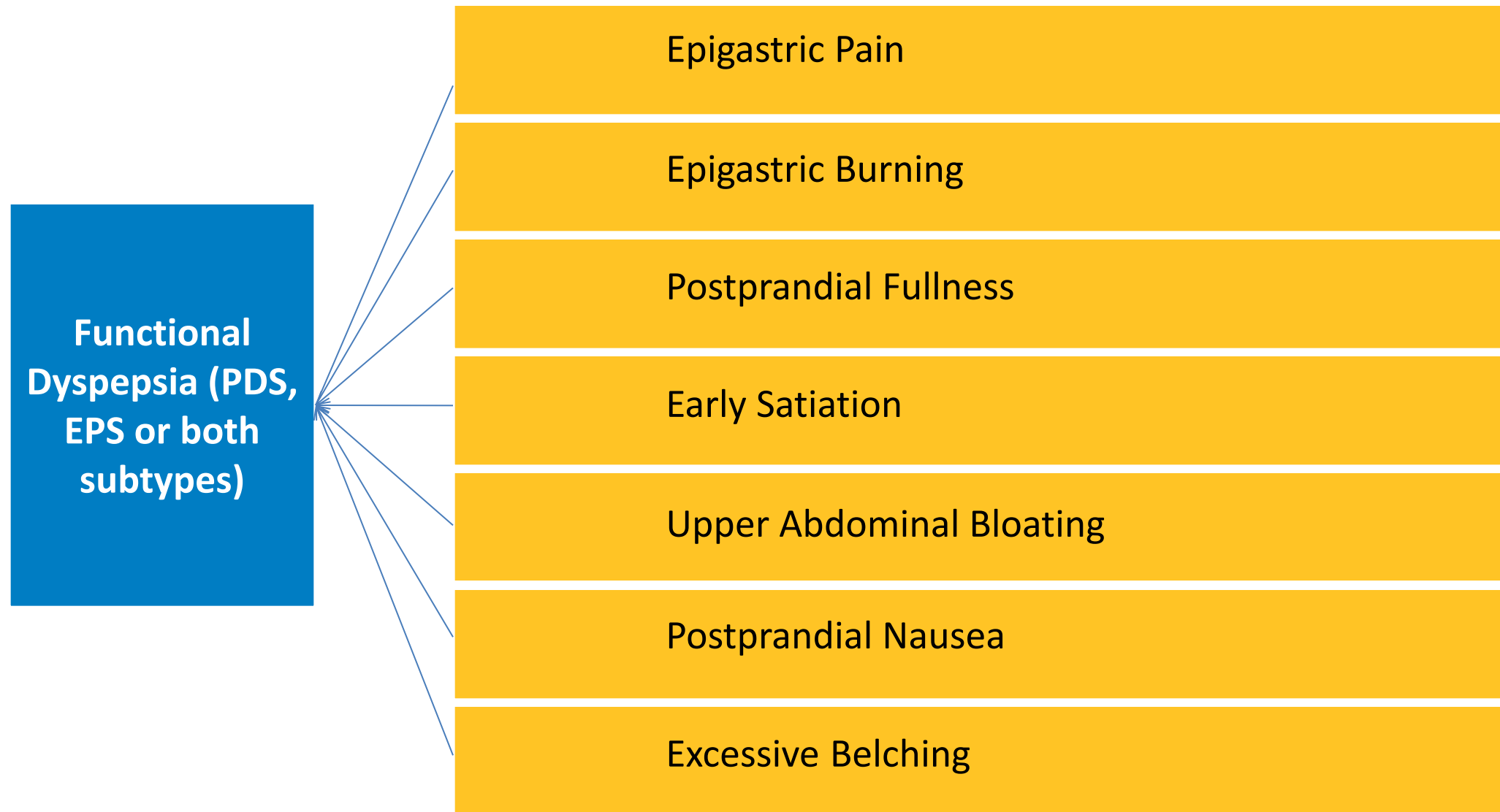


Functional Dyspepsia Working Group

Presented at the Fourth Annual PRO Consortium Workshop – Silver Spring, MD – April 24-25, 2013

<h2>Background</h2> <h3>Rationale for Functional Dyspepsia (FD) Working Group (WG)</h3> <ul style="list-style-type: none">PRO Consortium member representatives and FDA advisors identified FD as an area lacking a “well-defined and reliable” measure of treatment benefit <h3>Goal of the FD WG</h3> <ul style="list-style-type: none">To develop a PRO instrument, in accordance with the FDA PRO Guidance, to measure the symptoms of FD for use in clinical trials as a primary endpoint to establish treatment benefit <h3>Targeted Labeling Language*</h3> <ul style="list-style-type: none">The PRO measure would support an indication of the treatment of the FD subtype as defined by the ROME III diagnostic criteria:<ol style="list-style-type: none">Postprandial distress syndrome (PDS), which includes symptoms such as postprandial fullness and early satiation;Epigastric pain syndrome (EPS), which involves symptoms such as epigastric pain and burning; orCo-existing PDS and EPS subtypes <h2>Milestones</h2> <table><thead><tr><th>Milestone</th><th>Start Date</th><th>Completion Date</th></tr></thead><tbody><tr><td>FD WG established</td><td></td><td>2/7/2011</td></tr><tr><td>Scoping Stage</td><td>2/21/2011</td><td>2/29/2012</td></tr><tr><td>Further correspondence with Qualification Review Team to finalize target patient inclusion/exclusion criteria</td><td>3/21/2012</td><td>4/18/2012</td></tr><tr><td colspan="3">Content Validity Stage</td></tr><tr><td>RFP Issued/Proposals Received</td><td>4/2/2012</td><td>4/23/2012</td></tr><tr><td>Vendor selection</td><td>4/23/2012</td><td>9/18/2012</td></tr><tr><td>Finalization of Proposal/Contracting</td><td>9/18/2012</td><td>4/5/2013</td></tr><tr><td>Kick-off meeting with Adelphi Values</td><td>4/17/2013</td><td>4/17/2013</td></tr><tr><td>Completion of initial qualitative research (concept elicitation, concept selection, item generation, and expert panels)</td><td>1 Q 2014</td><td></td></tr><tr><td>Refining initial instrument (cognitive interviewing, final expert panel, identification of ePRO platform, translatability assessment)</td><td>2 Q 2014</td><td></td></tr><tr><td>Quantitative evidence of content validity</td><td>3 Q 2014</td><td></td></tr><tr><td>Content Validity Summary document submitted to FDA for interim review</td><td>4 Q 2014</td><td></td></tr><tr><td>Psychometric Analysis Stage</td><td colspan="2">TBD</td></tr><tr><td>Qualification of Instrument</td><td colspan="2">TBD</td></tr></tbody></table>			Milestone	Start Date	Completion Date	FD WG established		2/7/2011	Scoping Stage	2/21/2011	2/29/2012	Further correspondence with Qualification Review Team to finalize target patient inclusion/exclusion criteria	3/21/2012	4/18/2012	Content Validity Stage			RFP Issued/Proposals Received	4/2/2012	4/23/2012	Vendor selection	4/23/2012	9/18/2012	Finalization of Proposal/Contracting	9/18/2012	4/5/2013	Kick-off meeting with Adelphi Values	4/17/2013	4/17/2013	Completion of initial qualitative research (concept elicitation, concept selection, item generation, and expert panels)	1 Q 2014		Refining initial instrument (cognitive interviewing, final expert panel, identification of ePRO platform, translatability assessment)	2 Q 2014		Quantitative evidence of content validity	3 Q 2014		Content Validity Summary document submitted to FDA for interim review	4 Q 2014		Psychometric Analysis Stage	TBD		Qualification of Instrument	TBD	
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<h2>Content of Interest</h2> <h3>Endpoint model for treatment of FD – Postprandial Distress Syndrome(PDS) Subtype</h3> <table><thead><tr><th>Endpoint Hierarchy</th><th>Concept(s)</th><th>Clinical Outcome Assessment (COA)/Biomarker/Survival</th></tr></thead><tbody><tr><td>Primary</td><td>FD-PDS Subtype<ul style="list-style-type: none">PDS Symptoms Score</td><td>PRO instrument under development</td></tr></tbody></table> <h3>Endpoint model for treatment of FD – Epigastric Pain Syndrome (EPS) Subtype</h3> <table><thead><tr><th>Endpoint Hierarchy</th><th>Concept(s)</th><th>Clinical Outcome Assessment (COA)/Biomarker/Survival</th></tr></thead><tbody><tr><td>Primary</td><td>FD-EPS Subtype<ul style="list-style-type: none">EPS Symptom Score</td><td>PRO instrument under development</td></tr></tbody></table> <h3>Endpoint model for treatment of FD – Co-existing PDS and EPS symptoms</h3> <table><thead><tr><th>Endpoint Hierarchy</th><th>Concept(s)</th><th>Clinical Outcome Assessment (COA)/Biomarker/Survival</th></tr></thead><tbody><tr><td>Primary</td><td>FD<ul style="list-style-type: none">PDS and EPS Symptoms Score</td><td>PRO instrument under development</td></tr></tbody></table> <h3>Target Population</h3> <ul style="list-style-type: none">U.S. adult patients aged 18 years and older, with a diagnosis of FD (including PDS, EPS, or both) according to the Rome III diagnostic criteria, inclusive of a recent negative endoscopyExclusion criteria include the following conditions: patients with gastroparesis, active irritable bowel syndrome, active chronic constipation, and active GERD (list not exhaustive) <h3>Hypothesized Conceptual Framework*</h3>  <ul style="list-style-type: none">The conceptual framework was developed for the Summary Stage Scoping Document based on a preliminary review of the literature			Endpoint Hierarchy	Concept(s)	Clinical Outcome Assessment (COA)/Biomarker/Survival	Primary	FD-PDS Subtype <ul style="list-style-type: none">PDS Symptoms Score	PRO instrument under development	Endpoint Hierarchy	Concept(s)	Clinical Outcome Assessment (COA)/Biomarker/Survival	Primary	FD-EPS Subtype <ul style="list-style-type: none">EPS Symptom Score	PRO instrument under development	Endpoint Hierarchy	Concept(s)	Clinical Outcome Assessment (COA)/Biomarker/Survival	Primary	FD <ul style="list-style-type: none">PDS and EPS Symptoms Score	PRO instrument under development
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<h2>Updates</h2> <ul style="list-style-type: none">Obtained agreement from the FDA Qualification Review Team (QRT) to enter the qualification program for a PRO measure in FD - February 29th, 2012Obtained further clarification on patient inclusion/exclusion criteria from QRT on April 18, 2012Scoping Stage Summary Document revised to reflect discussions with QRTVendor selection complete and contracting with Sponsors completed April 5, 2013<ul style="list-style-type: none">Adelphi Values selected as vendor collaborator <h2>Working Group Plans</h2> <h3>Next Steps</h3> <ul style="list-style-type: none">Kickoff of Content Validity Stage with Adelphi Values held April 17, 2013Discussions ongoing regarding identification of key opinion leaders for expert panel engagement <h3>Dissemination Plan</h3> <ul style="list-style-type: none">To be developed <h2>Topics for Discussion</h2> <h3>Unique Issues for the Working Group and the Resolution</h3> <ul style="list-style-type: none">Lack of agreement with FDA QRT regarding a consensus definition of FD leading to challenges with defining the target patient population<ul style="list-style-type: none">The FD WG was able to negotiate a path forward with the FDA. <h3>Lessons Learned</h3> <ul style="list-style-type: none">Timely feedback from FDA QRT is critical to inform progress of WGComposition of working group with both PRO, clinical, and regulatory representatives has been useful in providing different perspectives <h2>Working Group Participants</h2> <table><thead><tr><th>Organization</th><th>Name</th></tr></thead><tbody><tr><td>Forest Research Institute, Inc.</td><td>Robyn Carson, MPH (Co-Chair), Steven J. Shiff, MD</td></tr><tr><td>Ironwood Pharmaceuticals, Inc.</td><td>Brooke Dennee-Sommers, Gregory Gordon, JD, MD</td></tr><tr><td>Shire Development Inc.</td><td>Linda Deal, MS (Co-Chair), Debra G. Silberg, MD, PhD</td></tr></tbody></table> <table><thead><tr><th>Contract Research Organization</th><th>Research Team</th></tr></thead><tbody><tr><td>Adelphi Values</td><td>Alan Shields, PhD; Fiona Taylor, MBiochem; Patrick Marquis, MD, MBA; Farrah Pompilus, MA; Catherine Foley, MPH, MA; Ramon Iovin, PhD; Megan Daggett, BA</td></tr></tbody></table> <p>* Note: Prior to conducting qualitative research with patients, it is not known whether a separate symptom complex exists between the two individual subtypes of FD (EPS and PDS), nor is it known at this point whether these subtypes would be evaluated in a particular clinical trial. Target labeling language and the conceptual framework will evolve based upon patient feedback and qualitative findings.</p>		Organization	Name	Forest Research Institute, Inc.	Robyn Carson, MPH (Co-Chair), Steven J. Shiff, MD	Ironwood Pharmaceuticals, Inc.	Brooke Dennee-Sommers, Gregory Gordon, JD, MD	Shire Development Inc.	Linda Deal, MS (Co-Chair), Debra G. Silberg, MD, PhD	Contract Research Organization	Research Team	Adelphi Values	Alan Shields, PhD; Fiona Taylor, MBiochem; Patrick Marquis, MD, MBA; Farrah Pompilus, MA; Catherine Foley, MPH, MA; Ramon Iovin, PhD; Megan Daggett, BA
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