at a glance™

AXSOME THERAPEUTICS

EVENT RICH QUARTER IS HERE: Key data in Alzheimer's disease agitation coming before year-end, plus the start of a late-stage trial in narcolepsy, the newest addition to Axsome's Central Nervous System (CNS) portfolio. A successful webcast R&D Day on October 18 underscored the unmet needs and opportunities in treating Alzheimer's disease agitation, a key indication in Axsome's expanding late-stage CNS portfolio.

Key Considerations

•Axsome is a broad-based pharmaceutical company with superior strengths in CNS disorders and medicinal chemistry.

•Its lead drug candidate AXS-05 is currently in four late-stage clinical trials in four different CNS disorders.

•The most advanced AXS-05 program is in treatment-resistant depression, followed by Alzheimer's disease agitation, major depressive disorder, and smoking cessation.

•All four programs are in either Phase 2 or Phase 3 clinical trials; two of the four will report key data around year-end. Two have been granted FDA Fast Track designations.

•AXS-05 is a proprietary combination of dextromethorphan (DM) and bupropion (BUP), both potent neurotherapeutics with long safety histories.

•Axsome's other key CNS candidates include AXS-07 for acute migraine headache (Phase 3 to start 4Q18), and AXS-12 for narcolepsy (Phase 2 to start 4Q18).

•The recent creation of the Axsome Pain and Primary Care business unit facilitates corporate priorities and sets the stage for business development initiatives for AXS-02 and AXS-06, the company's non-CNS assets for chronic pain indications including knee (Phase 3 underway), lower back, osteoarthritis, and rheumatoid arthritis.

About Dextromethorphan (DM)

Dextromethorphan (DM) is a potent neurotherapeutic with known activity at multiple CNS receptors, importantly NMDA and sigma-1, which strongly influence numerous neurological functions.

Full appreciation of DM's attributes didn't become more widely recognized until 2014 when Avanir Pharmaceuticals released results of a double-blind, placebo-controlled Phase 2 trial of DM + quinidine in Alzheimer's disease agitation. The study drug reduced agitation/aggression by 46 percent vs. 24 percent for placebo.

The robust data, coupled with the size of the market opportunity, quickly moved Avanir's market cap to the mid-nine-figure range, and then to roughly a billion dollars. Shortly thereafter, the company was acquired for $3.5 billion cash by Otsuka Pharmaceutical of Japan.

The FDA had previously raised issues about the toxicity of quinidine, the drug Avanir chose to combine with DM to boost its bioavailability and assure sufficient plasma concentrations for CNS indications.

The concern was that the quantity of quinidine used may potentially cause sudden cardiac arrest and death in susceptible patients.

To address this issue, Avanir/Otsuka decided to reduce the level of quinidine rather than replace it, risking the potential continuation of clinical and FDA concerns.

Axsome, on the other hand, developed a new investigational medicine (AXS-05) that combines standard DM and bupropion, instead of quinidine, with the hope and expectation of accomplishing two outcomes: (1) added pharmacological synergy with DM since bupropion is a widely used antidepressant; and (2) higher blood levels of DM while avoiding cardiac issues caused by quinidine.

Three Phase 1 clinical trials confirmed that bupropion + DM increased DM's bioavailability to levels 60 times greater than the blood levels achieved by DM alone. Importantly, these trials showed that AXS-05 dosing resulted in DM plasma levels that were shown to be efficacious in Alzheimer's disease agitation as well as in pseudobulbar affect.

Axsome CNS Portfolio

AXS-05 is Axsome's most advanced CNS candidate, now in late-stage clinical trials in four indications, all with major unmet needs: Alzheimer's disease agitation, treatment-resistant depression, major depressive disorder, and smoking cessation. Axsome's two other CNS candidates are AXS-07 for migraine, and its newest, AXS-12 for narcolepsy.

Axsome Therapeutics, Inc.

(Nasdaq: AXSM)

Recent Price:	**$3.78**
Approx. Shares O/S:	**26.5 Million**
Approx. Mkt Cap:	**$100 Million**
Fiscal Year Ends:	**December 31**

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AXS-05
Alzheimer's Disease Agitation

Alzheimer's disease agitation is the leading reason why Alzheimer's patients leave home for nursing homes and other extended care facilities.

The telltale signs are agitation, aggressive behavior, and disinhibition, among others, all of which make home care increasingly problematic for families and caregivers.

Agitation nearly doubles the cost of caring for Alzheimer's patients, accounting for roughly 12 percent of the healthcare and societal costs of Alzheimer's disease, currently estimated at $256 billion a year.

Avanir's highly successful Phase 2 in Alzheimer's disease agitation provided strong proof of concept for AXS-05 in this indication and demonstrated the high value of a potentially successful candidate.

A successful drug in this indication could save billions of dollars annually in healthcare costs.

A multicenter Phase 2/3 trial of AXS-05 in Alzheimer's disease agitation is underway.

Approximately 435 patients will be

Planned Milestones

4Q18 – P2/3 AD Agitation futility interim

4Q18 – P2 Narcolepsy start

1Q19 – P2 Major depressive disorder top-line

1Q19 – P3 Migraine start

1Q19 – P3 T-R depression efficacy top-line

1Q19 – P2 Smoking cessation top-line

1H19 – P2 Narcolepsy top-line

2019 – P3 Migraine top-line

2019 – P2/3 AD Agitation efficacy interim

Narcolepsy AXS-12

The newest addition to Axsome's CNS portfolio is AXS-12 for narcolepsy, a debilitating orphan neurological condition characterized by excessive daytime sleepiness and cataplexy, a frequent comorbidity, which causes a sudden reduction or loss of muscle tone while the patient is awake.

The active ingredient in AXS-12 is reboxetine, a highly selective and potent norepinephrine reuptake inhibitor with an extensive safety record achieved through its long-time use as an antidepressant in Europe and in more than 40 other countries.

In well-established genetic animal models of narcolepsy, reboxetine significantly and dose-dependently reduced narcoleptic episodes. An open-label pilot trial was supportive of these findings.

AXS-12 will enter Phase 2 testing 4Q18, with top-line results anticipated 1H19.

Narcolepsy is estimated to afflict an estimated 185,000 individuals in the US, 70 percent of whom are believed to also suffer from cataplexy.

ASX-12 was granted an Orphan Drug designation by the FDA in October 2018.

randomized 1:1:1 to either study drug, placebo, or bupropion alone, the latter arm required to meet the FDA's combination products rules.

Two interim analyses by an Independent Data Monitoring Committee (IDMC) are planned, one for futility, the other for efficacy. These built-in steps help reduce development risk and potentially provide opportunities for incremental value recognition.

The interim analysis for futility is scheduled for 4Q18 after approximately 30 percent of the randomized patients have completed treatment.

The interim analysis for efficacy will be conducted in 2019 after 60 percent of the randomized patients have completed treatment.

An estimated two million Americans suffer from Alzheimer's disease agitation. It's a major unmet need with no currently approved therapies. The FDA assigned Fast Track designation to AXS-05 for this indication in May 2017.

Treatment-Resistant Depression

Treatment-resistant depression is suffered by roughly three million people in the US, all of whom have responded inadequately to initial or subsequent treatments.

AXS-05 combines the mechanisms of action of four distinct antidepressant drug classes in one novel oral therapeutic.

The AXS-05 program to treat this type of depression was accorded Fast Track designation by the FDA in February 2017, owing to the magnitude of the unmet need and the serious nature of the disease (for example, the high suicide rate among these individuals).

In an open-label Phase 2 trial conducted at Mt. Sinai Medical Center of 21 subjects who failed two to ten prior treatments for severe depression, DM + quinidine produced a 50-percent-or-greater reduction in depressive symptoms in roughly half the patients, an encouraging proof-of-concept for DM in this setting.

Axsome enrolled approximately 250 patients in its pivotal Phase 3 trial of AXS-05 in treatment-resistant depression. It is designed as a head-to-head comparison between single-agent bupropion, a widely used antidepressant, and AXS-05, a combination of DM and bupropion.

In April 2018, an Independent Data Monitoring Committee (IDMC) conducted a planned interim analysis for futility after approximately 40 percent of the randomized patients completed treatment in the Phase 3 trial. The IDMC recommended continuation of the trial and reported that AXS-05 was safe and generally well-tolerated.

Top-line results are scheduled for 1Q19.

Major Depressive Disorder

Major depressive disorder is a condition suffered by roughly 16 million Americans. On June 5, 2018, Axsome announced the start of a Phase 2 trial of AXS-05 in major depressive disorder. The intent of this study is to explore AXS-05 as frontline therapy in the broader depression population.

The Phase 2 trial is a double-blind, randomized, active-controlled trial. Approximately 74 patients will be randomized in a 1:1 ratio to receive AXS-05 or bupropion for six weeks.

Top-line results are expected 1Q19.

Smoking Cessation

Separate from Axsome, researchers at the Duke Center for Smoking Cessation had been conducting preclinical studies in animal models showing DM (the main ingredient of AXS-05) had a potent effect in reducing nicotine-seeking behavior in rats that were nicotine-dependent.

As the time for human studies drew near, they knew DM's bioavailability had to be increased to achieve the required therapeutic plasma levels.

A search of the literature brought them to Axsome as the leader in technology to stabilize DM.

What's more, it turns out that bupropion, the drug Axsome uses to stabilize DM in AXS-05, is FDA-approved as a smoking cessation agent under the brand name Zyban®.

Axsome and Duke formed a collaboration in late 2017 and on April 25, 2018, they announced enrollment of the first patient in a Phase 2 clinical trial of AXS-05 in smoking cessation at the Duke Center for Smoking Cessation.

Top-line data is due in 1Q19.

Migraine Headache AXS-07

If you are among the 37 million Americans who suffer acute migraine headaches, the last thing you want is a remedy that works too slowly and doesn't last.

Enter AXS-07. Axsome created it by combining two FDA-approved drugs with a proprietary delivery system designed to speed drug absorption.

One of the components is the anti-inflammatory meloxicam, and the other is rizatriptan, a widely prescribed triptan for migraine.

Meloxicam is a COX-2 preferential inhibitor and a potent NSAID-like pain killer. It's marketed under the name Mobic® for chronic arthritis and other inflammatory conditions. Meloxicam is long acting. Its main pharmacokinetic drawback is incredibly slow bioavailability: it takes about five hours to reach a desired therapeutic blood level. In its current form, a pill in the morning wouldn't provide relief until after lunch.

In AXS-07, Axsome sought to preserve meloxicam's long half-life, and to combine that feature with rapid onset of therapeutic activity.

In a Phase 1 proof-of-concept study of meloxicam encapsulated in Axsome's rapid absorption drug delivery technology, therapeutic blood levels were achieved in just 15 minutes, nine-fold faster than standard meloxicam.

What's more, there was no change observed in the durability of meloxicam's plasma concentrations, which spanned 20 hours, the same as standard meloxicam.

A Phase 3 pivotal trial of AXS-07 in migraine headache is scheduled to start 1Q19. If successful, it may be the only one required before filing for approval, according to written guidance from the FDA.

Summary Points

- **Broad-based pipeline in billion dollar-plus indications**
- **Interim Phase 2/3 in Alzheimer's disease agitation due this quarter**
- **Top-line Phase 3 in treatment-resistant depression due 1Q19**
- **Top-line Phase 2 in Major depressive disorder due 1Q19**
- **Top-line Phase 2 in smoking cessation at Duke due 1Q19**
- **Top-line Phase 2 in narcolepsy due 1H19**
- **$23 million pro forma cash/equivalents at 9/30/18, including $8.9 million new equity invested 9/28/18 by three leading institutions**

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