Forward-Looking Statements

This presentation by TherapeuticsMD, Inc. (referred to as “we” and “our”) may contain forward-looking statements. Forward-looking statements may include, but are not limited to, statements relating to our objectives, plans and strategies, as well as statements, other than historical facts, that address activities, events or developments that we intend, expect, project, believe or anticipate will or may occur in the future. These statements are often characterized by terminology such as “believe,” “hope,” “may,” “anticipate,” “should,” “intend,” “plan,” “will,” “expect,” “estimate,” “project,” “positioned,” “strategy” and similar expressions and are based on assumptions and assessments made in light of our managerial experience and perception of historical trends, current conditions, expected future developments and other factors we believe to be appropriate.

Forward-looking statements in this presentation are made as of the date of this presentation, and we undertake no duty to update or revise any such statements, whether as a result of new information, future events or otherwise. Forward-looking statements are not guarantees of future performance and are subject to risks and uncertainties, many of which may be outside of our control. Important factors that could cause actual results, developments and business decisions to differ materially from forward-looking statements are described in the sections titled “Risk Factors” in our filings with the Securities and Exchange Commission, including our most recent Annual Report on Form 10-K and Quarterly Reports on Form 10-Q, as well as our current reports on Form 8-K, and include the following: our ability to maintain or increase sales of our products; our ability to develop, protect and defend our intellectual property; our ability to develop and commercialize our hormone therapy drug candidates and obtain additional financing necessary therefor; the length, cost and uncertain results of our clinical trials; potential adverse side effects or other safety risks that could preclude the approval of our hormone therapy drug candidates; our reliance on third parties to conduct our clinical trials, research and development and manufacturing; the availability of reimbursement from government authorities and health insurance companies for our products; the impact of product liability lawsuits; the influence of extensive and costly government regulation; the volatility of the trading price of our common stock; and the concentration of power in our stock ownership.

PDF copies of press releases and financial tables can be viewed and downloaded at our website: www.therapeuticsmd.com/pressreleases.aspx.
YUVVEXY™ (TX-004HR) Clinical Development Program

YUVVEXY™ is an investigational drug and is not approved for use by the FDA. This is a non-promotional presentation of scientific and development information intended for investor audiences only.
1. Introduction to Vulvar and Vaginal Atrophy (VVA)
2. Rationale for Development
3. Presentation of REJOICE Trial Data
4. Labeling Implications
5. Questions/Answers
Panelists

• Robert Finizio – Co-founder and Chief Executive Officer, TherapeuticsMD

• Brian Bernick, M.D. – Co-founder and Chief Clinical Officer, TherapeuticsMD

• Sebastian Mirkin, M.D. – Chief Medical Officer, TherapeuticsMD

• Sheryl Kingsberg, Ph.D. * – Chief, Division of OB/GYN Behavioral Medicine, UH Case Medical Center, Board of Trustees of the North American Menopause Society (NAMS)

• Lisa Rarick, M.D. * – Former FDA Medical Officer & Division Director Center for Drug Evaluation and Research (CDER) and FDA Office of Women’s Health

• Ginger Constantine, M.D. * – President Endorheum Consultants, Former Wyeth Women’s Health and Musculoskeletal VP and Therapeutic Area Director, Clinical Research and Development

• James Simon, M.D. *† – Professor of Ob/Gyn, George Washington University, Past President of the North American Menopause Society (NAMS), President Elect of the International Society for the Study of Women’s Sexual Health (ISSWSH)

• Steven Goldstein, M.D. * – Professor of Ob/Gyn, New York University, Past President of the North American Menopause Society (NAMS)

* Consultant to TherapeuticsMD
† Clinical Investigator for TX-004HR REJOICE Trial
Women’s Attitudes and Behaviors towards Vulvar and Vaginal Atrophy (VVA)

Sheryl Kingsberg, PhD
University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH
The Scope of the Problem

Many women are unaware that symptoms progress without treatment, and that safe and effective treatments are available

The Survey Says….

• Several recent surveys on the impact of VVA on Quality of Life, 3 large surveys published within the past 2 years
  – REVIVE: Real Women’s Views of Treatment Options for Menopausal Vaginal Changes
  – VIVA: *Vaginal Health: Insights, Views, and Attitudes*
    Nappi RE, Kokot-Kierepa M. *Maturitas* 2010;67(3):233-238
  – CLOSER: *CLarifying Vaginal Atrophy’s Impact On SEX and Relationships*
    Nappi RE et al. *J Sex Med* 2013,10:2232-2241

• Conclusion:
  – Negative impact of VVA on sexual health and other activities of daily life
VVA Market Dynamics - Ready for New Product

Only 2.3MM U.S. women treated with Rx product¹

Vaginal Creams
- Messiness²
- Reusable Applicator
- Long-term safety²
- Dose preparation by user required³

Mean treatment duration
46 days⁴

Vaginal Tablets
- Efficacy²
- Applicator
- Long-term safety²
- Systemic absorption²

Mean treatment duration
103 days⁴

Women primed for conversion to new product

¹ IMS Health Plan Claims (April 2008-Mar 2011).
⁴ Portman, D, et al. One Year Treatment Persistence with Local Estrogen Therapy in Postmenopausal Women Diagnosed as Having Vaginal Atrophy. Menopause. 2015; 22 (11) 1197-203.
VVA Market Opportunity

Brian Bernick, M.D.
– Co-founder & Chief Clinical Officer TherapeuticsMD
YUVVEXY™ (TX-004HR): Rationale for Development

• TX-004HR is an investigational **applicator-free** vaginal softgel capsule that contains solubilized **17β-estradiol**

• TX-004HR is designed to provide **improved efficacy, early onset of action** and **lower systemic estrogen** levels vs. currently available products

• TX-004HR is designed to fulfill an unmet need for a more **user-friendly** modern treatment
Established VVA Market

- U.S. sales approximately $1.5 billion in 2015\(^1\)
- U.S. sales more than doubled since 2008\(^1\)
- Global market expected to be $2.1 billion in 2022\(^4\)
- Currently no generic competition
- 32 million U.S. women currently experiencing VVA symptoms\(^5,6\)

<table>
<thead>
<tr>
<th>Premarin(^\circ)</th>
<th>Vagifem(^\circ)</th>
<th>Estrace(^\circ)</th>
<th>Osphena(^\circ)</th>
<th>Estring(^\circ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reusable Vaginal Applicator</td>
<td>Vaginal Applicator</td>
<td>Reusable Vaginal Applicator</td>
<td>Oral Daily SERM</td>
<td>Vaginal Ring</td>
</tr>
<tr>
<td>Vaginal Cream</td>
<td>Vaginal Tablet</td>
<td>Vaginal Cream</td>
<td>Oral Tablet</td>
<td>Vaginal Ring</td>
</tr>
<tr>
<td>$502MM(^1)</td>
<td>$456MM(^1)</td>
<td>$420MM(^1)</td>
<td>$66MM(^1)</td>
<td>$91MM(^1)</td>
</tr>
</tbody>
</table>

1) Symphony Health Solutions PHAST 2.0 Prescription Monthly Powered by IDV, 12 months as of December 31, 2015.
2) Femring data is excluded due to VMS indication.
3) Medi-Span Price Rx Basic as of 2/25/16. * For 18 tablets ($156.54 WAC for 8 tablets)
4) GlobalData July 2013 report GDHC54PIDR.

All trademarks are the property of their respective owners.
YUVVEXY™ (TX-004HR)

- Small digitally inserted rapidly dissolving softgel capsule
- No applicator
- Proposed dose packaging to optimize compliance and convenience

YUVVEXY™ is an investigational drug and is not approved for use by the FDA.
Presentation of REJOICE Trial Data

Sebastian Mirkin, M.D.
– Chief Medical Officer, TherapeuticsMD
YUVVEXY™ (TX-004HR)
Product Target Profile

- No systemic absorption
- Variable Dosing
- Early onset of action
- Highly Efficacious for full VVA symptoms
- High Satisfaction
Clinical Program: YUVVEXY™ (TX-004HR) (Completed)

✓ **Phase 1 Studies (499 and 500)**
  - Single dose, randomized, open label, two-way crossover vs. Vagifem®, bioavailability study

✓ **Phase 2 Study (TXV-13-01)**
  - A randomized, double blind, placebo controlled trial to evaluate the safety and efficacy of TX-004HR 10mcg on VVA
  - 2 weeks duration

✓ **Phase 3 study (TXV-14-01) - REJOICE Trial**
  - A randomized, double blind, placebo controlled trial to evaluated the safety and efficacy of TX-004HR 4, 10 and 25 mcg on VVA
Phase 3 Clinical Study
REJOICE TRIAL

■ 12 Week Randomized, Double-blinded, Placebo-controlled

■ Subjects: 764; 89 Sites across the United States and Canada

➤ Main inclusion criteria
   ▪ Postmenopausal
   ▪ Sexually active
   ▪ ≤ 5% superficial cells on vaginal smear
   ▪ Vaginal pH > 5
   ▪ Moderate to severe dyspareunia as most bothersome symptom

➤ 4 groups
   ▪ 4 mcg (N=191)
   ▪ 10 mcg (N=191)
   ▪ 25 mcg (N=190)
   ▪ Placebo (N=192)

REJOICE TRIAL
Co-Primary and Key Secondary Endpoints

FDA Required Co-Primary Endpoints – mean change from baseline to week 12 in\textsuperscript{1,2}:

- Vaginal superficial cells
- Vaginal parabasal cells
- Vaginal pH
- Moderate to severe dyspareunia (identified as the most bothersome symptom of VVA)

Key components of secondary endpoints:

- Efficacy of co-primary endpoints at week 2
- Vaginal dryness

AdditionalEndpoints:

- PK measures Days 1, 14, 84
- FSFI (Female Sexual Function Index)
- Acceptability survey

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1) Each arm (4 mcg, 10 mcg, and 25 mcg) tested against each co-primary endpoint.
2) The FDA has previously indicated to us that in order to approve the drug based on a single trial, the trial would need to show statistical significance at the 0.01 level or lower for each endpoint, and that a trial that is merely statistically significant at a higher level may not provide sufficient evidence to support an NDA filing or approval of a drug candidate where the NDA relies on a single clinical trial.
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>4 mcg N=191</th>
<th>10 mcg N=191</th>
<th>25 mcg N=190</th>
<th>Placebo N=192</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>59.8 ± 5.9</td>
<td>58.5 ± 6.3</td>
<td>58.9 ± 6.3</td>
<td>59.3 ± 6.1</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>87.4%</td>
<td>88.0%</td>
<td>86.8%</td>
<td>84.4%</td>
</tr>
<tr>
<td>Black</td>
<td>10.5%</td>
<td>11.0%</td>
<td>12.6%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Other</td>
<td>2.1%</td>
<td>1.0%</td>
<td>0.5%</td>
<td>3.1%</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>26.5 ± 4.9</td>
<td>26.8 ± 4.7</td>
<td>26.7 ± 4.8</td>
<td>26.6 ± 4.5</td>
</tr>
<tr>
<td><strong>Type of Menopause</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural</td>
<td>114 (59.7%)</td>
<td>114 (59.7%)</td>
<td>121 (63.7%)</td>
<td>127 (66.2%)</td>
</tr>
<tr>
<td>Surgical</td>
<td>77 (40.3%)</td>
<td>77 (40.3%)</td>
<td>69 (36.3%)</td>
<td>65 (33.9%)</td>
</tr>
</tbody>
</table>
### Discontinuation Rates by Reason

<table>
<thead>
<tr>
<th>Reason</th>
<th>4 mcg (N=191)</th>
<th>10 mcg (N=191)</th>
<th>25 mcg (N=190)</th>
<th>Placebo (N=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects Discontinued</strong></td>
<td><strong>16 (8.4%)</strong></td>
<td><strong>17 (8.9%)</strong></td>
<td><strong>13 (6.8%)</strong></td>
<td><strong>14 (7.3%)</strong></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>2 (1.0%)</td>
<td>3 (1.6%)</td>
<td>4 (2.1%)</td>
<td>5 (2.6%)</td>
</tr>
<tr>
<td>Investigator / Sponsor Decision</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>2 (1.0%)</td>
<td>2 (1.0%)</td>
<td>0 (0%)</td>
<td>4 (2.1%)</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>3 (1.6%)</td>
<td>3 (1.6%)</td>
<td>2 (1.1%)</td>
<td>4 (2.1%)</td>
</tr>
<tr>
<td>Protocol Violation</td>
<td>2 (1.0%)</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Withdrew Consent</td>
<td>6 (3.1%)</td>
<td>7 (3.7%)</td>
<td>5 (2.6%)</td>
<td>5 (2.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Co-Primary Efficacy Endpoints
LS Mean Change from Baseline to Week 12: Vaginal Superficial Cells

LS = Least Squares

Change in Percentage Superficial Cells

LS Mean ± SE

- 4 mcg: p<0.0001, N=186, 17%
- 10 mcg: p<0.0001, N=188, 17%
- 25 mcg: p<0.0001, N=186, 23%
- Placebo: 6%, N=187
LS Mean Change from Baseline to Week 12: Vaginal Parabasal Cells

Change in Percentage Parabasal Cells

LS Mean ± SE

4 mcg: N=186, p<0.0001, -41%
10 mcg: N=188, p<0.0001, -44%
25 mcg: N=186, p<0.0001, -46%
Placebo: N=187, -7%

LS = Least Squares
LS Mean Change from Baseline to Week 12: Vaginal pH

LS = Least Squares
LS Mean Change from Baseline to Week 12: Severity of Dyspareunia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS Mean ± SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mcg</td>
<td>-1.5</td>
<td>0.0149</td>
</tr>
<tr>
<td>10 mcg</td>
<td>-1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>25 mcg</td>
<td>-1.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>-1.3</td>
<td></td>
</tr>
</tbody>
</table>

N=151 for 4 mcg, N=154 for 10 mcg, N=159 for 25 mcg, N=163 for Placebo.
Key Components of Secondary Efficacy Endpoints
## Statistical Significance of LS Mean Change from Baseline Severity of Dyspareunia by Study Visit (Week)

<table>
<thead>
<tr>
<th></th>
<th>4 mcg</th>
<th>10 mcg</th>
<th>25 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>0.026</td>
<td>0.0019</td>
<td>0.0105</td>
</tr>
<tr>
<td>Week 6</td>
<td>0.0069</td>
<td>0.0009</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.0003</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Week 12</td>
<td>0.0149</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

MMRM P-value vs placebo
LS Mean Change from Baseline to Week 12: Severity of Vaginal Dryness

LS = Least Squares
Co-Primary and Key Secondary Endpoints
LS Mean Change from Baseline to Week 12
Compared to Placebo

<table>
<thead>
<tr>
<th></th>
<th>4 mcg</th>
<th>10 mcg</th>
<th>25 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial Cells</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parabasal Cells</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vaginal pH</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severity of Dyspareunia</td>
<td>0.0149</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severity of Vaginal Dryness</td>
<td>0.0014</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

MMRM P-value vs placebo
## Efficacy and Onset of Action

Based on FDA-Approved Labeling and Not Head-to-Head Comparative Studies

<table>
<thead>
<tr>
<th>Onset of Action</th>
<th>Premarin®</th>
<th>Vagifem®</th>
<th>Estrace®</th>
<th>Osphena®</th>
<th>Estring®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspareunia</td>
<td>Week 4+</td>
<td>Week 8 (composite score)</td>
<td>Approval without dyspareunia and dryness data</td>
<td>Week 12</td>
<td>Approval without dyspareunia and dryness data</td>
</tr>
<tr>
<td>Dryness</td>
<td>Not demonstrated</td>
<td>Not demonstrated</td>
<td>Not demonstrated</td>
<td>Not demonstrated</td>
<td>Not demonstrated</td>
</tr>
</tbody>
</table>

Onset of Action = First efficacy observation
Responder Analysis: Severity of Dyspareunia at Week 12

Percentage of subjects with a decrease in severity of dyspareunia of 2+ points

- 4 mcg: 41.0% (N=151), p=0.0317
- 10 mcg: 47.4% (N=154), p=0.0006
- 25 mcg: 55.4% (N=159), p=0.0001
- Placebo: 35.8% (N=163)

Responder defined as reduction of 2+ points
Results from Pharmacokinetics Substudy
### Arithmetic Mean Estradiol Serum Concentrations - Unadjusted TX-004HR 4 mcg (N=18)

**Mean Serum Estradiol Concentration (pg/mL)**

![Graph showing mean serum estradiol concentrations](image)

- **Hours after capsule insertion Day 14** (represents day 84)

<table>
<thead>
<tr>
<th></th>
<th>$AUC_{0-24}$ (pg.h/mL)</th>
<th>$C_{avg(0-24)}$ (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mcg</td>
<td>87.22 (42.77)</td>
<td>3.634 (1.78)</td>
</tr>
<tr>
<td>Placebo</td>
<td>104.16 (66.38)</td>
<td>4.34 (2.76)</td>
</tr>
<tr>
<td><strong>P-value vs Placebo</strong></td>
<td>0.3829</td>
<td>0.3829</td>
</tr>
</tbody>
</table>

(N=18)
Arithmetic Mean Estradiol Serum Concentrations - Unadjusted
TX-004HR 10 mcg (N=19)

<table>
<thead>
<tr>
<th></th>
<th>AUC_{0-24} (pg.h/mL)</th>
<th>C_{avg(0-24)} (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mcg</td>
<td>110.14 (54.57)</td>
<td>4.58 (2.27)</td>
</tr>
<tr>
<td>Placebo</td>
<td>104.16 (66.38)</td>
<td>4.34 (2.76)</td>
</tr>
<tr>
<td>P-value vs Placebo</td>
<td>0.7724</td>
<td>0.7724</td>
</tr>
</tbody>
</table>

Hours after capsule insertion Day 14
(◯ represents day 84)
Arithmetic Mean Estradiol Serum Concentrations - Unadjusted
TX-004HR 25 mcg (N=18)

<table>
<thead>
<tr>
<th></th>
<th>AUC$_{0-24}$ (pg.h/mL)</th>
<th>C$_{\text{avg}(0-24)}$ (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mcg</td>
<td>171.56 (80.13)</td>
<td>7.14 (3.33)</td>
</tr>
<tr>
<td>Placebo</td>
<td>104.16 (66.38)</td>
<td>4.34 (2.76)</td>
</tr>
<tr>
<td>P-value vs Placebo</td>
<td>0.0108</td>
<td>0.0108</td>
</tr>
</tbody>
</table>

Hours after capsule insertion Day 14
(loit represents day 84)
Acceptability of Product Administration
**Was the product easy to use?**

<table>
<thead>
<tr>
<th></th>
<th>4 mcg (N=181)</th>
<th>10 mcg (N=181)</th>
<th>25 mcg (N=184)</th>
<th>Placebo (N=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>171 (94.5%)</td>
<td>172 (95.0%)</td>
<td>175 (95.1%)</td>
<td>164 (88.9%)</td>
</tr>
</tbody>
</table>

Overall p-value = 0.035
How would you rate the ease of insertion of the capsule?

<table>
<thead>
<tr>
<th>Rating</th>
<th>4 mcg (N=181)</th>
<th>10 mcg (N=181)</th>
<th>25 mcg (N=184)</th>
<th>Placebo (N=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>79 (44.0%)</td>
<td>83 (46.0%)</td>
<td>83 (45.0%)</td>
<td>65 (35%)</td>
</tr>
<tr>
<td>Good</td>
<td>77 (43.0%)</td>
<td>72 (40.0%)</td>
<td>74 (40.0%)</td>
<td>79 (43%)</td>
</tr>
<tr>
<td>Fair</td>
<td>20 (11.0%)</td>
<td>23 (13.0%)</td>
<td>18 (10.0%)</td>
<td>25 (14%)</td>
</tr>
<tr>
<td>Poor</td>
<td>5 (3.0%)</td>
<td>3 (1.7%)</td>
<td>9 (5.0%)</td>
<td>16 (9.0%)</td>
</tr>
</tbody>
</table>

Overall p-value = 0.037
## Level of satisfaction with the product

<table>
<thead>
<tr>
<th></th>
<th>4 mcg  (N=181)</th>
<th>10 mcg (N=181)</th>
<th>25 mcg (N=184)</th>
<th>Placebo (N=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Satisfied</strong></td>
<td>74 (40.1%)</td>
<td>84 (46.4%)</td>
<td>83 (45.1%)</td>
<td>41 (22.2%)</td>
</tr>
<tr>
<td><strong>Satisfied</strong></td>
<td>57 (31.5%)</td>
<td>55 (30.4%)</td>
<td>62 (33.7%)</td>
<td>68 (36.8%)</td>
</tr>
<tr>
<td><strong>Unsure</strong></td>
<td>23 (12.7%)</td>
<td>28 (15.5%)</td>
<td>21 (11.4%)</td>
<td>39 (21.1%)</td>
</tr>
<tr>
<td><strong>Dissatisfied</strong></td>
<td>19 (10.5%)</td>
<td>9 (5.0%)</td>
<td>12 (6.5%)</td>
<td>20 (10.8%)</td>
</tr>
<tr>
<td><strong>Very Dissatisfied</strong></td>
<td>8 (4.4%)</td>
<td>5 (2.8%)</td>
<td>6 (3.3%)</td>
<td>17 (9.2%)</td>
</tr>
</tbody>
</table>

Overall p-value <0.0001
Safety Endpoints
## Overview of Adverse Events (AEs) (Safety Population)

<table>
<thead>
<tr>
<th>Condition</th>
<th>4 mcg (N=191)</th>
<th>10 mcg (N=191)</th>
<th>25 mcg (N=190)</th>
<th>Placebo (N=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Subject with Reported AE</td>
<td>113 (59.2%)</td>
<td>105 (55.0%)</td>
<td>107 (56.3%)</td>
<td>124 (64.6%)</td>
</tr>
<tr>
<td>Any Subject with Reported TEAE</td>
<td>96  (50.3%)</td>
<td>91  (47.6%)</td>
<td>90  (47.4%)</td>
<td>104  (54.2%)</td>
</tr>
<tr>
<td>Any Subject with Drug Related TEAE</td>
<td>38  (19.9%)</td>
<td>28  (14.7%)</td>
<td>34  (17.9%)</td>
<td>47  (24.5%)</td>
</tr>
<tr>
<td>Any Reported Serious TEAE</td>
<td>0  (0.0%)</td>
<td>2   (1.0%)</td>
<td>3   (1.6%)</td>
<td>1   (0.5%)</td>
</tr>
<tr>
<td>Any AE Leading to Discontinuation</td>
<td>2  (1.0%)</td>
<td>3   (1.6%)</td>
<td>4   (2.1%)</td>
<td>5   (2.6%)</td>
</tr>
</tbody>
</table>

TEAE – Treatment Emergent Adverse Event
### TEAEs by Preferred Term Occurring ≥ 3% (Safety Population)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>4 mcg (N=191)</th>
<th>10 mcg (N=191)</th>
<th>25 mcg (N=190)</th>
<th>Placebo (N=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>5 (2.6%)</td>
<td>6 (3.1%)</td>
<td>7 (3.7%)</td>
<td>10 (5.2%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (2.6%)</td>
<td>6 (3.1%)</td>
<td>3 (1.6%)</td>
<td>5 (2.6%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (2.6%)</td>
<td>5 (2.6%)</td>
<td>8 (4.2%)</td>
<td>4 (2.1%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>9 (4.7%)</td>
<td>1 (0.5%)</td>
<td>4 (2.1%)</td>
<td>7 (3.6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (6.3%)</td>
<td>14 (7.3%)</td>
<td>5 (2.6%)</td>
<td>14 (7.3%)</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>5 (2.6%)</td>
<td>6 (3.1%)</td>
<td>4 (2.1%)</td>
<td>13 (6.8%)</td>
</tr>
<tr>
<td>Vulvovaginal pruritus</td>
<td>4 (2.1%)</td>
<td>2 (1.0%)</td>
<td>7 (3.7%)</td>
<td>10 (5.2%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>6 (3.2%)</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

TEAE – Treatment Emergent Adverse Event
Safety Protocol Procedures

- No significant difference in safety labs or vital signs
- No increase in estrogen sensitive tests (i.e., SHBG, Triglycerides)
- No significance difference in EKG findings
- No signal of estrogenic stimulation of the endometrium
Conclusions

TX-004HR at 4, 10 and 25 mcg demonstrated a positive benefit/risk profile for the proposed indication of “treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause”

- Increased percentage of vaginal superficial cells
- Decreased percentage of vaginal parabasal cells
- Decreased vaginal pH
- Improved dyspareunia as the most bothersome symptom
- Improved vaginal dryness
- Efficacy observed at week 2

• No difference compared to placebo in incidence of TEAEs or SAEs
• Negligible to very low systemic absorption of 17-β estradiol
  - Significantly lower than Vagifem
• High patient acceptability and satisfaction rates
• Easy to use and insert without the need of an applicator
Regulatory Strategy

• **Proposed Indication**: Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause

• **Clinical Program Completed**

• **Positive Benefit/Risk** profile demonstrated for 4, 10 and 25 mcg

• **Planned NDA under 505(b)(2) pathway** for the 3 doses
  
  • Strategy confirmed at Pre-NDA meeting

• **TherapeuticsMD to propose a highly differentiated label**
  
  • Negligible to very low systemic absorption of 17 β-estradiol
  • Early efficacy/onset of action
  • Applicator-free
Yuvvexy™ (TX-004HR)
Proposed US Regulatory Approach/Labeling

Lisa Rarick, M.D.
Former FDA—Center for Drug Evaluation and Research (CDER)
Medical Officer & Division Director (Division of Bone, Reproductive and Urologic Products)
and FDA Office of the Commissioner, Office of Women’s Health (OWH)
• “On the topic of the labeling for lower-dose estrogen products delivered vaginally…”

• “Lower-dose estrogen products [below 0.625 mg conjugated estrogens used in WHI, and below 0.0375 mg of estradiol products] are now approved for treatment of VVA due to menopause, and some in the scientific/medical community have questioned whether the current ‘Boxed Warnings’ section in the labeling is applicable in whole or in part to these lower-dose estrogen products.”

• FDA seeking input on Boxed Warnings section, estrogen exposure data and PK/PD information relative to labeling lower-dose estrogen products...

TherapeuticsMD proposal for US Labeling—Governed by Regulations and Guidance

- Yuvvexy™ (TX-004HR)—Sections of label to be considered for modification
  - Highlights of Prescribing Information
  - Boxed Warnings
  - Contraindications
  - Warnings and Precautions
  - Adverse Reactions
  - Clinical Pharmacology
  - Clinical Studies
  - Dosage and Administration
  - Patient Counseling/Patient Labeling
Proposed Elimination or Modifications to Boxed Warning

- Estrogen-alone boxed warning information
  - Propose removal from Boxed Warning
  - Propose modified language in the “Warnings and Precautions” Section

- Estrogen + Progestin boxed warning information
  - Propose removal from Boxed Warning
  - Propose removal or modification throughout the label
  - Provide data to support that progestin not needed for endometrial protection
Contraindications

- Possible opportunity to remove or modify current Contraindication “Known, suspected, or history of breast cancer”
Warnings and Precautions

• Proposed modification re: “Risks from Systemic Absorption”

• Propose modification of each of the current Warnings with draft language such as “When estrogens are used with resulting systemic absorption higher than demonstrated for Yuvvexy™, an increased risk of XX has been reported”

• May need to add “Although Yuvvexy™ use does not result in the level of systemic exposure associated with this increased risk, long-term safety studies with Yuvvexy™ are not available.”

• Proposed removal of “addition of a Progestin” section
Adverse Reactions
Clinical Pharmacology
Clinical Studies

• Adverse Reactions tables/listings specific to Yuvvexy™ clinical trials
• Clinical Pharmacology to reflect Yuvvexy™ pK data (negligible to very low systemic absorption)
• Clinical Studies
  • Results for co-primary endpoints
  • May be able to include first efficacy timepoint/onset of action (statistical significance at week 2)
  • Propose to include vaginal dryness efficacy
Dosage and Administration

2. DOSAGE AND ADMINISTRATION
“A single YUVVEXY capsule should be administered digitally intravaginally.”
YUVVEXY™ (TX-004HR)
TherapeuticsMD Label Proposal

• Potential Modification of Boxed Warnings
  Estrogen Warnings
  — Potential removal from Boxed Warning section
  — Potential modifications of estrogen warnings
  Estrogen + Progestin Warnings
  — Potential removal from Boxed Warning section
  — Potential removal of progestin use for endometrial protection

• DOSAGE AND ADMINISTRATION
  — Potential language to administer “digitally intravaginally” without instruction for an applicator
  — Potential removal of progestin use for endometrial protection

• WARNINGS AND PRECAUTIONS
  — Potential modification of warnings related to higher dose estrogens
  — Potential removal (or modification) of warnings related to estrogen + progestins
  — Potential modification of systemic absorption warnings

• CLINICAL STUDIES
  — Results for co-primary endpoints
  — Potential labeling to include language regarding demonstration of statistical significance over placebo for the four co-primary endpoints being demonstrated at study visits, including week 2
  — Potential labeling to include vaginal dryness efficacy
• Robert Finizio – Co-founder and Chief Executive Officer, TherapeuticsMD

• Brian Bernick, M.D. – Co-founder and Chief Clinical Officer, TherapeuticsMD

• Sebastian Mirkin, M.D. – Chief Medical Officer, TherapeuticsMD

• Sheryl Kingsberg, Ph.D. * – Chief, Division of OB/GYN Behavioral Medicine, UH Case Medical Center, Board of Trustees of the North American Menopause Society (NAMS)

• Lisa Rarick, M.D. * – Former FDA Medical Officer & Division Director Center for Drug Evaluation and Research (CDER) and FDA Office of Women’s Health

• Ginger Constantine, M.D. * – President Endorheum Consultants, Former Wyeth Women’s Health and Musculoskeletal VP and Therapeutic Area Director, Clinical Research and Development

• James Simon, M.D. *† – Professor of Ob/Gyn, George Washington University, Past President of the North American Menopause Society (NAMS), President Elect of the International Society for the Study of Women’s Sexual Health (ISSWSH)

• Steven Goldstein, M.D. * – Professor of Ob/Gyn, New York University, Past President of the North American Menopause Society (NAMS)

* Consultant to TherapeuticsMD
† Clinical Investigator for TX-004HR REJOICE Trial
THANK YOU
YUVVEXY™ (TX-004HR) – Target Product Profile

Target Goals

Efficacy

Low systemic exposure

Fast onset of action

New lower effective dose

Improved user experience

Phase 3 Supportive Data

Phase 3 data demonstrated statistical significance for all 3 doses on the 4 co-primary endpoints

Negligible to low systemic absorption with 4 mcg, 10 mcg and 25 mcg observed in phase 1 and 3

Efficacy observed at Day 14 in phase 2 and 3

Phase 3 evaluated broad range of doses, including 4, 10, and 25 mcg; 4 mcg represents potential new lowest strength dose

Phase 3 data included patient satisfaction; 95% said “easy to use”

Digitally inserted – No applicator

Phase 3 data suggests no clinically significant differences vs. placebo; no drug-related serious adverse events
Phase 1 Single Dose PK Studies
TX-004HR vs. Vagifem®

Systemic absorption AUC (0-24 hours) and $C_{\text{avg}}$ (0-24 hours) for estradiol is 2- to 3-fold lower with TX-004HR relative to Vagifem® ($p < 0.0001$)

Vagifem is a registered trademark of Novo Nordisk A/S Corp.
The Female Sexual Function Index (FSFI) Total Score

Less Sexual Dysfunction

- 4 mcg: N=153, P=0.9075
- 10 mcg: N=152, P=0.0492
- 25 mcg: N=156, P=0.0019
- Placebo: N=158

Total Score Range: 2.0 to 36.0
YUVVEXY™ (TX-004HR) Medical Differentiation Index

PROGRAM IMPLICATIONS

- Negligible to Low Systemic Absorption
- Variable Dosing
- 2 week onset of action
- Highly Efficacious for VVA/GSM
- High Satisfaction

DOSAGE

- E2 absorption range: 0% to 80%
- Dosage: 4 mcg, 10 mcg, 25 mcg, 30 mcg
- Onset of action: 2 week, 12 week

EFFICACY

- Efficacy: 50%, 100%
- User experience: 20%, 95%, 100%

TX-004HR Data results