Multi-Database Study Accepted by FDA in Place of a Cardiovascular Outcomes Trial in Drug Approval: Case Study of Prucalopride

Presented at CER Symposium
Chronic Idiopathic Constipation

• What?
  – <3 spontaneous complete bowel movements per week
  – Duration at least six months
  – No known cause

• Why is it important?
  – Decreased quality of life and productivity
  – Risk of serious complications (fecal impaction, diverticular disease, rectal prolapse)

• Why do we need additional treatments?
  – Inadequate response to:
    • Lifestyle changes
    • Over-the-counter laxatives, bulking agents, stool softeners, stimulants
    • Prescription prosecretory agents
Prucalopride

- A selective, high-affinity serotonin 5-HT4 receptor agonist\(^a\)
- Stimulates colonic peristalsis in patients with chronic idiopathic constipation to increase intestinal motility
- Induces high-amplitude propagating contractions
- Approved in Europe for laxative-resistant chronic constipation (since 2009 for women and 2015 for men)\(^b\)

\(^c\)
Why Not in The US? What to do?

• Other agents that bind to the 5HT4 receptor were associated with adverse CV events, leading to market withdrawal\textsuperscript{a}
  – Cisapride: arrhythmia (QTc prolongation)
  – Tegaserod: ischemic events
• No CV signal for prucalopride was observed in preclinical, clinical or postmarketing experience despite extensive testing
• However FDA required additional demonstration of CV safety prior to approval (rule out an increased risk of 3-fold or greater)
• CV outcome trial was considered not to be feasible
• Prucalopride use in Europe allowed real world data to be harnessed in a robust noninterventional study

\textsuperscript{a} Tack et al. \textit{Aliment Pharmacol Ther}. 2012 Apr;35(7):745-67.
Primary Objective
• To compare the CV safety of prucalopride versus polyethylene glycol 3350 (PEG) in adult new users (EU PAS Register #: EUPAS9200)

Primary Endpoint
• MACE (major adverse cardiac events) composite
  – Hospitalization for acute myocardial infarction
  – Hospitalization for stroke
  – In-hospital CV death
  – *(Out-of-hospital CV death included in sensitivity analysis)*

Study Design
• Population-based cohort multidatabase study of patients initiating prucalopride or PEG in selected European countries

Data Sources: United Kingdom

- **Clinical Practice Research Datalink (CPRD)**
  - United Kingdom (UK) primary care electronic medical records
  - Linked to hospital inpatient data
  - Linked to cause-of-death data
- **The Health Improvement Network (THIN)**
  - UK primary care electronic medical records
- **Information Services Division (ISD) Scotland**
  - Patient roster file
  - All prescriptions and hospitalizations in Scotland
Data Sources: Sweden

Swedish National Registers (SNR)
- National Patient Register
- Prescribed Drug Register
- Cause-of-Death Register
- Total Population Register
- Swedish Cancer Register
Data Sources: Germany

German Pharmacoepidemiological Research Database (GePaRD)
- Claims database of four statutory health care insurance providers

Note: Excluded from final pooled analyses
Methods

Study Population

• First-ever prescription of either prucalopride or PEG (> 4 days duration) to adult patients during the study period
• At least 12 months of data prior to first-ever exposure
• Matched on age, sex, and calendar year of first prescription

Study Observation

• Period: 2010 to 2016
• Events occurring during exposure (+7 days) included
Methods

**Primary Analysis**

- Pooled adjusted incidence rates (IRs) and incidence rate ratios (IRRs) with 95% confidence intervals (CI) of MACE were derived by standardizing to database-specific propensity score deciles and across the 4 data sources.

**Sensitivity Analyses**

- Add out-of-hospital coronary heart disease and cerebrovascular deaths to MACE definition.
- Assess the potential impact on estimates of unmeasured variables.
- Additional sensitivity analyses conducted for manuscript.

**Other Analyses**

- Age, sex, sex-age, and history of CV disease subgroup analyses.
Research Collaboration

• RTI as Coordinating Center and lead investigator for one database (CPRD)
• Close collaboration with all research partners
  – Common protocol
  – Common statistical analysis plan
  – Study data development plan with site-specific details
  – Results, reports and manuscripts
• Sharing of aggregated data via database rather than tables
• Local and central quality checks
• Outcome validation with adjudication in three sites
Heterogeneity of Data Sources

• Exposures measured differently
  – Dispensing, prescription

• Outcomes captured differently
  – Different records available
  – Different coding schemes
  – Out of hospital deaths not available in Germany

• Confounders
  – Direct vs indirect measures (e.g., BMI vs weight loss treatment)

• Outcome validation
  – CPRD – MD questionnaires
  – THIN – free text
  – Scotland – medical records
  – Sweden and Germany - none (reliance on prior research)
Challenges with Multi-database Study

• Difference clinical practice patterns
  • Reimbursement issues in Germany created distinct cohorts (could not control for this level of confounding) and exclusion from pooled results
  • Prescribing of PEG before surgery in Sweden (could control with additional matching variables)

• No sharing of person-level data
  • Work at aggregate level (e.g., propensity score deciles)

• Balance transparency of results with privacy concerns
  – Mask small cell sizes by pooling results across study sites
Results

Number of Patients by Data Source Included in Final Pooled Analyses

<table>
<thead>
<tr>
<th></th>
<th>Prucalopride</th>
<th>PEG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPRD (UK)</td>
<td>866</td>
<td>4,254</td>
<td>5,120</td>
</tr>
<tr>
<td>THIN (UK)</td>
<td>501</td>
<td>2,543</td>
<td>3,044</td>
</tr>
<tr>
<td>ISD Scotland (UK)</td>
<td>1,154</td>
<td>5,806</td>
<td>6,960</td>
</tr>
<tr>
<td>SNR (Sweden)</td>
<td>3,194</td>
<td>16,769</td>
<td>19,963</td>
</tr>
<tr>
<td><strong>Total number patients</strong></td>
<td><strong>5,715</strong></td>
<td><strong>29,372</strong></td>
<td><strong>35,087</strong></td>
</tr>
</tbody>
</table>
Results

Standardized Incidence Rates (SIR) and Incidence Rate Ratio (SIRR) of MACE Comparing Prucalopride and PEG Users

<table>
<thead>
<tr>
<th></th>
<th>Prucalopride (N=5,715)</th>
<th>PEG (N=29,372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted incidence rate / 1000 patient years (95% CI)</td>
<td>6.57 (3.90, 10.39)</td>
<td>10.24 (6.97, 14.13)</td>
</tr>
<tr>
<td>Adjusted incidence rate ratio (95% CI)</td>
<td>0.64 (0.36, 1.14)</td>
<td></td>
</tr>
</tbody>
</table>

- IRs standardized (SIR) to database-specific propensity deciles and across the 4 data sources

CI = confidence interval; PEG = polyethylene glycol 3350; SIR = standardized incidence rates.
Results: Pooled Adjusted IRR (95% CI) Overall and by Sex, Age, Sex-Age Strata, and History of Cardiovascular Disease at Baseline

- There were small number of events overall, and especially by subgroups

CI = confidence interval; CV = cardiovascular; PEG = polyethylene glycol 3350; SIRR = standardized incidence rate ratio.
Key CV Evidence for Approval

- Preclinical and mechanistic studies, pharmacology
- Careful adjudication of cases in clinical trials
- Extensive post-market experience outside US
- Study 802
  - Rigorous protocol and analysis plan
  - Main analysis and multiple sensitivity and bias analyses
  - Careful quality control procedures
  - Sufficient transparency despite inability to share person-level data from some sources

No further CV study was requested
What isn’t in the product label? CV safety warning or precaution.

**motegrity™**
**(prucalopride) tablets 1mg, 2mg**

**IMPORTANT SAFETY INFORMATION**

**Contraindications**

- Hypersensitivity to Motegrity. Reactions including dyspnea, rash, pruritus, urticaria, and facial edema have been observed.
- Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn’s disease, ulcerative colitis, and toxic megacolon/megarectum

**Warnings and Precautions**

**Suicidal Ideation and Behavior:** In clinical trials, suicides, suicide attempts and suicidal ideation have been reported. A causal association between treatment with Motegrity and an increased risk of suicidal ideation and behavior has not been established. Monitor patients for persistent worsening of depression and emergence of suicidal thoughts and behavior. Instruct patients to discontinue Motegrity immediately and contact their healthcare provider if their depression is persistently worse, or they
Observational Cardiovascular Cohort Study

The overall cardiovascular safety of MOTEGRITY was assessed using European healthcare databases in a population-based, retrospective, observational, cohort study of adults with constipation. New users of MOTEGRITY (N=5715) were matched to new users of polyethylene glycol 3350 (PEG) (N=29,372) to estimate the standardized incidence rate ratio (SIRR) for MACE, pooled across four data sources. The 95% confidence interval for the pooled estimate of the SIRR did not demonstrate an increased MACE risk and excluded a pre-specified safety margin of a three-fold risk of MACE during prucalopride use relative to PEG use.

https://www.shirecontent.com/PI/PDFs/MOTEGRITY_USA_ENG.pdf
Other References


• FDA Gastrointestinal Drugs Advisory Committee, Oct. 18, 2018 slides and briefing books from FDA and Sponsor
Discussion/Questions?
Back-up
FDA’s Assessment of Study 802

• A useful source of reassuring evidence about the cardiovascular safety of prucalopride
• Satisfies a pre-NDA expectation for an observational study that reasonably excludes 3-fold MACE risk from prucalopride
## Pharmacology

### Receptor Binding Profile at Therapeutic Concentrations

<table>
<thead>
<tr>
<th>Drug</th>
<th>5-HT&lt;sub&gt;4&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;3&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;2&lt;/sub&gt;</th>
<th>5-HT&lt;sub&gt;1&lt;/sub&gt;</th>
<th>hERG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prucalopride</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisapride</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tegaserod</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>

+ indicates affinity for the receptor subtype that is clinically relevant at concentrations necessary for therapeutic action.

Prucalopride

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- Stimulates colonic peristalsis in patients with chronic idiopathic constipation to increase intestinal motility
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Polyethylene Glycol (PEG)

- Osmotic agent, causing excess water to be retained in the stool, stimulating a bowel movement\(^c\)
- Most common prescription treatment for chronic constipation in Europe at time of study implementation
- Considered neutral for cardiovascular (CV) risk

Results: Sensitivity Analyses

(1) Standardized Incidence Rate Ratio of MACE Plus Out-of-Hospital Cardiovascular Deaths

<table>
<thead>
<tr>
<th>Overall pooled analyses</th>
<th>Prucalopride Events</th>
<th>PEG Events</th>
<th>SIRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE + OOH CV deaths</td>
<td>18</td>
<td>74</td>
<td>0.64 (0.36, 1.13)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>120</td>
<td>0.43 (0.25, 0.73)</td>
</tr>
</tbody>
</table>

- After including OOH CV deaths in the MACE definition, the SIRR (0.43; 95% CI, 0.25-0.73) was lower than that of the main analysis (0.64; 95% CI, 0.36-1.13).

(2) Impact of Unmeasured Variables

- Varying the potential impact of variables not measured (i.e., potential confounders not found in the database) did not change the direction of the association.

CI = confidence interval; CV = cardiovascular; OOH = out of hospital; PEG = polyethylene glycol 3350; SIRR = standardized incidence rate ratio.
Study Conclusions

• The main results did not show evidence of increased risk of MACE in new users of prucalopride compared with new users of PEG in a population that was > 90% female and many were younger than 55 years of age

• Small numbers of exposures and events limit the precision of subgroup analyses (e.g., a larger number of exposures in older men would be needed to further evaluate potential risk in this subpopulation)

• The main results were robust to sensitivity analysis and bias analyses of unmeasured confounding
RTI-HS Project Team

- Elizabeth Andrews, Senior Project Advisor, former PI
- Alicia Gilsenan, Co-PI, Project Director
- Joan Fortuny, Co-PI
- Estel Plana, Lead Biostatistician
- Ryan Zimiecki, Project Analyst
- Jennifer Bartsch, Project Analyst
- Debbie Crozier, Project Administration Manager
- Alyona Chorna, Meeting Coordinator
- Abenah Harding, Project Epidemiologist & Manager
- Miguel Cainzos, Clinical Consultant
- Ken Rothman, Epidemiological Methods Consultant
- Leah McGrath, Former Project Manager and Project Epidemiologist

- Pat Tennis, original PI until retirement
- Susana Perez participated in FDA discussions
- Brian Calingaert contributed to early stages of protocol development
- Cristina Varas-Lorenzo, clinical consultant until retirement