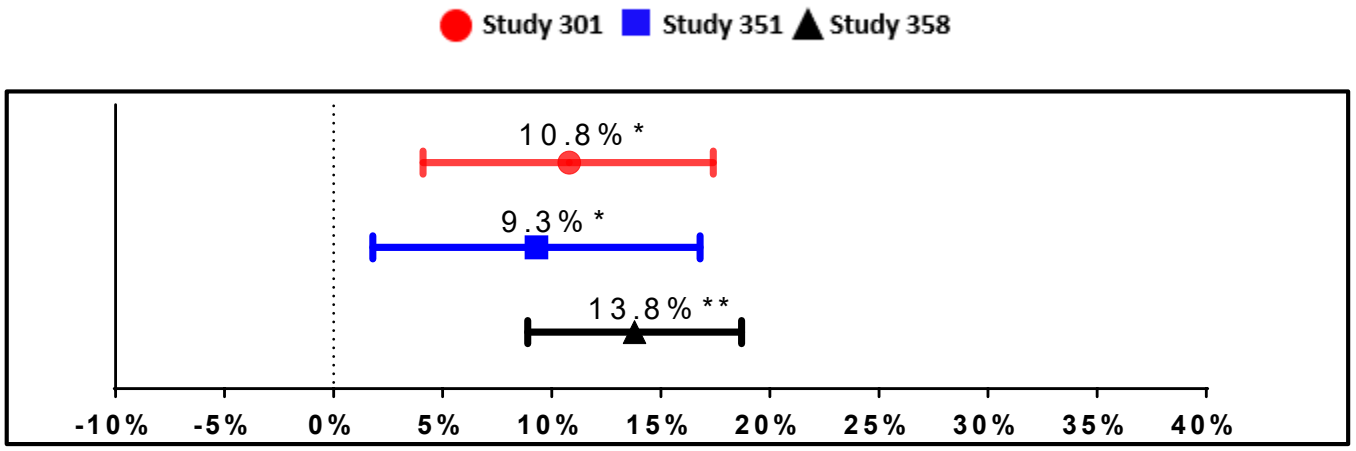
Subjects' Assessment of Overall Relief



- Responder definition: complete or considerable relief at least 50% of the time OR at least somewhat relieved 100% of the time for the last 4 weeks

* $p<0.05$
** $p<0.001$

Results Based on Variation of 2012 IBS Trial Guidance



Therapeutic Gain (%)
(% Responder Zelnorm - % Responder Placebo)

Weekly responder for <u>6 weeks of 12-week</u> treatment defined as a patient who experiences:

- A reduction of 30% or more from baseline in average pain/discomfort score; AND,
- An increase of one or more bowel movements per week from baseline for at least half of the study's duration

* $p<0.05$
** $p<0.001$

Efficacy and Safety Profiles in Various IBS-C Populations Based on CV Risk

- Females
- Females under 65
- Females under 65 without a history of ischemic disease (proposed population)
- Females under 65 without a history of ischemic disease and with no more than one CV risk factor

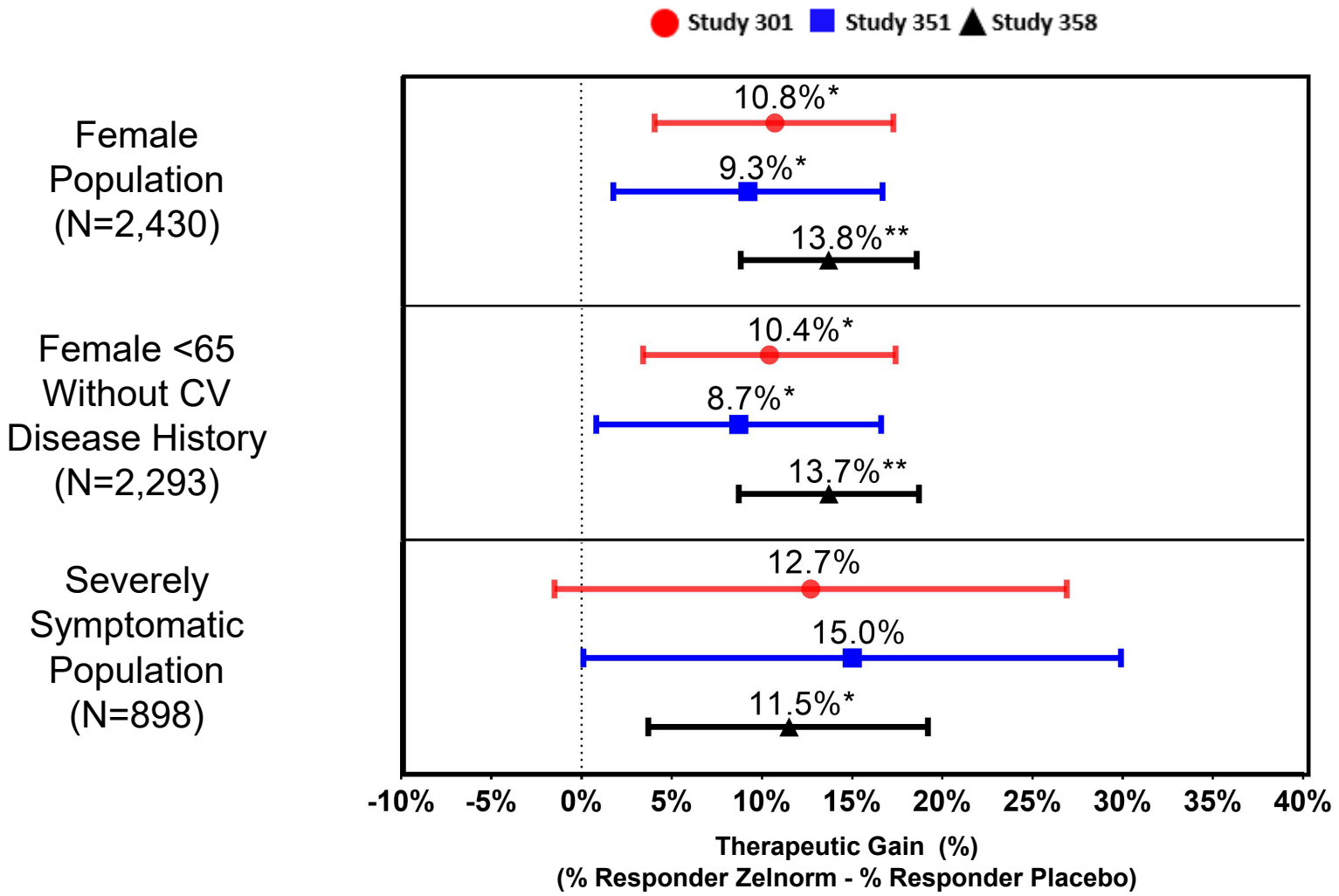
Efficacy and Safety Profiles in Various IBS-C Populations Based on Disease Severity

- FDA requested the Sponsor to define a severe IBS-C population (2016)
- Definition
  - Women with IBS-C:
    - 3 or more days per week with severe abdominal pain/discomfort;

    AND

    - 5 or more days per week with hard, very hard, or no stools

Therapeutic Gain in Subpopulations – Variation of 2012 IBS Trial Guidance



* p<0.05
** p<0.001

Treatment Emergent Adverse Events Reported in ≥1% Patients and Greater than Placebo

	Current Label (Females Only)		
	Zelnorm 6 mg BID N=1,477	Placebo N=1,459	Difference
Headache (%)	13.7	12.2	1.5
Abdominal Pain (%)	12.5	11.5	1.0
Diarrhea (%)	8.7	4.0	4.7
Nausea (%)	8.0	6.8	1.2
Flatulence (%)	6.7	5.3	1.4
Dizziness (%)	3.7	3.4	0.3
Dyspepsia (%)	4.5	3.5	1.0

IBS-C Studies 301, 351, 307 and 358

Other Considerations – Suicide Ideation and Behavior

- Imbalance of events observed (all had history of psychiatric disorders)
  - 8 (0.07%) events Zelnorm vs. 1 (0.02%) events on placebo
- Results from a observational study in more than 100,000 patients either initiating Zelnorm compared to non-initiators support no association between self-injury or death
  - Self-injury adjusted HR=0.74 (0.44-1.25)
- No remarkable findings for death, psychiatric or misuse in the postmarket database
- Nonclinical studies support no mechanistic link with tegaserod having minimal penetration across the blood-brain barrier
- Agreement to update label with description of events in Warnings and Precautions

Overall General Safety and Efficacy Conclusions

- Zelnorm has been conclusively shown to offer a variety of benefits in the treatment of IBS-C
  - Include improvements in abdominal pain/discomfort, stool frequency, bloating, and overall symptom relief
  - Therapeutic gains observed are of similar magnitude to available treatment options and reaffirms using primary endpoints in line with current FDA regulatory standards (2012 Guidance)[a]
- Efficacy is sustained in the sponsors' proposed population for reintroduction as well as the severely symptomatic population
- Favorable safety profile in IBS-C studies
  - Low incidence of AEs among Zelnorm-treated subjects and similar to those seen in placebo-treated subjects, consistent across subpopulations
  - Discontinuations consistent across groups
  - Label updates with respect to this class will be implemented including suicidal ideation

a. Guidance for Industry: Irritable Bowel Syndrome- Clinical Evaluation of Drugs for Treatment: FDA; 2012

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Closing Remarks	**Kristen Gullo** *VP, Development & Regulatory Affairs* *US WorldMeds*

Medical Landscape and Benefit-Risk

Colin Howden, MD
Chief, Division of Gastroenterology
University of Tennessee Health Science Center

IBS-C

Disease Characteristics

- Diagnosis of IBS by Rome criteria[1]:
  - Abdominal pain and altered bowel habit for at least 3 months
- IBS-C is a multifactorial, functional bowel disorder
  - Not associated with structural or biochemical abnormalities that are detectable via routine diagnostics[2]
- Symptoms are chronic with fluctuations in severity

1. Lacy et al. Gastroenterology. 2016
2. Enck et al. Nat Rev Dis Primers. 2016: 2: 16014

IBS-C
Impact on Patients

- IBS-C has a substantial negative impact on quality of life
- Frequent reason for loss of time from work or school
- Frequent physician and ER visits
- Invasive diagnostic tests and surgical procedures
- Dissatisfaction with medical care
- Perception that symptoms are not taken seriously

IBS-C

Unmet Medical Need and Patients' Perception

- 3 treatments approved for IBS-C
  - Address constipation by stimulating intestinal secretion
- Still some remaining dissatisfaction among IBS-C patients with over the counter and Rx medicines

Lubiprostone Amitiza® (Type II chloride channel activator)
Linaclotide Linzess® (GC-C agonist)
Plecanatide Trulance™ (GC-C agonist)

Zelnorm Addition to Treatment Paradigm

- Different mechanism of action
- Increases GI motility
- Reduces pain signaling through interactions with nerves
- Provides an additional treatment option to help address identified unmet medical need

Zelnorm's Benefit

- Shown to improve key IBS-C symptoms across severity spectrum
  - Abdominal pain / discomfort
  - Stool frequency
  - Bloating
- Provides patients with overall relief
- Efficacious when assessed by a variation on FDA 2012 guidance
- Confirmed efficacy in the proposed reintroduction population

Risk Assessment

- Small numerical imbalance in CV events from clinical trial database
  - All had confounding risk factors
  - Majority with history of ischemic CV disease
- Two epidemiological studies in different populations found no association between Zelnorm treatment and ischemic CV events
- Low incidence of SAEs, AEs, including those of special interest

Benefit Risk Summary

- Benefits are clear, meaningful and consistent
- Potential risks appropriate in the context of medical need
- Proposed reintroduction population to mitigate risk and optimize net clinical benefit
- Further restricting eligibility could deprive many patients of a potentially effective therapy

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Closing Remarks

Kristen Gullo
VP, Development & Regulatory Affairs
US WorldMeds

Populations Voting Question

5. **VOTE:** In which patient population would you expect the benefits to outweigh the risks for patients treated with tegaserod?
   A. IBS-C females
   B. IBS-C females at low CV risk
   C. IBS-C females who are severely symptomatic
   D. IBS-C females at low CV risk and who are severely symptomatic
   E. Other

   Discuss your answer.

IBS-C Females (Option A)

- Overall benefit risk established
- Some limitation prudent in consideration of risk uncertainty
  - Limiting to those with lower background risk of CV events

  OR

  - Limiting to those with severe symptoms

IBS-C Females at Low CV Risk and Who Are Severely Symptomatic (Option D)

- Applies criteria to both reduce background risk and increase risk tolerance
- Extent of restrictions may limit goal to address unmet need in IBS-C

IBS-C Females Who Are Severely Symptomatic (Option C)

- Efficacy established across full spectrum of severity
- Excludes patients with significant complaints who do not meet formal definition

IBS-C Females at Low CV Risk (Option B)

Sponsor's Proposal

- Balances benefit and risk considerations
- Utilize clear operational criteria for patient selection to remove patients predisposed for cardiovascular health problems
- Defined as female IBS-C patients
  - Age <65
  - No history of ischemic CV disease

Sponsor's Proposal

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   D. IBS-C females at low CV risk and who are severely symptomatic
   E. Other

   Discuss your answer.

Sponsor's Commitments to Support Reintroduction

- Label updates
  - Indications
  - Contraindications
  - Warnings and precautions
  - Current guidance
- Medication guide
- Enhanced pharmacovigilance
- Support of appropriate utilization:
  - Commercial focus on physicians currently treating IBS-C
- Support appropriate patient selection through education
- Continued development in GI areas with significant unmet need

Additional Responders

James Longstreth, PhD	Pharmacokinetics, Clinical Pharmacology
Caroline Bell, PhD	Nonclinical Toxicology and Pharmacology
Paul Gurbel, MD	Cardiology
Neal Osborne, MD	Gastroenterology
Thomas Clinch	Biometrics, Statistics
Salvatore Colucci, PhD	Statistics
John Seeger, PharmD, DrPH	Epidemiology
Judith Jones, MD PhD	Drug Safety, Epidemiology

Sponsor Backup Slides Shown

Number of Ischemic Events per 1000 Patient-Years in Long Term Open Label Studies (DB14) in Second External Adjudication

- The frequency of CV events in the open label database (DB14) (n=3,289) were similar to that in the placebo controlled trials

Database	Treatment	Total N	Exposure (years)	Numbers of patients with events	Estimated frequencies per 1000 patient years (95% CI)
Long term (DB14)	Zelnorm	3,289	2,046	4	1.95 (0.73, 5.21)

Database	Rx	Total N	Exposure (years)	Pts with events	Estimated frequencies per 1000 patient years (95% CI)
Long term (DB14)	Zelnorm	3,289	2,046	4	1.95 (0.73, 5.21)
Short term (DB15)	Placebo	7,031	1,107	1	0.90 (0.13; 6.41)

Discontinuations Database 15

	Tegaserod All N=11,651 n (%)	Placebo N=7,051 n (%)
Complete Study		
Yes	**9906 (85.0)**	**6116 (86.7)**
No	**1744 (15.0)**	**935 (13.3)**
Reason for discontinuation		
Adverse event(s)	**640 (5.5)**	**256 (3.6)**
Unsatisfactory therapeutic effect	**325 (2.8)**	**209 (3.0)**
Patient withdrew consent	**352 (3.0)**	**200 (2.8)**
Lost to follow-up	**231 (2.0)**	**139 (2.0)**
Other	**196 (1.7)**	**131 (1.9)**

Incidence of CV Ischemic and MACE: DB15 and D14 Second External Adjudications

		DB15	DB14
		Zelnorm N=11,614 /1000 PY (n)	Zelnorm N=3,289 /1000 PY (n)
Years of Exposure		1,805	2,046
Second Adjudication	**CV Ischemic Events**	3.9	1.95
	MACE	2.2	0.49

PY=patient years, (n)=observed counts of patients

Women's Health Study: A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women (NEJM. 352;13 March 31, 2005)

- 39,876 initially healthy women
  - Excluded women with prior CV events
- 45 years of age or older
  - Mean age: 54
- Randomized to low dose aspirin and placebo
- Endpoint: MACE (i.e., nonfatal myocardial infarction, non-fatal stroke, or cardiovascular death)
- Conducted 1992-2004

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J. Michael Gaziano, M.D., JoAnn E. Manson, M.D., Charles H. Hennekens, M.D., and Julie E. Buring, Sc.D.

Demographics Females >45 years Compared to Women's Health Study

	DB15		
	Zelnorm Females >45 years N=4,599 %	Placebo Females >45 years N=2,725 %	WHS Females N=39,876 %
Age mean (SD)	54.3 (7.6)	55.0 (7.7)	54.6 (7.0)
Age category (years) %			
<45	0	0	0
45–54	59	55	60
55–64	30	33	30
≥65	11	12	10
Body-mass index %			
<25	47	45	51
25–<30	32	33	31
≥30.0	21	22	18
CV risk factor %			
≥1 risk factors	70	72	58
≥2 risk factors	40	41	24
History of CV Ischemic disease %	4	4	0

Incidence Rates for MACE Events from 2nd External Adjudication

Females >45 years No Hx of CV Disease

	N	Person-years	Events	Incidence Rate (events per 1,000 patient years)
Zelnorm	**4122**	**640.4**	**1**	**1.56**
Placebo	**2465**	**383.4**	**0**	**0**
WHS	**39876**	**394972.8**	**999**	**2.52**

Step Back

- Comprehensive evaluation
- Small signal – CV – psych
  - Not Validated
  - Missing data

BUT

- We have data on two populations, one very large
  - Exposed
  - Non-exposed
- No difference

} Matched