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A Summary of the Study of a Polyclonal Human IVIG with Standardized High-Levels of RSV Neutralizing Antibodies

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RSV pulmonary infection in the immune suppressed patient population is a disease with a high reported morbidity and mortality particularly in patients who receive stem cell and solid organ transplants. To enhance the resistance of immune deficient patients to RSV infection and its inflammatory effects and to provide these patients with background immunity, ADMA Biologics Inc. prepared a plasma derived, human polyclonal immune globulin using plasma obtained from donors tested to contain high neutralizing titers to RSV using a microneutralization assay (ADMA Biologics). To ascertain whether the polyclonal RSV enriched immunoglobulin antibodies translated into in vivo efficacy, we used the well described cotton rat model for RSV infection for this study. Animals were injected with the investigational product, RI-002, 10% IGIV, Human, ADMA Biologics, and one day later, animals were infected intranasally with RSV/A/Long 105 pfu/ animal. Four days after infection with RSV, animals were euthanized and nose and lungs were harvested for viral titrations. Plaques were counted and viral titers were expressed as plaque forming units per gram of tissue. Control group treated with saline had mean titers of ~4.7 Log10 PFU/g of tissue and the experimental groups given 500, 750, and 1000 mg/kg showed reduced viral titers of RSV in the lungs to undetectable levels in all animals. In the nasal tissues the control group had mean titers in the nose of ~5 Log10 PFU/g of tissue on day 4 post-infection and the experimental groups given 750 and 1000 mg/kg reduced viral titers of RSV in the nose to undetectable levels, whereas in animals treated with 500 mg/kg, there was undetectable levels of virus in three animals and minimal virus titers in 2 of the 5 animals (mean titer of 2.1 Log10 PFU/g tissue). The first clinical trial conducted with this RSV immune globulin product was a Phase II, multicenter, randomized, double-blind, placebo-controlled study conducted in 21 patients over 2 RSV seasons at multiple sites in the US, Canada, Australia and New Zealand. Patients were randomized into one of three arms at a 1:1:1 ratio, high dose RSV enriched IGIV (1500 mg/kg followed by a second dose two days later of 750 mg/kg), low dose RSV enriched IGIV (750 mg/kg followed by a second dose two days later of 750 mg/kg) or placebo (saline). Patients were aged 2-65 years and had undergone a BMT/HSCT or a cadaveric solid organ transplant within 2 years prior to randomization and were taking concurrent immunosuppressive therapy at the time of their upper respiratory tract RSV infection and randomization in the study. The trial's primary endpoint was to determine a dose that produced an anti-RSV antibody titer mean increase of at least 4 fold at day 18 post infusion relative to baseline. Serum RSV neutralizing titers eighteen days after infusion in patients receiving high dose regimen had a mean increase of 9.24 fold relative to the titers seen in the placebo group while those in the low dose group had a 4.85 fold increase in their titers. No drug related adverse events were noted and the infusions were well tolerated by study subjects.

Concurrently with the Phase II study, the sponsor received unsolicited compassionate use requests for their RSV enriched IGIV product. From April 2009 through February 2011, 15 compassionate use patients aged 3 months to 71 years were treated with this investigational RSV enriched immune globulin at a dose of 1,500mg/kg followed by 750mg/kg on day three. These patients were deemed to be immunosuppressed or had undergone a hematopoietic stem cell transplant or solid organ transplant. Many of these patients had been ill with RSV for days or weeks prior to their compassionate use requests and these patients received commercially available, yet unapproved therapies for the treatment of their

RSV infections such as aerosolized ribavirin and palivizumab. Serum samples were obtained from 13 out of 15 compassionate use patients (we did not receive samples for 2 patients who were administered palivizumab). These samples, when tested in the RSV microneutralization assay showed that patient's RSV neutralization titers measured on day 8 had a four-fold or greater rise from baseline. Investigators reported improved outcomes in most patients and the majority were discharged from the hospital. This RSV enriched polyclonal immune globulin was well tolerated and there were no reports of serious adverse events attributable to the study drug.). These data support the continued study of ADMA's product for the prevention and treatment of RSV disease in the immune suppressed population. This investigational product is currently being evaluated in a Phase III trial as a therapy for patients diagnosed with Primary Immune Deficiency Disease.