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1) **MoA and modality:** $K_{Ca}3.1$ channel opener; small molecule; Peripheral action unlike other CNS targeted SOCs.

2) **Status:** P2a FM study completed. The data of efficacy and clean safety was well accepted by KOLs.

3) **Competition:** Minimum. Treatment options are limited to CNS acting agent with tolerability issues. There's nothing promising in development pipeline outside Astellas, other than ASP0819.

4) **LOE:** 2034 + extension (max 5yrs).

5) **Potential to be pain platform with a single agent:** Additional indications are OA pain and visceral pain.
FIBROMYALGIA (FM) OVERVIEW

Disease Overview

1. **Patient Characteristics**
   - 80 - 90% of patients are women.
   - The average age at diagnosed is 35 to 45 years old.

2. **Clinical Symptoms**
   - **Widely spread, severe pain**: pain in the muscles, abdomen, back or neck. The pain can be chronic, diffuse, sharp or severe, muscle tenderness, muscle spasms.
   - **Other symptoms**: difficulty falling asleep, sleep disturbances, anxiety, mood swings, fatigue, IBS etc.
   - Cause of FM is not well known.

3. **Diagnosis**
   - Diagnosis can be confirmed when pressure is applied to specific areas of your body, called tender points. At least 11 of the 18 spots have to test positive for tenderness to diagnose FM.

3: https://www.mayoclinic.org/tender-points/img-20007586
ASP0819, a $K_{Ca}3.1$ channel opener, can improve muscle pain via peripheral mechanisms.

- ASP0819 is a first-in-class $K_{Ca}3.1$ channel opener of FM.
- $K_{Ca}3.1$ channels express in Aδ- and C-fibers and DRG neurons which are involved in sensory signals via primary afferent nerve system.
- Activation of $K_{Ca}3.1$ reduces neuronal excitability with an enhancement of the afterhyperpolarization (AHP).
- ASP0819 exhibits poor brain penetration.
## ASP0819 PROFILE SUMMARY

### Pharmacology
- Potassium channel opening activity in CHO cells expressed human \( K_{Ca} \)3.1 channel: \( EC_{50} \)=102.4 nmol/L.
- Off target selectivity: no appreciable affinity for about 60 receptor binding sites, ion channels and transporters tested at 10 μmol/L.
- Potent analgesic effects in several animal models of fibromyalgia.

### ADME
- \( C_{max} \) and AUC\(_{24} \) were dose proportional at 3-30 mg/kg in rats and dogs.
- In vitro human plasma protein binding ratio: 99.82% - 99.97% at 1 - 100 μg/mL.
- No human-specific metabolites in liver microsomes or hepatocytes.
- IC\(_{50} \) values for CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 were ≥ 9.10 μmol/L with no time-dependent inhibition.
- IC\(_{50} \) values for CYP3A were > 50 (midazolam) and 35.1 μmol/L (testosterone) with time-dependent inhibition.

### Tox
- Thirteen-week tox studies: findings at the LOAEL restricted to the stomach in rats and dogs; additionally hematological and biochemical changes noted at higher doses in rats or dogs.
- Preliminary embryo-fetal toxicity in rats: growth retardation associated with maternal toxicity.
- Genotoxicity and phototoxicity: negative
ASP0819 significantly improved muscle pain and visceral pain in the rat models.
Spontaneous and mechanically-evoked nerve firing in single primary sensory neuron of dorsal root were recorded in urethane anesthetized RIM rats.

Data are expressed as the mean ± SEM (n=8-10) in each group. ###P < 0.001, statistically significant compared to vehicle-treated group at same time points (Student's t-test). *P < 0.05, **P < 0.01, ***P < 0.001, statistically significant compared to vehicle-treated group at same time points (Dunnett's multiple comparison test).

Intravenous infusion of ASP0819 (0.3-1 mg/kg/h) significantly reduced the spontaneous activity and mechanically-evoked responses in Aδ-fibers in a rat RIM model.
### PHARMACOLOGY SUMMARY: IN VIVO MODELS

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Endpoint</th>
<th>Efficacy (mg/kg, po)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FM</strong></td>
<td><strong>RIM model</strong></td>
<td>Muscle pain</td>
</tr>
<tr>
<td></td>
<td><strong>FM model</strong></td>
<td>0.1***, 0.3***, 1***</td>
</tr>
<tr>
<td></td>
<td><strong>VIM model</strong></td>
<td>Muscle pain</td>
</tr>
<tr>
<td></td>
<td><strong>VIM model</strong></td>
<td>0.1***, 0.3***, 1***</td>
</tr>
<tr>
<td><strong>OA</strong></td>
<td><strong>AIA model</strong></td>
<td>NSAIDs-sensitive OA pain</td>
</tr>
<tr>
<td></td>
<td><strong>OA model</strong></td>
<td>0.3, 1**, 3***</td>
</tr>
<tr>
<td></td>
<td><strong>MIA model</strong></td>
<td>NSAIDs-insensitive OA pain</td>
</tr>
<tr>
<td></td>
<td><strong>MIA model</strong></td>
<td>0.1*, 0.3**, 1**</td>
</tr>
<tr>
<td><strong>IBS</strong></td>
<td><strong>CRD model</strong></td>
<td>Visceral pain</td>
</tr>
<tr>
<td></td>
<td><strong>IBS model</strong></td>
<td>0.1, 0.3$, 1$$$$</td>
</tr>
</tbody>
</table>


*P < 0.05, **P < 0.01, ***P < 0.001, statistically significant compared to the vehicle-treated group (Dunnett's multiple comparison test).

$P < 0.0166 and $$$P < 0.000333, statistically significant compared to vehicle-treated group (Dunnett's multiple comparison tests with Bonferroni correction).

References

Preclinical Effective Dose Range of ASP0819: 0.1-3 mg/kg, po
ADME PROFILE

◆ PK in animals
  ❖ In 4-week toxicokinetic studies of ASP0819 at doses of 3, 10, and 30 mg/kg per day in rats and dogs, the $C_{\text{max}}$ and $AUC_{24}$ were dose proportional in both sexes of each species. In the 1000 mg/kg per day dosing group in dogs, a less than dose proportional increase in $C_{\text{max}}$ and $AUC_{24}$ was observed. No gender differences or marked differences in $C_{\text{max}}$ or $AUC_{24}$ values were observed after repeated dosing.

◆ Plasma protein binding
  ❖ The in vitro plasma protein binding ratios at concentrations of 1, 10, and 100 $\mu$g/mL were 99.97%, 99.93%, and 99.82% in humans.

◆ Brain transfer
  ❖ The brain to plasma concentration ratio of ASP0819 was low (0.00775 to 0.00854 in rats).

◆ Metabolic profile
  ❖ No human-specific ASP0819 metabolites were formed by liver microsomes or hepatocytes.

◆ CYP inhibition
  ❖ The IC$_{50}$ values for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were $\geq$ 9.10 $\mu$mol/L with no time-dependent inhibition. For CYP3A, the IC$_{50}$ values were $> 50$ (midazolam) and 35.1 $\mu$mol/L (testosterone) with time-dependent decreases in IC$_{50}$. 
TOX PROFILE

◆ **Rat 13-week tox study (0, 3, 10, 30 mg/kg/day):**
  ❖ NOAEL was 3 mg/kg for males and 10 mg/kg for females.
  ❖ In a male at 10 mg/kg, atrophy of the mucosal epithelium in the glandular stomach was observed. In males and females at 30 mg/kg, hematological changes indicative of anemia and histopathological findings in the stomach were observed. All changes showed reversibility.

◆ **Dog 13-week tox study (0, 3, 10, 30 mg/kg/day):**
  ❖ NOAEL was 3 mg/kg/day for males and females.
  ❖ In males and females at 10 mg/kg, atrophy of the fundic mucosal epithelium and degeneration/necrosis of the parietal cells in the stomach were noted. In males and females at 30 mg/kg, increased serum AST (males only), ALT and cholesterol, histopathological changes in the stomach and atrophy of the thymus were observed. All changes showed reversibility.

◆ **Rat preliminary embryo-fetal developmental tox study (0, 3, 10, 60 mg/kg/day):**
  ❖ At 60 mg/kg, decreases in body weight and food consumption were noted in dams. In fetuses at the same dose, findings secondary to generalized growth retardation related to maternal toxicity were observed.

◆ **Genotoxicity and phototoxicity**
  ❖ Negative
ASP0819 CLINICAL STUDY

Two clinical studies completed

- **0819-CL-0101**: A 2-part study - the first part for SAD evaluation and a second part for MAD evaluation in healthy subjects.

- **0819-CL-0201**: A Phase 2a, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess the Analgesic Efficacy and Safety of ASP0819 in Patients with Fibromyalgia

**Astellas Clinical Trial Data Disclosure:**
[https://astellasclinicalstudyresults.com/ASP0819](https://astellasclinicalstudyresults.com/ASP0819)
0819-CL-0201 STUDY DESIGN

Screening | Wash-out

Up to 42 days

Baseline Diary Run-in

1 week

Randomization

8 weeks

Follow-up

2 weeks

PBO

ASP0819

Sample Size: ~89 per arm (N=178 at protocol completion)
Primary Endpoint: Change from Baseline to Week 8, Mean Daily Average Pain Score
The results of the primary analysis of the primary endpoint of change from baseline to week 8 in mean daily average pain score using MMRM demonstrated a reduction (improvement) from baseline in mean daily average pain score at week 8, which was numerically greater in magnitude in the ASP0819 treatment group compared with the placebo group, but was not statistically significant (P = 0.086).

The result of the primary analysis was shown consistent by the sensitivity analyses using discontinuation-reason based multiple imputation (Least squares (LS) mean difference: -0.34; P = 0.091) and modified baseline observation carried forward (mBOCF) imputation LS mean difference: -0.37; P = 0.060).

There was evidence of moderate activity as seen by LS mean treatment differences between ASP0819 and placebo of -0.37 (P = 0.030), -0.42 (P = 0.033), -0.45 (P = 0.026), and -0.34 (P = 0.086) at weeks 2, 6, 7 and 8, respectively, in change from baseline in mean daily average pain.
Change From Baseline overtime in Mean Daily Average Pain Score

- **Placebo**
- **ASP0819 15 mg**

Significance levels:
- **p = 0.033** for ES 0.28
- **p = 0.026** for ES 0.30
- **p = 0.086** for ES 0.21
TEAEs (≥ 5% in Any Treatment Group) by Preferred Term (SAF)

<table>
<thead>
<tr>
<th>MedDRA v20.0 Preferred Term</th>
<th>Placebo (N = 94)</th>
<th>ASP0819 15 mg (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>53 (56.4)</td>
<td>62 (68.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (11.7)</td>
<td>12 (13.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (3.2)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (2.1)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (3.2)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (4.3)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>5 (5.3)</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (6.4)</td>
<td>2 (2.2)</td>
</tr>
</tbody>
</table>

MedDRA: Medical Dictionary for Regulatory Activities; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

- There were no clinically meaningful changes for ASP0819 compared to placebo on vital signs, ECGs, or laboratory values including LFTs.
- Safety and tolerability of ASP0819 was comparable to placebo.
INTELLECTUAL PROPERTY STATUS

- Astellas Patent
  - ASP0819 substance and use patent
    - International publication number: WO2014/196644, filing date: June 6, 2014
    - The patent has been granted in filing countries sequentially.
  - ASP0819 method patent
    - Methods of treating sleep disorders associated with pain
    - International publication number: WO2021/016338, filing date: July 22, 2020