TAS-108: A Novel Steroidal Anti-Estrogen for Treatment of Breast Cancer

Potential Indications

- Neo-adjuvant therapy for ER$^+$ primary breast cancers in premenopausal women
- Adjuvant therapy for ER$^+$ premenopausal women with recurrent or metastatic breast cancer
- Adjuvant therapy in ER$^+$ postmenopausal women with recurrent or metastatic disease
Who We Are
SRI is a world-leading independent R&D organization

• Founded in 1946 as Stanford Research Institute
  – Independent in 1970; became SRI International in 1977
  – Opened Center for Advanced Drug Research in 2006
  – More than 2,100 staff members (more than 800 with advanced degrees) at more than 20 locations worldwide; 2011 revenue: $585M

• Biosciences Division: ~270 staff at four locations
  – Basic research, drug discovery, and preclinical development in cancer, infectious diseases, neuroscience, metabolic diseases, autoimmune and inflammatory diseases
  – Developed >100 drugs to IND; >10 to market with corporate, government, academic, and foundation partners
TAS-108 Executive Summary

Available for licensing

• Clinical benefit: efficacy against tamoxifen- (TAM) and aromatase inhibitor (AI)-resistant breast cancers
• Improved safety profile in bone and uterus, compared to AIs and TAM
• Convenient, once-daily oral administration
• Substantial clinical data; five Phase I and two Phase II trials
  – Phase II data (n=242) from multi-center, multi-national trial
    Principal Investigator: Dr. Aman Buzdar, MD Anderson
• Composition of Matter Patent (Expiration Dec 2017); use and process patents under consideration; orphan drug application in preparation
• Multiple, efficient clinical paths to registration
• Worldwide rights, except Japan, available for licensing
TAS-108
Development history

• Discovered (SR16234) and developed to IND filing by SRI’s Biosciences Division

• Licensed to Taiho Pharmaceutical Co., Ltd. for clinical development and commercialization

• Worldwide rights, except Japan, returned to SRI January, 2010 following successful completion of Phase II trials
## Clinical Profile of Ideal SERM
Adapted from Taylor Menopause 2009

<table>
<thead>
<tr>
<th>Site of Action</th>
<th>Effect</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>ER agonist</td>
<td>Prevent osteoporosis Reduce fracture risk</td>
</tr>
<tr>
<td>CNS</td>
<td>ER agonist</td>
<td>Reduce hot flushes Reduce other menopausal symptoms</td>
</tr>
<tr>
<td>Breast</td>
<td>ER neutral or antagonist</td>
<td>Prevention or no increase in breast cancer Limit cancer proliferation</td>
</tr>
<tr>
<td>Cardiovascular/Lipids</td>
<td>ER agonist</td>
<td>Lower CV risk Lower levels of circulating cholesterol</td>
</tr>
<tr>
<td>Uterus</td>
<td>ER neutral or antagonist</td>
<td>Prevention or no increase in endometrial cancer Limit cancer proliferation</td>
</tr>
</tbody>
</table>
## Introduction: TAS-108
Superior clinical efficacy and safety profile

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anti-Tumor Activity</th>
<th>No Endometrial Thickening</th>
<th>Maintains Bone Mineral Density</th>
<th>Efficacy vs. TAM/AI Resistant Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAS-108</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AIs</td>
<td>✓</td>
<td>✓</td>
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</tbody>
</table>

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Summary: TAS-108
Preclinical profile

• Binds ERα with high affinity, similar to estradiol
• Pure ERα antagonist and partial ERβ agonist
  – Specifically recruits co-activator (TIF2) to ERβ, which may prevent bone loss
• Greater in-vivo anti-tumor activity than TAM or fulvestrant
• Inhibits growth of tamoxifen-resistant tumors; active against cell lines with reduced sensitivity to TAM, fulvestrant, raloxifene and estrogen-independent lines
• Few estrogen-like effects on rat uteri
• Prevents reduction of bone density in animal models
• Lowers total serum cholesterol and LDL in rats
Summary: TAS-108
Phase I studies

• Five Phase I trials (3 US / 2 Japan, n=67):
  – Rapidly absorbed after oral dose, reaching $T_{\text{max}}$ in ~3-5 hr
  – Terminal $t_{1/2}$ was ~8-11 hr
  – Postprandial $C_{\text{max}}$ and $\text{AUC}_{0-t}$ significantly higher than fasting
  – Exposure ($\text{AUC}_{0-t}$) increased linearly with dose up to 120 mg
  – Repeat doses of 40, 80, 120 mg
  – Plasma levels of TAS-108 and its metabolite increased in a linear dose-dependent manner
  – Steady state plasma levels achieved after 2 weeks
  – No clinically significant AEs or SAEs; no apparent dose related AE trend
  – No significant endometrial thickening or changes in bone mineral density
Summary - TAS-108
Phase II studies

• Two randomized Phase II studies (n=242):
  – Optimal antitumor dose is 40mg/day by oral administration
  – Significant antitumor activity seen in 2nd and 3rd line breast cancer patients resistant to TAM and/or an AI
  – Clinical Benefit (CB) = Complete Response + Partial Response + Stable Disease >24 weeks; rate of 30.3% and 28.3% in the two Phase II studies, respectively
  – Time to Progression (TTP) was 120 days and 105 days for the two studies, respectively
  – All TAS-108 dose levels were well tolerated, with most AEs being Grade 2 or lower
  – No significant endometrial thickening or changes in bone mineral density
Clinical Development Pathway

• Special Protocol Assessment (SPA) filed with FDA
  – “A Double Blind, International Multicenter, Two-Arm, Parallel, Randomized Phase 3 Study Evaluating the Efficacy and Safety of TAS-108 Versus Fulvestrant in Postmenopausal Women with Hormone Receptor-Positive (HR+) Advanced Breast Cancer with Disease Progression after Prior Therapy with Tamoxifen and an Aromatase Inhibitor with or without One Prior Chemotherapy.”
  – A SPA is a declaration from the Food and Drug Administration that a Phase III trial's design, clinical endpoints, and statistical analyses are acceptable for FDA approval.
Next Steps

- Execute Confidential Disclosure Agreement (CDA) with SRI International
- Detailed information on preclinical development studies available under CDA