**Witness Testimony**

Anish Bhatnagar, MD
Chief Executive Officer, Soleno Therapeutics

Chairman Casey, Ranking Member Braun, and Honorable Members of the U.S. Senate Special Committee on Aging, I am honored to testify at today's hearing. Thank you for inviting me.

I am a physician by training. My 25-year career, almost entirely at small companies has involved developing treatments for cancer, and neurological, psychiatric, cardiovascular and other diseases and for the last several years, rare diseases.

None of my work, including that on lifesaving cancer drugs, has been as meaningful as working with this amazing community of families who have children and adults with Prader Willi syndrome (PWS). While the regulatory challenges across therapeutic areas are similar, there is a much more disproportionate impact on patients with rare diseases. A similar disproportionate impact is seen on small companies like ours, which do a large proportion of the high-risk work. We have a single lead program, and our survival as a company is determined by the progress on that program. Our ability to raise money and continue our work depends prominently on regulatory clarity. If the minutes of an FDA meeting do not clearly state a path forward or if a company receives inconsistent feedback, it could be the difference between having money to carry out a pivotal trial or giving up on a drug to treat a disease that has no options.

Speaking of diseases with no options, PWS is a rare and life-threatening genetic condition which occurs randomly and affects 10-20,000 patients in the United States. Children with PWS are often recognized within a few weeks of birth because newborns with PWS have a constellation of symptoms that raise suspicion for the condition, including low muscle tone (they are floppy babies) and complete lack of desire to feed – which is remarkable, considering what comes later in life for these individuals. Children will be prescribed growth hormone – which may normalize their stature, improve body composition, developmental milestones and cognition – but will not do anything for the hallmark symptom of the disease, hyperphagia. By the age of 3 to 4 years, children will start to show more of an interest in food, which increases over time until they ultimately develop the hallmark symptom of hyperphagia – an insatiable desire to eat, the brain telling you that you are starving, even as you eat. Individuals affected by PWS never feel full and are constantly focused on one thing - food, and how to get it. Left unsupervised, they have the potential to literally eat themselves to death – much like a situation described by a mother of a teenager with PWS who ran away from home, begged strangers at a restaurant for food, ate enough that his stomach ruptured, and he passed away. The only remedy for hyperphagia today is to restrict access to food – closed kitchens, locked refrigerators and pantries, motion activated cameras and alarms. Families live in the constant fear of problematic behaviors resulting in extreme outcomes such as 911 calls from school, visits to ERs, police intervention and, in many situations, the need to be cared for in an institutionalized setting. Unaffected siblings will often have PTSD, and families have trouble staying together. And invariably, there is need for constant supervision for life.

Numerous drugs have been tested to treat hyperphagia in PWS in late-stage trials, each one of them has failed and many companies have been dissolved. Our drug, DCCR, is a once-a-day pill which was evaluated in an approval-directed study from 2018 through 2020, ending a few months after the start of

the Covid-19 pandemic. The study missed its primary endpoint, but analysis of the pre-Covid data showed statistical significance in favor of DCCR. Long term data, now up to 4 years in some patients, and comparisons to the natural history of the disease show statistical significance as well as clinically meaningful improvements with the drug. We have heard from families and physicians that children on DCCR have significantly improved academic performance, participate in varsity sports and extracurricular activities, go on dates, have sleepovers, go to prom without parents having to supervise them – essentially, they can live their lives as typical kids/young adults. We have been asked to generate additional controlled data before submitting a marketing application for DCCR. We have just completed that study, which shows highly statistically significant and clinically meaningful benefits of DCCR, and we hope to submit an NDA to the FDA next year.

We need a regulatory framework that recognizes the novel, complex and heart-breaking nature of diseases such as PWS. We cannot continue to apply the same regulatory paradigm to all diseases and all drugs – context must play a role. It is amazing to see new options available for people with ALS, and the first approval of a drug for Friedrich's Ataxia. But there are also diseases like Barth syndrome, where a drug with promising data may not have a path forward and the program may shut down. Regulatory delays such as our 3+ year back-and-forth with the FDA, have real-life impacts. For companies such as ours, programs will be cut, and some will even have to shut their doors. Every day, every week, every month, every year – symptoms will worsen, sometimes in irreversible manners, and patients may even die as they wait for treatments.

The FDA is and needs to remain the premier regulatory body of its kind in the world. What is desirable is a rigorous regulatory process, but one that balances the risk of approving a drug with the risk of having no treatments available for a desperate population. The Promising Pathway Act is a significant step in the right direction. Time-limited provisional approval would allow patients the ability to access potentially life-changing treatments as additional meaningful data is generated to justify their use. Availability of such treatments would be driven by clinically relevant data, and final approval would come only upon rigorous analysis of data generated from natural history studies and/or patient registries.

In closing, I truly appreciate the opportunity to share Soleno's story and highlight the significant unmet need for rare disease communities, and, in particular, the PWS community. Thank you Chairman Casey, Ranking Member Braun, and members of the Committee for your time. I look forward to your questions and discussion.