BIOWORLD™ TODAY
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FEBRUARY 26, 2015
VOLUME 26, NO. 38
SPECIAL REPRINT

'Titer'-ing on brink of BLA, Adma's added endpoints encourage outcomes in RSV

By Randy Osborne, Staff Writer

Recent outbreaks of respiratory syncytial virus (RSV) in Alabama, Arizona and Colorado children put renewed attention on the disease for which there is no approved therapy in adults, just as Adma Biologics Inc. reported more data from the pivotal phase III trial with RI-002 in primary immune deficiency (PIDD) that included encouraging results in RSV and other pathogens.

"We're unable to draw any conclusions about efficacy [against the specific infectious agents] from these increases in antibody titers, but it's good to note that from the patients the trial was based on, we were able to generate this type of dose response, if you will," Adam Grossman, Adma's CEO, told *BioWorld Today*. "We think it's encouraging, and we think that clinicians, patients and payers want to know that, by infusing IVIG products, they're getting this bump" in protection.

Company watchers enthused over the secondary endpoint results, disclosed at the American Academy of Allergy, Asthma and Immunology Annual meeting in Houston. Although Ramsey, N.J.-based Adma's shares closed Wednesday (NASDAQ:ADMA) at $10.05, flat, analysts at Ladenburg Thalman set a $17.50 price target, Maxim Group went higher to $18 and Laidlaw & Co. forecast $20.

In December, Adma made known top-line data demonstrating that RI-002, a plasma-derived, polyclonal, intravenous immune globulin (IVIG) product, achieved its primary endpoint of preventing serious bacterial infections: zero, which is even below the FDA's requirement of less than one per patient-year. The pharmacokinetic profile of total immunoglobulin G was consistent with the FDA's guidance, too. (See *BioWorld Today*, Dec. 4, 2014.)

Added results made RI-002's picture even brighter. In the multisite study of 59 patients diagnosed with PIDD, researchers reported secondary endpoints that included a total of 93 days, or 1.66 days per patient per year lost from work or school due to infection, and one hospitalization due to an infection of only five days duration in the entire study, with immunoglobulin G trough levels above those required by the FDA for IVIG products.

A marked increase in all of the measured specific antipathogen antibodies turned up, with the greatest increase, 5.3-fold, seen in the level of neutralizing antibody titers to RSV, which "offers an area of potential differentiation from other IVIG products and is in line with our expectations, based on the donor-screening profile," wrote Ladenburg analyst Kevin DeGeeter in a research report. "However, we were surprised to learn that patients also reported a statistically significant increase in antibody titers against two other common respiratory pathogens," which means the compound "may have the potential to protect against a broad range of clinically important respiratory pathogens, which could strengthen the argument for premium pricing compared to other IVIG products." Specifically, the findings showed an increase in *H. influenzae* antibodies and in *S. pneumoniae* antibodies.

'MARATHON, NOT A SPRINT'

"When we conducted market research using third parties, depending on the age of PIDD patients and other underlying risk factors, they rank RSV as the number three to number 11 most concerning infectious pathogen," Grossman said. Bacterial pneumonia tops the list across the board, but "I think we can say that RSV is certainly of heightened awareness and concern, especially during the winter months, amongst PIDD patients," he said. "But with respect to going after an indication for RSV prophylaxis or treatment, this is something that we may consider down the road."

RSV is a severe problem in the immunocompromised bone marrow/solid organ transplant population, with an incident rate of 10 percent to 15 percent in the winter. Doctors use aerosolized ribavirin, which is toxic with dubious efficacy, or Synagis (palivizumab, Astrazeneca plc), which is costly, or one of the eight available IVIGs. Synagis was approved in June 1998 for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of the disease. (See *BioWorld Today*, June 22, 1998.)

Laidlaw analyst Yale Jen found that the level of days lost from work or school due to infection "might be substantially fewer than many other approved IVIGs (2.6 days or much

more). This is a measure that could further enhance the buy-in by prescribing physicians and third-party payers, given the practical real world benefits," Jen wrote in a research report.

Jason Kolbert, of Maxim, noted that the market for plasma products in the U.S. is $3.5 billion and worldwide is $15 billion. Though RI-002 is indicated for PIDD, Adma developed it using a micro-neutralization assay to identify and isolate donor plasma with high levels of anti-RSV antibodies in order to standardize RI-002 potency, unlike other IVIGs. "This approach produces a superior product at [potentially] a premium price," in Kolbert's view. "Adma has the potential to penetrate markets for other immune-compromising conditions, including autoimmune diseases, immune suppression arising from cancer chemotherapy (or underlying malignancy), and neuropathy."

PIDD comprises about 150 different types of genetic defects that affect certain aspects of the immune system. In the U.S., about 250,000 patients have one or more forms of PIDD, with half requiring monthly infusions of IVIG to support their systems. Adma expects to file a biologics license application (BLA) in the first half of this year, and RI-002 could be on the market in 2016. "There may be some other additional ad hoc analyses that we put together as we are drafting the clinical study report for RI-002's trial," Grossman said, but otherwise the next news should be the BLA filing.

"I don't see any negative in these data," Grossman said. "Some people think this is a differentiation risk. I think that we're clearly differentiated. There could be some commercialization risk – is this a $5 million drug or a $500 million drug? I don't know, you'll have to read the analysts' reports. We don't give guidance on where we think the product will come out."

As for the stock price, "I don't let it affect me," Grossman said. "In fact, I haven't even looked today."

The company, he noted, is very closely held by insiders. "At best, maybe there are 900,000 shares in the public float, from what we can determine, maybe even fewer than that," he said. "I think Adma is dealing with a liquidity issue. You never know why someone sells a stock. I'm not worrying about it – this is a marathon, not a sprint."