Isis Pharmaceuticals Reports Data from ISIS-SMN Rx in Children with Spinal Muscular Atrophy

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Continued increases observed in multiple measures of muscle function in SMA children treated with ISIS-SMN Rx

CARLSBAD, Calif., June 22, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today provided an update on children with spinal muscular atrophy (SMA) who have completed the open-label, Phase 2 multiple-dose study of ISIS-SMN_{Rx} and are continuing to receive treatment in an open-label extension (OLE) study. Consistent with earlier observations, increases in muscle function scores and additional motor function tests were observed in children treated with ISIS-SMN_{Rx}. Isis is currently collaborating with Biogen to develop and commercialize ISIS-SMN_{Rx} to treat patients with SMA.

"The natural course for children with untreated type II or type III SMA typically experience loss of muscle function that develops slowly and continually over time, a sustained increase of three or more points in HMFSE scores represents a significant departure from the natural course and is unusual for these children," said Dr. Darryl De Vivo, Professor of Neurology and Pediatrics, Columbia University Medical Center.

In the OLE study, a total of 30 children with Type II or Type III SMA received 12 mg of ISIS-SMN_{Rx} dosed intrathecally every six months. Children who enrolled in the OLE study had completed the open-label Phase 2 study of ISIS-SMN_{Rx} in which they had received multiple doses of either 3 mg, 6 mg, 9 mg, or 12 mg of ISIS-SMN_{Rx}. Clinical endpoints were measured every three months and compared to each patient's Phase 2 baseline score. These endpoints included measurements of muscle function using the Hammersmith Functional Motor Scale-Expanded (HFMSE), the six minute walk test (6MWT) for ambulatory patients and the upper limb module (ULM) test for non-ambulatory patients.

An analysis, which was performed on May 15, 2015, showed continued and durable increases in measures of muscle function with 57% of children with SMA achieving increases in HFSME scores of at least three points.

Analysis of muscle function measures at the nine month evaluation in the OLE study showed:

- A mean increase of 3.8 points in HFMSE score (n=22)
  - In a subgroup analysis of children who had incoming HFMSE scores that met the inclusion criteria for the ongoing Phase 3 CHERISH study (³ 10 and ≤ 54; n=17), the mean increase in HFMSE score was 4.4 points.
- A mean increase of 55 meters in 6MWT score (n=11).
- A mean increase of 2 points in ULM test, which measures muscle function on an 18-point scale (n=12)

In addition, a review of the safety profile of ISIS-SMN_{Rx} in children with SMA provided further support for continued development.

- Intrathecal administration has been well tolerated and shown to be feasible with no drug-related serious adverse events in either the Phase 2 or the open-label extension studies.
- Most adverse events reported as mild or moderate in severity.
- There were no changes in the safety profile with repeated doses of ISIS-SMN_{Rx}.

"In these studies using multiple measurements of muscle and motor function changes, we observed encouraging results that were consistent with earlier results from our open-label Phase 2 study. Taken together, these data suggest that ISIS-SMN_{Rx} could provide benefit to patients with SMA beyond halting their disease progression," said C. Frank Bennett, Ph.D., senior vice president of research at Isis Pharmaceuticals. "The safety and tolerability profile that we have observed across all of our ISIS-SMN_{Rx} studies support the ongoing Phase 3 programs in both infants and children with SMA."

ABOUT SMA

SMA is a severe genetic disease that affects approximately 30,000 to 35,000 patients in the United States, Europe and Japan. There are no approved treatments for SMA. The disease is caused by a loss of, or defect in, the survival motor neuron 1 (SMN1) gene, leading to a decrease in the survival motor neuron protein. SMN is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuromuscular growth and function. One in 50 people, the equivalent of about six million people in the United States, are carriers of a defective SMN1 gene, which is unable to produce fully functional SMN protein. Carriers experience no symptoms and do not develop the disease. However, when both parents are carriers, there is a one in four chance that their child will have SMA. Type I is the most severe form of SMA and most infants with Type I SMA die in infancy. The severity of SMA correlates with the amount of SMN protein. Infants with Type I SMA produce very little SMN protein and have a life expectancy of less than two years. Children with Type II have greater amounts of SMN protein but still have a shortened lifespan and are never able to stand independently. Children with Type III have a normal lifespan but accumulate life-long physical disabilities as they grow.

ABOUT ISIS-SMN_{Rx}

ISIS-SMN_{Rx} is designed to alter the splicing of SMN2, a gene that is closely related to SMN1, to increase production of fully functional SMN protein. The United States Food and Drug Administration granted orphan drug status and fast track designation to ISIS-SMN_{Rx} for the treatment of patients

with SMA. Isis is currently collaborating with Biogen to develop and potentially commercialize the investigational compound, ISIS-SMN_{Rx}, to treat SMA. Under the terms of the January 2012 agreement, Isis is responsible for global development and Biogen has the option to license the compound. In addition to the pivotal studies described below, Biogen is operationalizing two Phase 2 studies (NURTURE & EMBRACE) to augment the ongoing Phase 3 program.

Isis is conducting two Phase 3 studies of ISIS-SMN_{Rx}. One Phase 3 study, ENDEAR, in infants with SMA and a second Phase 3 study, CHERISH, in children with SMA. The ENDEAR study is a randomized, double-blind, sham-procedure controlled thirteen month study in approximately 110 infants diagnosed with SMA. The study will evaluate the efficacy and safety of ISIS-SMN_{Rx} with a primary endpoint of event-free survival. The CHERISH study is a randomized, double-blind, sham-procedure controlled fifteen month study in approximately 120 non-ambulatory children with SMA. The study will evaluate the efficacy and safety of ISIS-SMN_{Rx} with a primary endpoint of a change in Hammersmith Functional Motor Scale-Expanded.

For further study information, please visit www.clinicaltrials.gov and search for ISIS-SMN_{Rx} or visit the ISIS-SMN_{Rx} study site at www.smastudy.com.

Isis acknowledges support from the following organizations for ISIS-SMN_{Rx}: Muscular Dystrophy Association, SMA Foundation, Cure SMA and intellectual property licensed from Cold Spring Harbor Laboratory and the University of Massachusetts Medical School.

ABOUT ISIS and BIOGEN

Isis and Biogen have a broad strategic alliance focused on leveraging antisense technology to advance the treatment of neurological and neuromuscular disorders. This alliance combines Isis' expertise in antisense technology to evaluate potential neurological targets and discover antisense drugs with Biogen's capability to develop therapies for neurological disorders. Isis is primarily responsible for drug discovery and early development of antisense therapies. Biogen has the option to license each antisense program at a particular stage in development. Current development-stage programs include antisense drugs to treat patients with spinal muscular atrophy (SMA), ISIS-SMN_{Rx}, myotonic dystrophy type 1 (DM1), ISIS-$DMPK_{Rx}$, and two undisclosed neurodegenerative diseases, ISIS-$BIIB3_{Rx}$, and ISIS-$BIIB4_{Rx}$. In addition to these four drugs, Isis and Biogen have numerous opportunities to evaluate additional targets for the development of drugs to treat neurological disorders.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in RNA-targeted technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 38 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe/rare diseases and cardiovascular diseases. These include ISIS-$APOCIII_{Rx}$, a drug Isis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with familial chylomicronemia syndrome and familial partial lipodystrophy; ISIS-TTR_{Rx}, a drug Isis is developing with GSK to treat patients with the polyneuropathy and cardiomyopathy forms of TTR amyloidosis; and ISIS-SMN_{Rx}, a drug Isis is developing with Biogen to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis' alliance with Biogen, the discovery, development, activity, therapeutic and commercial potential and safety of ISIS-SMN_{Rx} and the discovery, development and therapeutic potential of an antisense drug for the treatment of spinal muscular atrophy. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2014, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

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