Preclinical Pharmacology of Solriamfetol: Potential Mechanisms for Wake Promotion

Hema Gursahani, PhD1; Thierry Jolas, PhD2; Maryse Martin2; Sandrine Cotier2; Sandrine Hughes3; Wayne Macfadden, MD1, Gregory Parks, PhD4, Craig Chepke, MD5,6

1Jazz Pharmaceuticals, Palo Alto, CA, USA; 2Eurofins Cerep, Celle-Lévescault, France; 3E-Phy-Science, Blot, France; 4Assome Therapeutics, New York, NY, USA; 5Excel Psychiatric Associates, Huntersville, NC, USA; 6Atrium Health, Charlotte, NC, USA

Introduction

- Solriamfetol is a wake-promoting agent (WPA) approved for the treatment of excessive daytime sleepiness associated with narcolepsy (75-150 mg/day) and obstructive sleep apnea (OSA; 37.5-150 mg/day) in the US and EU.1,2

- The wake-promoting mechanism of solriamfetol may result from dopamine and norepinephrine reuptake inhibition (DNRF)1,2, but its additional molecular targets are not fully characterized.”3

- Preclinical studies in rodents and non-human primates indicate that TAAR1 agonists may have wake promoting properties.4-8

- Traditional stimulants (e.g. amphetamine) have long been known to activate TAAR1.1,3

Objective

To understand the molecular targets and effects of solriamfetol in vitro and in vivo in the context of other WPAs and stimulants

Methods

- In vitro binding and functional studies were conducted in a panel of cell lines or membrane preparations expressing transmembrane receptors and monoamine transporters including dopamine and norepinephrine transporters (DAT, NET, respectively), trace amine-associated receptor 1 (TAAR1), and serotonin 1A receptor (5-HT1A) to measure the activity of solriamfetol and comparator WPAs and DNRFs.

- Data for stimulants (e.g. amphetamine, methamphetamine) were obtained from published literature.

- The firing frequency of ventral tegmental area (VTA) dopaminergic neurons (n=4-8 cells/experiment) in acute slice preparations was recorded using electrophysiology and analyzed.

- Brain slices (250 µm thickness) containing VTA from male C57BL/6J mice were prepared using standard procedures.

- Slices were perfused with artificial cerebrospinal fluid (aCSF) and spontaneous action potentials were recorded from dopaminergic neurons in current clamp conditions using Axopatch 700B and pClamp10 (Axon Instruments).3

- Open field locomotor activity was assessed using an automated Omnimed Digiscan (AccuScan Instruments, Columbus, OH).

Results

Figure 1. Solriamfetol is a DNRi that activates TAAR1 and 5-HT1A in vitro at clinically relevant plasma concentrations

Table 1. TAAR1 and 5-HT1A functional activities differentiate solriamfetol from other WPAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>DAT EC50 µM</th>
<th>NET EC50 µM</th>
<th>TAAR1 EC50 µM (Emax)</th>
<th>5HT1A EC50 µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPA or hDAT/hNET inhibitor</td>
<td></td>
<td></td>
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<tr>
<td>Solriamfetol</td>
<td>3.21</td>
<td>14.4</td>
<td>10–16 (100%)</td>
<td>25</td>
</tr>
<tr>
<td>Modafinil</td>
<td>2.8</td>
<td>&gt;100</td>
<td>No dose response*</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bupropion</td>
<td>0.26</td>
<td>2.79</td>
<td>No dose response*</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

5-HT1A: serotonin 1A receptor; EC50: half maximal effective concentration; Emax, maximal effect; DAT, dopamine transporter; NET, norepinephrine transporter; TAAR1, trace amine-associated receptor 1; IC50, half maximal inhibitory concentration; WPA, wake-promoting agent.

*Data based on current studies and confirmed by published literature.4,5

Figure 2. Solriamfetol inhibited firing frequency of VTA neurons in a D2-sensitive manner

- After finding that solriamfetol demonstrated functional activity as a TAAR1 agonist in vitro, it was tested to determine if its activity is consistent with that of a known TAAR1 agonist, RO5256390.

Figure 3. Solriamfetol inhibited hyperlocomotion in DAT+/- mice

- Solriamfetol did not increase locomotor activity in wild type mice, unlike a stimulant.

- Solriamfetol reduced hyperlocomotion in DAT+/- mice, similar to a stimulant.

Conclusions

- Solriamfetol activates TAAR1, a recently recognized component of the endogenous wake-promoting system, in vitro at potencies that are consistent with its clinically relevant plasma concentration range and overlap with observed DAT/NET inhibitory potencies.6

- No TAAR1 activity was observed for the WPA modafinil or the DNRi bupropion.

- Solriamfetol shows agonist activity at the TAAR1 receptor and a lower agonist potency at 5-HT1A.

- This activity, in addition to its established activity as a DNRi, may contribute to the wake-promoting effects of solriamfetol.2

- Similar to known TAAR1 agonists, solriamfetol reduced the firing frequency of mouse VTA dopamine neurons in a D2-sensitive manner.

- Unlike amphetamine, solriamfetol did not promote hyperlocomotion in naive mice; however, it did dose-dependently inhibit hyperlocomotion in DAT-/- mice similar to both amphetamine and a known TAAR1 agonist.

- Solriamfetol has not been tested in models of schizophrenia or other psychiatric disorders.