ZS Pharma (ZSPH)

ZS Pharma Announced Positive Results from Second Phase III Trial; Full Data at AHA

On September 23rd, ZS Pharma (NasdaqGM: ZSPH) announced positive topline data from a second Phase III trial (ZS004; HARMONIZE) supporting the use of ZS-9 in patients with chronic hyperkalemia. All three doses of ZS-9 (5, 10, and 15 grams) met the primary endpoint of mean serum potassium compared when to placebo between days 8 and 28. Full data is expected to be presented at the 2014 American Heart Association (AHA) Scientific meeting. The positive data combined with results from an earlier Phase III trial put ZS Pharma on track for an NDA filing in the first half of 2015.

- **ZS-9 for Hyperkalemia Addresses an Unmet Medical Need.** ZS Pharma is focused on the development of ZS-9, a novel, oral, non-absorbable, and highly selective binder that traps excess potassium (hyperkalemia) in the gastrointestinal tract and facilitates its removal from the body. Hyperkalemia causes disturbances in the cellular electrochemical gradient, which can lead to cardiac arrhythmias and sudden cardiac death. No treatments for hyperkalemia are able to effectively reduce serum potassium over the long-term and the current standard of care is poorly tolerated. This highlights the need for therapies such as ZS-9 that can safety treat chronic cases of hyperkalemia.

- **Positive HARMONIZE Data Confirm ZS-9's Potential in Long-Term Treatment Setting.** The HARMONIZE trial enrolled 258 patients with hyperkalemia who were treated with 10 grams of ZS-9 three times per day during a 48 hour acute phase. Patients who achieved normokalemia (potassium of 3.5-5 mEq/L) were randomized to once daily ZS-9 (5, 10, or 15 grams) or placebo for 28 days as part of a randomized withdrawal period. A significant number of patients at all doses of ZS-9 maintained normokalemia from day 8 to day 28, providing evidence that ZS-9 can help patients sustain normal potassium levels for 3 weeks. This adds to data from a previous Phase III trial (ZS003) where normokalemia was maintained for 12 days. In addition, the safety of ZS-9 in HARMONIZE was similar to previous trials, supporting its use as a maintenance therapy.

- **Full Data Expected at the 2014 American Heart Association Scientific Meeting.** ZS Pharma is scheduled to report full data from the HARMONIZE trial at the 2014 AHA Scientific meeting taking place November 15-19 in Chicago. The results were selected for presentation in a late-breaking clinical science special reports session. The details of the presentation are as follows:

  - **Title**: Efficacy and Safety of ZS-9 in Patients with Hyperkalemia: Results from the HyperkAlemia RandoMized interventiON multi-dose ZS-9 maintEnance (HARMONIZE) Clinical Trial.
  - **Session**: Management of Cardiovascular Disease.
  - **Day and Time**: November 17th, 2014 at 7:22am-7:32am.
  - **Room**: S100ab

Analysts

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Market Data

Price	$37.02
Market Cap (M)	$771
EV (M)	$661
Shares Outstanding (M)	20.8
Fully Diluted Shares (M)	26.8
Avg Daily Vol	103,927
52-week Range:	$25.51 - $43.00
Cash (M)	$130.0
Net Cash/Share	$5.28
Annualized Cash Burn (M)	$40.0
Years of Cash Left	3.3
Debt (M)	$20.0
Short Interest (M)	0.72
Short Interest (% of Float)	3.5%

Financials

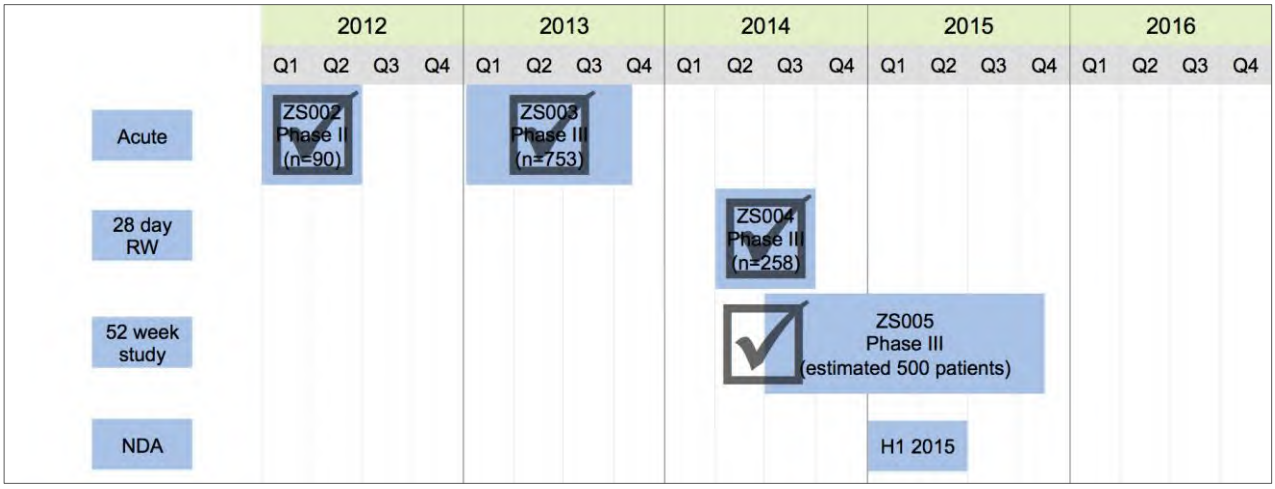
FY Dec		2013A	2014A
EPS	Q1	NA	NA
	Q2	(4.81)A	(4.72)A
	Q3	NA	NA
	Q4	NA	NA
	FY	NA	NA

Based on the similarity in design to ZS003, we anticipate that the full HARMONIZE results will be in line with previously reported data. Important data points are the time to onset, safety profile, and the response in patients with chronic kidney disease (CKD), heart failure (HF), diabetes, or those receiving renin angiotensin aldosterone system (RAAS) inhibitors. Time to onset will be analyzed in the acute phase of the study where patients receive 10 grams of ZS-9 three times daily. Data from ZS003 demonstrated a significant decrease in serum potassium as early as 1 hour post treatment. There was no upper limit regarding serum potassium levels in the HARMONIZE trial, compared to 6.5 mEq/L for ZS003. It will be useful to understand how ZS-9 performs in a population of patients with more advanced disease, especially considering that these patients are more likely to be hospitalized for hyperkalemia and seek acute treatment.

Of course the larger market opportunity is chronic hyperkalemia, which is why any data from subgroups such as those receiving RAAS inhibitors are important. Thus far ZS-9 is active across all patients regardless of the underlying disease contributing to hyperkalemia. Data released this summer also indicate that ZS-9 is as active in CKD and HF patients receiving RAAS inhibitors as patients not receiving these inhibitors. Patients on RAAS inhibitors are often recommended to reduce their dose to avoid hyperkalemia, even though the inhibitors are proven to reduce morbidity, mortality, and disease progression. Continued activity in these various populations will further validate the commercial prospects for ZS-9.

- **ZS Pharma is Checking the Boxes for NDA Submission in First Half of 2015.** The successful completion of the HARMONIZE trial takes ZS Pharma one step closer to an NDA submission in the first half of 2015. **Figure 1** shows the clinical development progress for ZS-9. Check marks indicate milestones the Company has completed and that are necessary for an NDA filing. ZS Pharma has completed Phase II and Phase III trials with ZS-9 demonstrating a significant impact on serum potassium in the acute setting, with the candidate working as quickly as 1 hour post treatment. The second Phase III study, HARMONIZE, had a 28-day randomized withdrawal (RW) period to establish safety and efficacy for up to 4 weeks. Additional data will continue to be collected from an extension phase of HARMONIZE (ZS004E), and ZS Pharma has initiated a 1-year Phase III (ZS005) long-term safety study. With the completion of these milestones, ZS Pharma is in a strong position to file an NDA in the first half of 2015.

Figure 1. ZS Pharma's Clinical Progress



Source: LifeSci Capital

- **HARMONIZE Trial Design.** HARMONIZE was a randomized, double-blind, placebo-controlled trial that enrolled 258 patients with hyperkalemia.[1] The population included patients with CKD, HF, diabetes, and those receiving RAAS inhibitors.

  The trial was conducted in two phases, an induction phase and randomized withdrawal period. Patients received 10 grams of ZS-9 three times per day for 48 hours in the open-label induction phase. They were monitored for how quickly serum potassium significantly reduced and the magnitude of reduction. Patients who achieved normokalemia defined as serum potassium of 3.5-5 mEq/L were randomized into the withdrawal period and received ZS-9 (5, 10, or 15 grams) or placebo. Patients were treated for 28-days. The primary endpoint was the mean serum potassium of each treatment group compared to placebo between days 8 and 28 of the randomized withdrawal period. The goal of the trial was to examine ZS-9's ability to help patients maintain normokalemia over 21-days of treatment, and safety over a 28-day period. Patients who completed the study were eligible to enroll in an open-label extension study (ZS004E) and will receive treatment for 5 additional months.

Expected Upcoming Milestones

- November 17th – Full data from ZS004 – a 1 month maintenance study with 5 month extension in patients with chronic hyperkalemia.
- H1 2015 – Expected NDA & MAA submission for ZS-9 for the treatment of hyperkalemia.

About ZS Pharma: More information on ZS Pharma can be found in our Initiation of Coverage Report at http://www.lifescicapital.com/equity-research/zs-pharma/.

[1] http://www.clinicaltrials.gov/ct2/show/NCT02088073

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