WORKSHOP REPORT

Overcoming Bottlenecks in Clinical Trials of Investigational Medicinal Products for Hyperphagia in Prader-Willi Syndrome

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EXECUTIVE SUMMARY

Prader-Willi syndrome (PWS) is the most commonly known genetic cause of life-threatening obesity. It is a complex neurodevelopmental disorder that presents with a range of mental and physical findings amongst which hyperphagia represents one of the most striking and life-long behavioral challenge for PWS patients and caregivers. No known pharmacological agent has been effective to treat hyperphagia to date. Novel therapeutic agents against hyperphagia are currently being tested in clinical trials for PWS, opening avenues for effective therapies in the near future. Several key challenges, however, remain to be resolved to ensure the success of upcoming and future trials for PWS. In this context, FPWR organized a workshop on July 22-23, 2015 gathering 34 international participants from industry, academia, non-governmental organizations and FDA to discuss about opportunities and identify key challenges for current and future clinical trials with the aim of creating an international precompetitive collaborative consortium working on key issues identified during the workshop. Four topics were discussed during the workshop including natural history of PWS, trial endpoints, trial design and benefit/risk assessment.

NATURAL HISTORY OF HYPERPHAGIA
The clinical description of seven nutritional phases by Miller and collaborators has helped the PWS community to better frame research on hyperphagia and provide valuable insights into the natural history of PWS. Many gaps, however, remain. Long-term longitudinal description of disease manifestations, their variability and their prognostic roles as well the aging process in PWS individuals are incompletely defined. Gaps also exist in understanding the co-morbidities of PWS; the relationship between genotype and phenotype; and the impact of various treatments such as growth hormone therapy on quality of life. Further work is needed to find biological correlates that support clinically-defined nutritional phases. Finally, participants stressed the need to further characterize the degree of hyperphagia and enrich the description of hyperphagic behaviors by including behaviors other than food-related behaviors. Leveraging information contained in several existing PWS registries could address some of the existing gaps. There is currently, however, no central or overarching PWS patient registry, and information is fragmented across many databases, countries and even continents. Most registries collect a single patient data point and long-term follow up is mostly lacking. In addition, data sources vary across registries, alternating between caregivers or clinicians being the primary providers, which may impact data quality and validity. More efforts should be devoted to optimize PWS registries so they can better inform the natural history of PWS.

CLINICAL TRIAL ENDPOINTS
Measuring the effect of a treatment on hyperphagia that is meaningful for patients within the limited time-frame of a clinical trial has proven to be challenging. Body mass index (BMI), DEXA and weight are useful as proxy measures of hyperphagia-induced obesity, but not in individuals whose weight is under control. In addition, these measures do not capture food-seeking abnormalities characteristics of individuals with PWS. The hyperphagia questionnaire developed by Dykens and al (2007) is currently

the most used outcome measure in clinical trials for hyperphagia in PWS. Although it provides a quantifiable measure of food-related behaviors, it does not fully assess the emotional and mental health challenges that are associated with hyperphagia. An increasing body of evidence points at treating children at an earlier stage of PWS, before hyperphagia starts. This would entail finding predictive biomarkers that are sensitive to changes in the non-hyperphagic to hyperphagic transition that could be used as surrogate markers. Several types of biomarkers that encompass the full spectrum of behavioral characteristics of hyperphagia in PWS patients should be developed including biological biomarkers that are thought to be involved in the pathophysiology of hyperphagia, biomarkers of mental health and metabolic biomarkers of nutritional phases. In addition, more efforts should be dedicated to develop structured clinical outcome assessments (COA) including patient (PRO) and caregivers reported outcome measures as meaningful trial endpoints.

TRIAL DESIGN

The design of clinical trials for PWS shares challenges common to other rare diseases, due to the paucity of patients that often leads to conducting multi-center and international trials to achieve adequate study power. Specific challenges for PWS are: the lack of knowledge of PWS natural history; the impact of current symptomatic treatments such as growth hormone therapy on the disease progression; and the lack of knowledge on demographics, health status and standards of care of the general PWS population. In this respect, PWS patient registries play a key role in identifying patients to be enrolled into clinical trials but also in collecting clinical and other health data that will help deciphering the natural history of PWS data and improve the design of clinical trials for PWS. Efforts should be made to recruit more patients, in particular those demographics that are currently under-represented in clinical trials, and gear registries for long-term follow-up of individuals with PWS.

BENEFIT/RISK ASSESSMENT

Patients are uniquely positioned to inform regulators` understanding of clinical context, i.e., the unmet needs and meaningful impacts of a treatment for PWS, and contribute to the benefit / risk analysis. In this regard, FPWR and other patient organizations have conducted surveys to better understand the caregivers` and patient views on PWS impact, severity, effectiveness of current treatment options, and attitudes towards clinical trials. Future work will consist in transforming these surveys into a more rigorous, generalizable and quantifiable risk-benefit assessment from the patient`s perspective. Understanding how disease severity vary across individuals with PWS and how it affects their quality of life will help design clinically meaningful outcome measures that better respond to unmet patient`s needs.

ESTABLISHING A PRECOMPETITIVE MULTI-STAKEHOLDERS CONSORTIUM TO ADVANCE PWS CLINICAL TRIALS

During the workshop, three working groups (WG) were established to develop solutions to the challenges that participants identified as major hurdles for the development of future clinical trials for PWS. These included: natural history, clinical trial endpoints and benefit/risk assessment. The WG on natural history will aim at establishing guidelines for nutritional phases designation, developing multimodal biomarker correlates of clinical description, performing an inventory of existing natural history data that can be leveraged from various databases and PWS registries and improving the PWS population representation of PWS registries. The WG on clinical trial endpoints will focus on developing age-specific PWS Food Behavior Questionnaires, and new biomarkers of treatment efficacy that can serve as clinical endpoints or surrogate markers. The WG on benefit/risk assessment will further develop patient surveys to formally incorporate patients and caregivers perspectives as scientific evidence into regulatory decision making process and use visual technologies to illustrate the impact of PWS on the quality of life of individuals with PWS and the surrounding family.

INTRODUCTION

Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by the absence of paternally-expressed imprinted genes on chromosome 15q11-13. Individuals with PWS present severe hypotonia and feeding problems in early infancy, followed during childhood and adulthood by cognitive impairment, maladaptive and compulsive behaviors, incomplete sexual development, and hyperphagia. Unless eating is externally controlled, the overwhelming drive to eat coupled with reduced energy expenditure and decreased caloric requirements leads to morbid obesity, making hyperphagia one of the most striking and life-long behavioral challenge for PWS. Growth hormone therapy is the only FDA-approved therapy for use in children with PWS since 2000. Despite beneficial effects on height, body composition, strength, endurance, bone mineral density, respiratory quotient and sense of well-being, it has no impact on hyperphagia. Novel therapeutic agents are currently being tested in clinical trials to reduce hyperphagia in PWS, giving real hope that effective therapies will emerge in the near future. Several key challenges, however, remain to be resolved to ensure the success of current and future trials for PWS. These include: understanding the disease cause; deciphering the physio-pathological mechanisms underlying hyperphagia; identifying the optimal time for intervention; understanding the natural course of the disease; measuring experimental treatment efficacy; developing and improving trial design to maximize the limited pool of patients, overcoming technical, clinical and regulatory hurdles related to multi-center and international trials; and understanding and integrating the patient`s perspective with respect to benefit risk assessment and therapeutic outcomes.

In this context, FPWR organized its first international workshop on clinical trials for hyperphagia, gathering 34 experts from academia, pharmaceutical industries, FDA and patient organizations. The aim was to identify key challenges hampering clinical trials for hyperphagia in PWS and establish a collaborative precompetitive consortium of key stakeholders to work together to develop solutions. The workshop focused on four topics including: natural history of PWS, trial endpoints, trial design and benefit/risk assessment.

NATURAL HISTORY OF HYPERPHAGIA

Food behavior in PWS is characterized by a switch from failure to thrive and disinterest in food to hyperphagia and an overwhelming drive to eat. The transition to hyperphagia is complex, however, and involves seven different nutritional phases, with five main phases through which individuals with PWS typically progress (Miller et al., 2011). Phase 0 occurs *utero,* with decreased fetal movements and growth restriction. In phase 1 the infant progressively evolves from hypotonia and feeding difficulties (phase 1a) to a normal weight increase (phase 1b). Phase 2 is characterized by weight gain (phase 2a) and an increased interest in food (phase 2b), but a normal satiety level. Phase 3 represents the hyperphagic stage typically accompanied by food-seeking and lack of satiety, which usually occurs around 8 years old. During this stage, eating behaviour is characterized by prolonged meal duration (Zipf and Berntsson 1987, Holland et al 1993), increased calorie intake (Holland et al 1993) and diminished satiety (Lindgren et al 2000). Concomitant to increased food intake, individuals with PWS develop an obsession with food combined with anxiety and compulsory attitude around food that impair their daily activities and often lead to temper outbursts and behavioral challenges. Although external food control by the surrounding family or caregivers has proven to be effective in keeping the weight of PWS patients under control and diminish morbid obesity and death, the compulsory aspects of food-seeking behavior prevents individuals with PWS from full access to autonomy and greatly impacts the daily life of individual as well as the family and caregivers. Some patients progress to phase 4 where individuals no longer have an insatiable

appetite and are able to feel full. Data is, however, lacking regarding the number of patients progressing from phase 3 to phase 4 and the mechanisms responsible for a decrease in hyperphagia.

The clinical description of various nutritional phases is helping the PWS community to better frame research on hyperphagia and provides valuable insights into the pathophysiology of PWS in general. An improved understanding of the various nutritional phases of PWS will not only benefit the management of individuals with PWS, but will also provide a better understanding on the natural history of PWS and will provide a framework for patient selection and outcome assessment in clinical trials. Future work should focus on finding biological and other biomarkers that distinguish clinically-defined nutritional phases, better characterizing the degree of hyperphagia, examining general behaviors other than food-related behaviors at various nutritional phases to better understand the mechanisms driving hyperphagia and developing rational treatments. A validated method (e.g., checklist) that will allow consistent determination of nutritional stage in individuals with PWS, across sites and clinicians, is expected to improve the precision of clinical trials.

Although numerous advances have been made to understand PWS, many gaps still remain. The natural history of many of the manifestations, their variability and their prognostic roles are not yet completely understood. Long-term longitudinal description of disease manifestations and their changes over time and in particular the aging process are limited. Gaps also exist in understanding the following aspects: co-morbidities of PWS; the relationship between genotype and phenotype; and the impact of various interventions and treatments, on the clinical trajectory and quality of life is needed. Existing PWS registries can address some of these gaps. For example, the French reference center for PWS has developed a registry containing medical, psychological and socio-demographic data of a cohort of 380 patients aged 0 to 20 years old. Medical and socio-demographic data are filled in by patient's physician whereas a familial psychological and quality of life form is filled in by the parents. Data is curated by a clinical research associate and a data follow-up is done on a yearly basis to allow longitudinal studies. The PWSA database contains medical data provided by caregivers of 1961 patients. The rare disease network natural history database (RDCN) contains information on the weight, behavior, nutritional phase, medical history and medications of 351 participants. Information is provided by clinicians and collected at several time points allowing longitudinal studies. The Global PWS Registry that was recently launched by FPWR contains an extensive range of medical information and history of more than 600 patients. Data is filled-in online by caregivers. Each of these registries contains useful information on the natural history of PWS, but there is currently no central or overarching PWS patient registry, and information is fragmented across many databases, countries and even continents. Most registries collect single patient data point and long-term follow up is mostly lacking. In addition, data sources vary across registries, alternating between caregivers or clinicians being the primary providers. This may impact data quality and validity. Except for Global PWS Registry, there is no unique personal identifier that allows for data linkage to other databases or biobanks. More efforts should be devoted to optimize PWS registries and so they can better inform on the natural history of PWS. In this regard, it will be important to establish a list of relevant information that is required to advance our knowledge on the natural history of PWS and to perform an inventory of information stored in various PWS databases and registries internationally. Future steps will require performing a data gap analysis across registries to identify missing data and establishing a uniform data and standardized quality process on how to collect and analyze data.

CLINICAL TRIAL ENDPOINTS

Measuring the effect of a treatment on hyperphagia within the limited time-frame of a clinical trial has proven to be challenging. Body mass index (BMI), DEXA and weight can be useful measures in overweight or obese patients who are in nutritional phase 3. These measures, however, are less relevant for patients whose weight is maintained by external control or for patients who are at an earlier stage of

the disease (pre-hyperphagic stage). In addition, these measures do not capture food-seeking abnormalities characteristic of individuals with PWS, such as food sneaking and theft, foraging through the trash for food, getting up at night for food seek and eating unpalatable items (Dykens 2000).

The hyperphagia questionnaire developed by Dykens and al (2007) addresses some of these issues and provides a quantifiable outcome measure for hyperphagia. The questionnaire is a 13-item instrument designed to measure food-related preoccupations and problems in PWS, as well as the severity of these concerns. The questionnaire is completed by parents and legal guardians who report on hyperphagic symptoms. The severity items is based on the definition of symptom-related impairment as operationalized by the American Psychiatric Association. The hyperphagia questionnaire is currently the most used outcome measure in clinical trials for hyperphagia in PWS. It does not, however, capture the full spectrum of behavioral characteristics of PWS patients such as the emotional and mental health challenges, and it does not specifically address the changes in food-related behaviors across nutritional stages. Experimental treatments for PWS-related hyperphagia may positively or negatively impact mental health and behavior and vice versa. In addition, neurobiological mechanisms underlying mental health challenges could play a role in hyperphagia. Developing trial outcome measures that encompass food behavior and non-food related behaviors across ages and nutritional stage is therefore important for assessing the impact of treatment on hyperphagia in PWS patients.

Biological biomarkers indicative of PWS disease progression are still missing. Quantitative biological markers that can be measured both in PWS disease models and in patients with PWS would help in translating basic research findings into clinical research and speed up drug development for PWS. In addition, finding biological correlates of eating behaviour dysfunctions will help refine clinically-defined nutritional phases described by Miller and collaborators (2011). An increasing body of evidence points at treating children at an earlier stage of PWS, before hyperphagia starts. This would entail finding predictive biomarkers that are sensitive to changes in the non-hyperphagic to hyperphagic transition. Several types of biomarkers should be developed including biomarkers that are thought to be involved in the pathophysiology of hyperphagia (e.g. unacetylated and acetylated ghrelin levels) or mental health and metabolic biomarkers of nutritional phases.

Developing a treatment that is meaningful to patients with PWS and caregivers depends on the patient and caregivers` perspective and perception of the treatment effect on disease aspects that matter the most to them. Despite the subjective nature of reports coming directly from patients or caregivers, without interpretation of clinicians and others, increasing efforts have been made to formalize and incorporate patients and caregivers reported outcome measures as evidence to support regulatory decision-making process. FPWR has developed with the help of PWSA an anonymous online survey to gather information about patient and parent views on PWS impact, severity and effectiveness of current treatment options, and attitudes towards clinical trials. Initial results show that hyperphagia and difficult behaviors around food represent the disease features that impact the most PWS patients and caregivers and for which a treatment is sought. Developing structured clinical outcome assessments (COA) derived from these surveys will guide the development of meaningful trial endpoints and inform regulators's understanding of clinical context (e.g. unmet needs, meaningful impacts) and contribute to the benefit / risk analysis of experimental treatments for PWS.

TRIAL DESIGN

PWS is a rare disease that occurs with a frequency of approximately 1/15,000 to 1/30,000, making the design of clinical studies with adequate statistical power difficult. An additional challenge is to identify

individuals with PWS eligible for recruitment into clinical trials and who are representative of the general PWS population. Only a fraction of the PWS population is currently enrolled into registries. For example, the Global PWS Registry contains currently data from 600 patients, the PWSA registry contains 1961 subjects and the French registry accounts for approximately 600 patients. Most of these patients are likely representative of a portion of the PWS population whose caregiver is well informed either through patient organizations and/or have access to internet. Efforts to reach out to under-represented PWS population or minorities would ensure a better representativeness of PWS population in registries and clinical trials, and would improve the generalizability of experimental treatment results to the global PWS population.

Our understanding of the natural history of PWS has many implications for the design and interpretation of trials. Selection criteria, time to intervention, outcome measurements, trial duration and definition of treatment success depends on our understanding of how PWS progress over time and how it is impacted by evolving standards of care and treatment (e.g. growth hormone therapy). Our knowledge on the natural history of PWS is still at its infancy mainly due to the complexity and the lack of a unifying model for PWS that integrates food-related and other behaviors and mental health challenges. In addition, longitudinal studies for PWS are limited, as they entail financial sustainability and human resources over a long-term period.

The paucity of patients scattered across regions, countries and continents often lead sponsors to conduct trials at multiple sites across different countries, adding additional cultural, technical and regulatory hurdles. These include: variation in trial quality assurance, heterogeneity of standards of care, and difference of experience of regulatory agencies with rare diseases or differences in regulations across countries. As more scientific evidence suggest that early treatment could have a bigger impact on PWS patients, conducting pediatric clinical trials also adds to the complexity of the regulatory landscape with often regulatory agencies requiring safety data on adult prior to exposure of the experimental treatment in children.

BENEFIT/RISK ASSESSMENT

Ensuring the safety, effectiveness and quality of human drugs is an increasingly complicated task that requires not only consideration of a multitude of complex factors but integration of multiple stakeholders' perspective. Current thinking, including that of regulatory agencies, recognizes that the clinical trial review process could benefit from a more systematic and expansive approach to obtaining the patient perspective on disease severity and current available options in a therapeutic area.

Patients are uniquely positioned to inform regulators` understanding of clinical context, i.e., the unmet needs and meaningful impacts of a treatment for PWS, and contribute to the benefit / risk analysis. In this regard, FPWR launched an anonymous online survey to gather information about caregivers` views on PWS impact, severity, effectiveness of current treatment options, and attitudes towards clinical trials. Preliminary results suggest that a majority of patients are willing to enroll into clinical trials and be tested for an experimental drug aimed at reducing hunger. Rare but serious side effects of a drug is the predominant concern of those who would consider participating in a clinical trial. A study recently performed by PWSA stresses the life-threatening impact of hyperphagia even when weight is adequately controlled. Hyperphagia without concomitant obesity often leads to death of individuals with PWS as a consequence of stomach necrosis, perforation, and clocking accidents. The PWS patient organizations

need now to leverage patient`s surveys and develop a more rigorous, generalizable and quantifiable risk-benefit assessment from the patients perspective. A deeper characterization of the PWS patient population including demographics, disease stage, standards of care and other specificities is needed before PROs and COA could be used as a measure of the patient perspective and be incorporated in the regulatory decision-making process. Understanding how disease severity vary across individuals with PWS and how it affects their quality of life will help design clinically meaningful outcome measures that better respond to unmet patient`s needs.

THE INTERNATIONAL CONSORTIUM TO ADVANCE CLINICAL TRIALS FOR PWS

The establishment of a collaborative, pre-competitive and international consortium was established during this workshop to leverage expertise and perspective of stakeholders from industry, academia, governmental agencies and patient organizations to address unmet scientific, technical, clinical and regulatory needs for clinical trials for PWS.

Three working groups (WG) were established to develop solutions on challenges that participants identified as major hurdles for the development of current and future clinical trials for PWS. These include: natural history, clinical trial endpoints and benefit/risk assessment.

The aims of the **WG on natural history** are to:

- Establish a guideline for nutritional phases designation and develop multimodal biomarker correlates of clinical description. This will consist in - establishing and validating a checklist that clinically defines each nutritional phase and- developing metabolic, behavioral and other biological biomarkers that correlate with nutritional phases.
- Develop an in-depth overview of existing natural history data. This will consist in performing an inventory of natural history data stored in various databases and PWS registries internationally.
- Improve the PWS population representation of PWS registries by increasing patient enrolment and access to PWS patients who are under-represented in PWS registries.

The **WG on clinical trial endpoints** will focus on improving current endpoints and developing new efficacy endpoints to assess treatment outcomes in a clinical trial for PWS. It will be important to first establish a list of ideal or acceptable characteristics for a clinical endpoint in the context of a clinical trial for PWS. Particular attention should be paid to develop measures that are reliable within defined PWS subgroups (age and living conditions), that are assessor-independent and sensitive to treatment differences within the limited time-frame of a clinical trial for PWS
The aims of the WG on clinical trial endpoint are to:

- Develop an age-specific food-behavior questionnaire. This will consist in- assessing the need to develop new questionnaires or adapt existing ones - developing and validating questionnaires and tools for young children and – determining the frequency of questionnaire administration
- Develop metabolic, behavioral, activity-based behavioral biomarkers and clinical outcome assessments that can be used as efficacy endpoints. With the increasing amount of evidence suggesting that treatment for PWS should be delivered at an early stage before manifestations of hyperphagia, the WG will pay particular attention to the development of biomarkers predictive of the transition from pre-hyperphagic to hyperphagic stage that could also serve as surrogate markers in a clinical trial for PWS.

The **WG on benefit/risk assessment** will further develop patient's surveys to formally incorporate patients and caregivers perspectives as scientific evidence into regulatory decision making process. In addition this group will use visual technologies to develop a video that illustrates the severity of PWS as well as the impact of PWS on the quality of life of individuals with PWS and the surrounding family taking into account the social, financial, psychological and technical aspects of the PWS disease spectra.

CONCLUSION

Creating a precompetitive space between all stakeholders should lower barriers to therapeutic development, and streamline the drug development process for PWS. Pooling resources, talent and expertise is a win-win situation that should help organizations to maximize their talent and resources, mitigate risk in clinical development, anticipate challenges, advance scientific knowledge, improve safety of trial participants and the reliability of study results,

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