Journal of Child and Adolescent Psychopharmacology

Journal of Child and Adolescent Psychopharmacology Manuscript Central:
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# Evaluation of Intravenous Immunoglobulin in Pediatric Acute-Onset Neuropsychiatric Syndrome

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| Journal: | *Journal of Child and Adolescent Psychopharmacology* |
| Manuscript ID | Draft |
| Manuscript Type: | Original Research |
| Date Submitted by the Author: | n/a |
| Complete List of Authors: | Melamed, Isaac; IMMUNOe Health and Research Centers<br>Kobayashi, Roger; University of California Los Angeles<br>O'Connor, Maeve; Allergy, Asthma & Immunology Relief<br>Kobayashi, Ai; Midlands Pediatrics<br>Schechterman, Andrew; Colorado Neurocognitive Consulting<br>Heffron, Melinda; IMMUNOe Health and Research Centers<br>Canterberry, Sharon; Midlands Pediatrics<br>Miranda, Holly; IMMUNOe Health and Research Centers<br>Rashid, Nazia; Dunwoody Consulting, |
| Keyword: | Other Disorders |
| Manuscript Keywords (Search Terms): | IVIG, PANS, PANDAS, Octagam |
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| | and up to 46 weeks in a subset of subjects.<br><br>Conclusions: In PANS, which may be associated with an underlying immune dysregulation, sequential infusions of IVIG [Octagam 5%] successfully ameliorated psychological symptoms and dysfunction, with sustained benefits for at least 8 weeks, and up to 46 weeks in a subset of patients. In addition, baseline immune and autoimmune profiles demonstrated significant elevations in a majority of subjects, which requires further evaluation, characterization, and study to clarify the potential immune dysfunction by which PANS manifests and progresses. |
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# Evaluation of Intravenous Immunoglobulin in Pediatric Acute-Onset Neuropsychiatric Syndrome

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**Funding Source:** This study was supported by a research grant from Octapharma AG.

**Running Head:** IVIG in PANS

## Abstract

**Objectives*:*** Pediatric acute-onset neuropsychiatric syndrome (PANS) is a clinical diagnosis in children who have an acute manifestation of varied neuropsychiatric symptoms, including obsessive compulsive disorder (OCD), eating disorders, tics, anxiety, irritability, and problems with attention/concentration. PANS may develop as a result of a post-infectious syndrome and may represent a new form of post-infectious autoimmunity. To test the hypothesis that PANS is related to an immune dysfunction, a multi-site, open-label study was designed to explore the efficacy of a novel IVIG treatment regimen.

**Methods:** The primary endpoint was evaluation of the efficacy of IVIG [Octagam 5%] in PANS over a period of 6 months (6 infusions) based on mean changes in psychological evaluation scores using 6 different assessments including the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), Clinical Global Impression of Severity, and the Parent-Rated PANS Scale.

**Results:** The final cohort consisted of 21 subjects (7 per site) with moderate to severe PANS. The mean age was 10.86 years (range: 4-16 years). Results demonstrated statistically significant reductions in symptoms from baseline to end of treatment in all 6 assessments measured. CY-BOCS results demonstrated statistically significant reductions in obsessive compulsive symptoms ($p<0.0001$), resulting in > 50% improvement sustained for at least 8 weeks after the final infusion and up to 46 weeks in a subset of subjects.

**Conclusions:** In PANS, which may be associated with an underlying immune dysregulation, sequential infusions of IVIG [Octagam 5%] successfully ameliorated psychological symptoms and dysfunction, with sustained benefits for at least 8 weeks, and up to 46 weeks in a subset of patients. In addition, baseline immune and autoimmune profiles demonstrated significant elevations in a majority of subjects, which requires further evaluation, characterization, and study to clarify the potential immune dysfunction by which PANS manifests and progresses.

## Introduction

In the late 1990s, a group of clinical researchers at the National Institutes of Mental Health (NIMH) described a subgroup of children who presented with obsessive-compulsive disorder (OCD) and/or tic disorders following streptococcal infections, and proposed the term pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) to describe the disorder (Swedo et al. 1998). The criteria established by the NIMH group for the diagnosis of PANDAS included: 1) the presence of OCD and/or a tic disorder; 2) pediatric onset; 3) an episodic course of symptom severity; 4) an association with streptococcal infections; 5) an association with neurological abnormalities, including piano-playing choreiform movements of the fingers and toes, which suggests that PANDAS may be similar to Sydenham's chorea (SC).

Difficulties establishing a precise link between the inciting streptococcal infection/exposure and the onset of OCD or tic symptoms, and the lack of reliable biological markers, led to a revision of the diagnostic criteria and to the proposal of a new clinical entity, pediatric acute-onset neuropsychiatric syndrome (PANS), in which the key clinical feature is ''acute and dramatic symptom onset'' of OCD and/or severely restrictive food intake with at least two coinciding abrupt onset, equally debilitating symptoms (anxiety; dysregulation; irritability, aggression, oppositionality; behavioral regression; cognitive deterioration; sensory or motor abnormalities; somatic symptoms) without any reference to their relationship with streptococcal infections (Swedo et al. 2012). Based on these new criteria, PANDAS would be included as a subgroup of PANS.

In 2013, the first PANS Consensus Conference was convened at Stanford University, with a geographically diverse group of clinicians and researchers from complementary fields of pediatrics: general and developmental pediatrics, infectious diseases, immunology, rheumatology, neurology, and child psychiatry. Participants were academicians with clinical and research interests in PANDAS/PANS. The goals were to clarify the diagnostic boundaries of PANS, to develop systematic strategies for evaluation of suspected PANS cases and to set forth the most urgently needed studies in this field. From this meeting, a Consensus Statement proposing recommendations for the diagnostic evaluation of youth presenting with PANS was developed (Chang et al. 2015).

Guidelines for treating PANS/PANDAS were published as a three-part series of articles published in 2017 (Cooperstock et al. 2017, Frankovich et al. 2017, Thienemann et al. 2017) by the PANS Research Consortium (PRC). Current treatment modalities for PANS include psychiatric and behavioral interventions as well as the use of nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotic therapy, corticosteroids, plasmapheresis, and intravenous immunoglobulin (IVIG). Per the guidelines, for moderate to severe PANS, oral or intravenous corticosteroids may be sufficient, however, IVIG is often the preferred treatment for these patients by most PRC members (Frankovich et al. 2017).

An increasing body of clinical, preclinical, and basic science research data support conceptualizing PANS and PANDAS as immune-mediated neurological disorders, similar to SC, and suggest that immune dysfunction may contribute to disease manifestation and progression (Frankovich et al. 2015, Murphy et al. 2015, Hornig 2013, Hornig and Lipkin 2013, Cutforth et al 2016). The hypothesis is that PANS may represent a new form of post-infectious autoimmunity, through molecular mimicry, suggesting a potential mechanism by which the disorder evolves. To test the hypothesis that PANS is related to an autoimmune dysfunction, a multi-site study was proposed to explore the efficacy of multiple, consecutive infusions of IVIG for PANS treatment.

## Methods

### *Participants and Study Design*

This open label study was conducted at three clinical/research sites in the United States: IMMUNOe Research Center, Centennial, Colorado; Midlands Pediatrics, Papillion, Nebraska; Allergy, Asthma & Immunology Relief Research Institute, Charlotte, North Carolina. A central Institutional Review Board approved the study (IntegReview). Participants were recruited from direct referrals from clinicians as well as ClinicalTrials.gov (NCT03348618). The parents of participants provided informed consent, and study participants provided assent, when appropriate.

To be eligible for the study, participants between 4 to 16 years of age were required to have a diagnosis of moderate to severe PANS based on accepted criteria (Swedo et al. 2012) as validated by the Pediatric Acute Neuropsychiatric Symptom Scale, Parent Version (PANS Scale) conducted during a prescreening phone call (for additional information, see Behavioral Assessments section)(PANS Scale 2012) (Appendix 1). It is also important to note that all patients presented with symptoms that were not controlled using standard PANS therapy (e.g., cognitive behavioral therapy, selective serotonin reuptake inhibitors, antibiotics, corticosteroids, etc.). Therefore, they required more aggressive immunomodulatory interventions (e.g., IVIG).

Participants who were using prophylactic antibiotics were required to be on a stable dose for ≥ 3 months. In addition, potential participants were excluded if they had a history of rheumatic fever, including SC (with neurologic manifestations), previous IVIG therapy within 6 months prior to screening, and/or use of corticosteroids within 6 weeks prior to screening. If potential participants had been prescribed antibiotics for an acute infection, a wash-out period of 7 days following completion of dose was required.

***Behavioral Assessments***

For the primary outcome measures, licensed independent (from the clinician's study center) psychologists administered validated psychometric scales including the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), Clinical Global Impression of Severity (CGI-S), Yale Global Tic Severity Scale (YGTSS), and the Anxiety Disorders Interview Schedule for DSM-IV, Child/Parent versions (ADIS). In addition to these assessments, two parent-rated questionnaires were utilized during the study. The PANS Scale, Parent Version (PANS Scale 2012)(Appendix 1) was administered as a prescreening measure for validation of the PANS diagnosis and to provide a baseline measurement of disease severity. Subsequent evaluations of the PANS Scale, following IVIG treatment, were also utilized to assess efficacy.

In addition to the PANS Scale, the Parent-Rated PANS Questionnaire (PRPQ) was developed specifically for this study and completed by parents at every treatment visit (Appendix 2). This questionnaire takes 10-20 minutes to complete and contains 58 items selected as key symptoms of interest for data analysis per the most important PANS characteristics reported in the literature (Swedo et al. 2012, Bernstein et al. 2010).

### *Exploratory Assessments*

Exploratory outcome measures included evaluation of key neuroimmune panels (Cunningham Panel, Neural Zoomer), as well as immune, infectious, and atopic laboratory panels.

Based on the work by Swedo et al (Swedo et al. 2012), motor abnormalities occurring in PANS include a variety of signs and symptoms. Dysgraphia and fine motor skills may abruptly deteriorate following onset of symptoms. Therefore, obtaining a drawing sample during the acute phase, and during an asymptomatic period, is a relatively simple way to document motor changes. For these reasons, optional drawing/writing samples were collected from participants as an additional measure of assessment both prior to and following treatment.

### *Safety Assessments*

All subjects were given a patient diary and were asked to catalog all adverse events (AEs). In addition, a follow-up phone call 72 hours post-infusion by a research coordinator was also implemented to gather AEs. The parents were instructed to record the following data in the diary: any suspected AEs, temperature (using same method for every time), infections (serious acute bacterial infections had to be validated), physician/emergency room visits, hospitalizations (overnight stays), school/work days missed because of infections or illness, concomitant medications, especially antibiotics. The diary was reviewed, and adverse events were monitored, at every treatment visit following the first IVIG infusion.

### *Visit Schedule and Procedures*

The study consisted of a pre-screening phone call, followed by 10 visits. During the pre-screening phone call, the PANS Scale (PANS Scale 2012)(Appendix 1) was administered to assess disease severity. If the potential participant met the criteria of moderate to severe PANS, a subsequent on-site screening/baseline visit (Visit 0) was scheduled. At Visit 0, medical history and concomitant medications were assessed, baseline psychometric evaluations were conducted (CY- BOCS, CGI-S, YGTSS, ADIS), and blood was drawn for initial panel, biomarker, and safety assessments. In addition, optional pre-treatment writing and/or drawing samples were gathered from participants and parents. Four (4) weeks later, eligible participants received IVIG infusions every 21 days (± 3 days) for a total of 6 infusions over a period of 18 weeks (Visits 1-

6). In addition to IVIG infusions, AEs (including review of diaries) and concomitant medications were assessed, and parents completed the PRPQ, at each treatment visit.

Follow-up included a visit approximately 1 week after the final infusion (Visit 7) and a visit 7 weeks after the final infusion (Visit 8), the latter of which was considered the end of study (EOS) visit. At Visits 7 and 8, all psychometric evaluations (CY- BOCS, CGI-S, YGTSS, ADIS) and the PANS Scale were administered. In addition, blood was drawn for post-treatment evaluation of all panel, biomarker, and safety assessments.

Study investigators subsequently added a late visit (up to 46 weeks following the final infusion) to the study design to gather additional psychometric evaluations (CY- BOCS, CGI-S, YGTSS, ADIS) in a subset of available participants (Visit 9) to assess durability of response.

***Study Drug and Dosage/Administration***

Intravenous immunoglobulin (IVIG) has been used to treat primary and secondary immunodeficiencies at replacement doses of 0.2 – 0.6 g/kg body weight every 3 to 4 weeks and enhances immune homeostasis by modulating expression and function of Fc receptors, interfering with activation of complement and production of cytokines, providing anti-idiotypic antibodies, and affecting the activation and effector functions of T- and B-cells (Cunningham-Rundles et al. 1984, Perez et al. 2017, Melamed et al. 2018). In higher doses of 1 to 2 g/kg body weight, IVIG has been shown to induce immune modulation and suppress systemic inflammation, and has long been used in the treatment of autoimmune and inflammatory conditions (Dwyer 1992, Nimmerjahn and Ravetch 2007, Ballow 2014, Joao 2018).

The design of the study included on-site administration of IVIG [Octagam 5%) at a dosage of 1 g/kg of body weight every 21 days (± 3 days) for a total of 6 infusions (cycles) over a period of 18 weeks. The study drug was provided in bottles from the manufacturer [Octapharma], and was labeled and stored appropriately for investigational use. The study drug was administered intravenously directly from the bottle by a healthcare provider according to the labeled infusion rates (which should not exceed 3.33 mg/kg/min [200 mg/kg/hr]). Vital signs were monitored were monitored throughout each infusion.

It is important to note that the number of sequential IVIG infusion cycles (x6) evaluated in this study is a unique treatment model that, to the best of our knowledge, has not been utilized in any previously reported assessment of IVIG treatment efficacy in the PANS population.

### *Statistical Analysis*

Unadjusted descriptive statistics were conducted to summarize the endpoints for eligible participants to detect the mean, standard deviation (SD) for continuous variables, and percentages for categorical variables. In adjusted descriptive statistics, outliers present in data sets will often be removed in order to determine the adjusted mean because they can have a large impact on the calculated means of small populations. To maintain the integrity of the data, we didn't adjust the statistics in this manner to correct statistical averages to compensate for data imbalances and variances. Differences between subjects were tested using Student's t test for continuous variables and Fisher's exact tests were used for categorical variables. Analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC). A two-sided p value $<0.05$ was considered statistically significant.

## Results

### *Study Population*

A total of 26 patients were screened and 21 patients met the criteria for participation in the study (7 participants at each site)(**Table 1**). The 5 screened patients who were unable to participate had scheduling conflicts related to IVIG infusion dates, decided they didn't want to participate, or did not meet inclusion criteria for severity. The enrolled patients included 13 males (62%) and 8 females (38%). The majority of patients were white with a mean age of 10.86 ± 2.88 and weight of 43.83 kg ± 21.88. As expected, the mean PANS Scale OCD Symptom Score at baseline was high at 21.32 ± 5.22 (scoring system of 0-25). Per the CGI-S, 10 (48%) of participants presented with moderate PANS symptoms, 6 (28%) with marked symptoms, and 5 (24%) were considered severe. Again, it should be noted that mean baseline serum measurements of the calcium

calmodulin-dependent protein kinase II (CaMKII) and anti-tubulin antibodies were both elevated.

***Primary Efficacy Endpoints***

The primary efficacy endpoints were validated psychometric assessments (CY-BOCS, CGI-S, YGTSS, ADIS) and parent observations (PANS Scale, PRPQ). Statistically significant improvements were demonstrated in all psychometric assessments and parent questionnaires from baseline to end of treatment and in early/late follow-up visits (**Figures 1-4**). In a subset of patients (n=12) who participated in a late follow-up visit (29-46 weeks following the final infusion), results indicate that tics returned, although they were still below baseline levels (see **Figure 3**). One of the most important assessments was the PRPQ in that it demonstrates the efficacy of IVIG following each infusion (see **Figure 4**). Statistically significant reductions in symptoms were noted by the third IVIG infusion.

***Exploratory Endpoints***

*Biomarker Evaluations*

Several baseline immune, atopic, and infectious laboratory variables as well as neuroimmune panels (Cunningham Panel, Neural Zoomer) were explored as possible predictors or moderators of response. Of these, only CaMKII elevation (n=7 [see **Table 1**]) was found to be potentially related to response based on CY-BOCS total scores at EOS. While there was a minor difference in mean CY-BOCS total score between the two groups (elevated CaMKII CY-BOCS score: 10.5; normal CaMKII CY-BOCS score: 7.4), the difference did not reach statistical significance. It is important to note the inherent difficulties in measuring systemic serum biomarkers for a localized brain disease such as PANS. It may be that the immunologic "action" is localized within brain tissue and central nervous system, and blood measurements are too remote, diffuse and insensitive. In animal models that include cerebrospinal fluid (CSF) measurements, brain tissue biopsies, etc., results are impressive and convincing. Obviously, such studies are difficult, if not impossible, to conduct in children for a variety of reasons.

*Drawing/Writing Samples*

A dramatic example of the potent effects of IVIG in this patient population is demonstrated in drawing and writing samples of the PANS subjects before and after the administration of IVIG (**Figure 5A, B**). As described, dysgraphia and fine motor skills may abruptly deteriorate following onset of symptoms with resolution following immunomodulatory treatment.

***Adverse Events***

Adverse effects of IVIG infusion included two severe headaches, which resolved without complication, and a low number of minor discomforts that also resolved. No serious adverse events occurred during the study.

## Discussion

To the best of our knowledge, this is the first study to assess a total of six (6) infusions for the treatment of PANS. The results of this prospective, open-label, proof-of-concept study substantiate earlier randomized, controlled clinical trials of the benefits of IVIG in controlling PANS symptoms (Perlmutter et al. 1998, Williams et al. 2016), however, the extended dosing strategy in this study demonstrated durability of effects up to 46 weeks following the final infusion. It is notable that per the interim measurements provided by the PRPQ, statistically significant drops in symptom scores did not occur until third infusion (see **Figure 4**). The dosing strategy in earlier randomized, controlled studies was 1 g/kg administered over two consecutive days (2 g/kg total) (Perlmutter et al. 1998, Williams et al. 2016). In this study, we utilized a total dose of 1 g/kg every 3 weeks for a total of 6 infusions. While a dose of 2 g/kg of IVIG is routinely used for immunomodulation in adults, it is a very large dose in the pediatric population and must be administered over 2 to 4 days. A dose of 1 g/kg can be administered in 1-2 days in the majority of pediatric patients, which is much more manageable in this population. In addition, a total immunomodulatory IVIG dose of 1 g/kg has been shown to be effective pediatric patients in immune thrombocytopenic purpura (Warrier et al. 1997).

In the first double-blind, placebo-controlled investigation conducted by Perlmutter et al, therapeutic plasma exchange (TPE) (5 single-volume exchanges over 2 weeks), IVIG (1 g/kg daily on 2 consecutive days), or placebo (saline solution given in the same manner as IVIG) were compared (Perlmutter et al. 1999). Results demonstrated that IVIG and TPE were both effective in reducing OCD symptoms in PANDAS patients (by 45% and 58%, respectively), whereas a placebo infusion had no discernable effect (Perlmutter et al. 1999). In contrast, non-PANDAS OCD (Nicolson et al. 2000) and tic disorders (Hoekstra et al. 2004) do not demonstrate benefits in TPE and IVIG, respectively.

Although the use of IVIG in the treatment of PANS has been utilized clinically, no additional placebo-controlled trials were conducted until 2016 (Williams et al. 2016). The study consisted of four visits: baseline, week 6 (end of the blinded phase), week 12 (end of the open-label phase), and week 24 (follow-up). At baseline, participants received either IVIG (2 g/kg per day administered at 1 g/kg over 2 days)(n = 17) or placebo (n = 18). Six weeks following baseline, participants were evaluated, and a "responder" was defined as a decrease in CY-BOCS score of ≥30%, and "Much" or "Very Much" improved rating on CGI-I. Nonresponders to the blinded infusion were offered an open-label IVIG infusion.

At 6 weeks, the mean decrease in OCD severity was greater in the IVIG cohort than in placebo, but this difference did not reach statistical significance. It was determined that the study's power to detect between-group differences was tempered by the high variability in individual improvement after double-blind administration of IVIG. It was also known to the participants and their parents that those who did not meet the criteria for a ''responder'' in the 6-week portion of the study would receive an open-label IVIG infusion. OCD severity scores for those receiving open-label IVIG (regardless of whether they had received a placebo or blinded IVIG infusion) decreased roughly 50% in 6 weeks. Because these improvements were only demonstrated during the open-label phase of the trial, it was not possible to definitively determine the efficacy of IVIG. In particular, participants may have over-reported symptom severity in the double-blind portion of the study to increase the possibility of getting open-label IVIG at 6 weeks.

The positive results from this study contribute to the gathering evidence in support of conceptualizing PANS as an immune-mediated brain disease, similar to SC, involving the caudate, putamen, and other basal ganglia structures. Published data support the premise that PANS is an autoimmune disorder in susceptible children resulting in immune dysregulation involving autoantibodies, autoreactive T-cells, disruption in T-regulatory cell function, microglial cell dysregulation, inappropriate release of or response to inflammatory cytokines, and autoreactive B-cells which result in an inflammatory disorder of the basal ganglia (Hornig 2013, Hornig and Lipkin 2013, Williams and Swedo 2015, Cutforth et al. 2016, Frick and Pittenger 2016, Frankovitch et al. 2017). Therefore, the use of a broad-spectrum immunomodulatory agent, such as IVIG, should result in changes in behavior brought on by abnormal inflammation (Ballow 2014, Spinello et al. 2016, Frankovitch et al. 2017, Joaõ et al. 2018). In other words, if PANS were not an autoimmune, autoinflammatory disease, then an immunomodulatory intervention, such as IVIG, should not have any impact on psychometric and clinical measurements. As the results of our study demonstrate, sequential infusions of IVIG had a significant, positive impact on PANS patients, supporting the characterization of PANS as an autoimmune disorder.

## Conclusions

The results of this study demonstrated that in PANS, which may be associated with an underlying immune dysregulation, sequential infusions of IVIG [Octagam 5%] successfully ameliorated psychological symptoms and dysfunction, with sustained benefits for at least 8 weeks, and up to 46 weeks in a subset of patients, following the final infusion. In addition, baseline immune and autoimmune profiles demonstrated significant elevations in a majority of subjects, which requires further evaluation, characterization, and study to clarify the potential immune dysfunction by which PANS manifests and progresses.

## Clinical Significance

The limitations of this open-label pilot study include the small sample size and lack of a control group. However, in PANS patients, all psychometric endpoints studied exhibited statistically significant decreases following 6 infusions of IVIG. These positive results warrant a randomized, placebo-controlled trial to definitively evaluate the impact of multiple, sequential IVIG infusions on PANS symptoms. The durability of response is also noteworthy. Although the majority of PANS symptoms were still under control at the late follow-up visit (up to 46 weeks), it is of interest that tics returned in a subset of patients following wash-out of IVIG. For these patients, additional infusions may be required to ameliorate recurrent symptoms.

## Acknowledgments

This work was supported by a financial grant from Octapharma. We also acknowledge the support of Shireen Dunwoody of Dunwoody Consulting for data interpretation and review, as well as assistance with development, review, and revisions of the manuscript. Cunningham Panel laboratory assessments and consulting expertise were provided by Moleculera Labs.

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**Figure Legends**

**Figure 1.** Unadjusted mean Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total scores (*$p < 0.05$ was considered statistically significant). Note that in a subset of patients (n=12) who participated in a late follow-up visit (29-46 weeks following the final infusion), results continued to improve as compared to baseline. The timing of evaluations is as follows:

Visit 7 (19 weeks after baseline), Visit 8 (26 weeks after baseline), Visit 9 (29-46 weeks after Visit 8/final infusion and 55-72 weeks after baseline).

**Figure 2.** Unadjusted mean Clinical Global Impression of Severity (CGI-S) scores (*p < 0.05 was considered statistically significant). Note that in a subset of patients (n=12) who participated in a late follow-up visit (29-46 weeks following the final infusion), results continued to improve as compared to baseline. The timing of evaluations is as follows: Visit 7 (19 weeks after baseline), Visit 8 (26 weeks after baseline), Visit 9 (29-46 weeks after Visit 8/final infusion and 55-72 weeks after baseline).

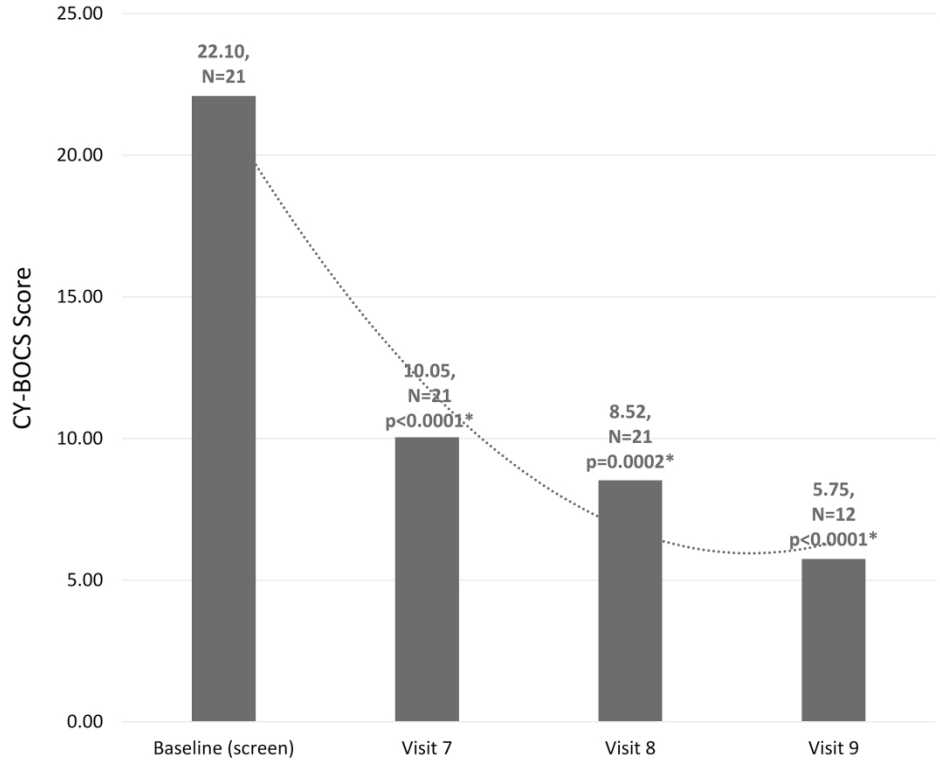
**Figure 3.** Unadjusted mean Yale Global Tic Severity Scale (YGTSS) scores (*p < 0.05 was considered statistically significant). Note that in a subset of patients (n=12) who participated in a late follow-up visit (29-46 weeks following the final infusion), results indicate that tics returned, although they were still below baseline levels. The timing of evaluations is as follows: Visit 7 (19 weeks after baseline), Visit 8 (26 weeks after baseline), Visit 9 (29-46 weeks after Visit 8/final infusion and 55-72 weeks after baseline).

**Figure 4.** Unadjusted mean scores from infusion 1 to infusion 6 (infusions occurred every 3 weeks) of the Parent-Rated Pediatric Acute-Onset Neuropsychiatric Syndrome Questionnaire (PRPQ)(Appendix 2) (*p < 0.05 was considered statistically significant). This questionnaire takes 10-20 minutes to complete and contains 58 items selected as key symptoms of interest for data analysis per the most important PANS characteristics reported in the literature. The importance of this assessment, as compared to the others conducted in this study, is that it demonstrates the efficacy of IVIG following each infusion. Statistically significant reductions in symptoms were noted by the third IVIG infusion.

**Figure 5.** The subject was asked to draw, "self and others." A) Subject's drawing prior to treatment. B) Subject's drawing following IVIG treatment.

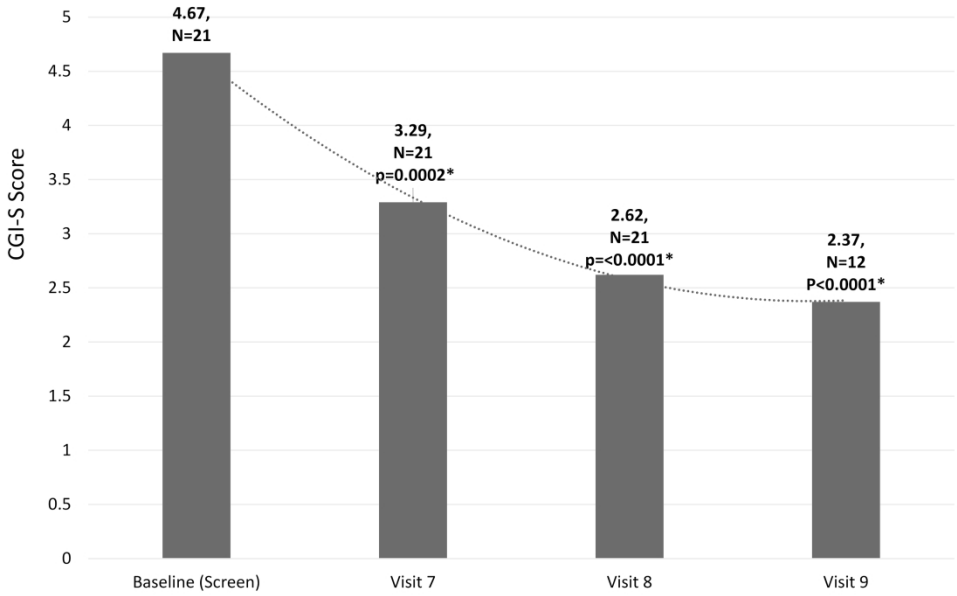
**Disclosures**

I.M. has received honoraria and research support from Octapharma AG; he has also received honoraria and research support from the Pharming group. R.H.K. has received honoraria and research support from Octapharma AG, research support and honoraria from Takeda (previously Baxalta/Shire), research support from the Vietnam Respiratory Society, Hanoi Vietnam, research support from Vietnam National Children and Hospital Hanoi, Vietnam, and personal fees/honoraria from UCLA School of Medicine. M.O. has received honoraria and research support from Octapharma AG. A.L.K. has received honoraria, research support from Octapharma AG. A.S., M.H., S.C., H.M., and N.R. have nothing to disclose other than their employment affiliations.



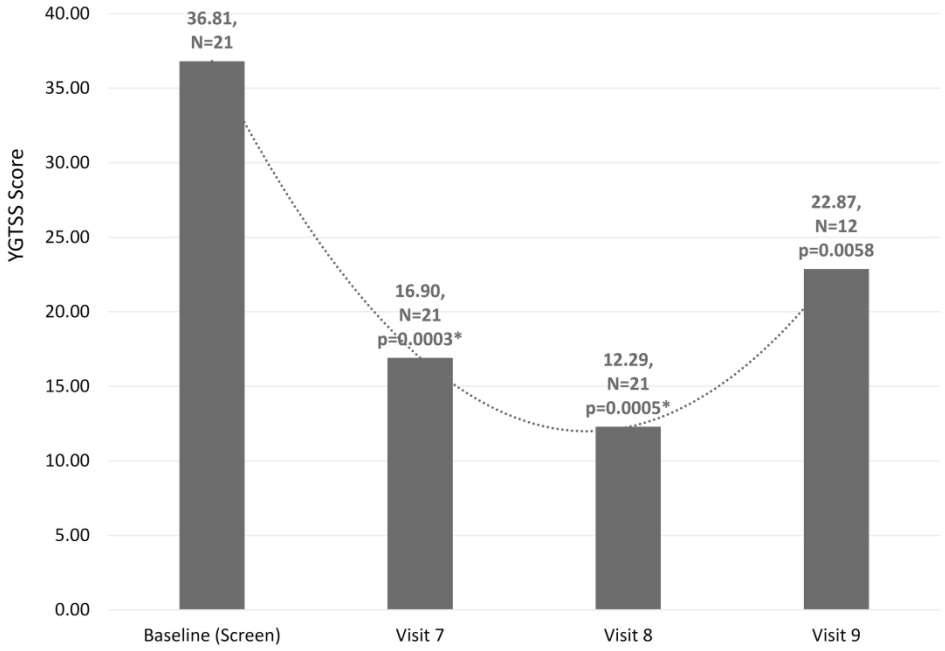

Unadjusted mean Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total scores (*p < 0.05 was considered statistically significant). Note that in a subset of patients (n=12) who participated in a late follow-up visit (29-46 weeks following the final infusion), results continued to improve as compared to baseline. The timing of evaluations is as follows: Visit 7 (19 weeks after baseline), Visit 8 (26 weeks after baseline), Visit 9 (29-46 weeks after Visit 8/final infusion and 55-72 weeks after baseline).

125x101mm (600 x 600 DPI)




Unadjusted mean Clinical Global Impression of Severity (CGI-S) scores (*p < 0.05 was considered statistically significant). Note that in a subset of patients (n=12) who participated in a late follow-up visit (29-46 weeks following the final infusion), results continued to improve as compared to baseline. The timing of evaluations is as follows: Visit 7 (19 weeks after baseline), Visit 8 (26 weeks after baseline), Visit 9 (29-46 weeks after Visit 8/final infusion and 55-72 weeks after baseline).

157x101mm (600 x 600 DPI)




Unadjusted mean Yale Global Tic Severity Scale (YGTSS) scores (*p < 0.05 was considered statistically significant). Note that in a subset of patients (n=12) who participated in a late follow-up visit (29-46 weeks following the final infusion), results indicate that tics returned, although they were still below baseline levels. The timing of evaluations is as follows: Visit 7 (19 weeks after baseline), Visit 8 (26 weeks after baseline), Visit 9 (29-46 weeks after Visit 8/final infusion and 55-72 weeks after baseline).

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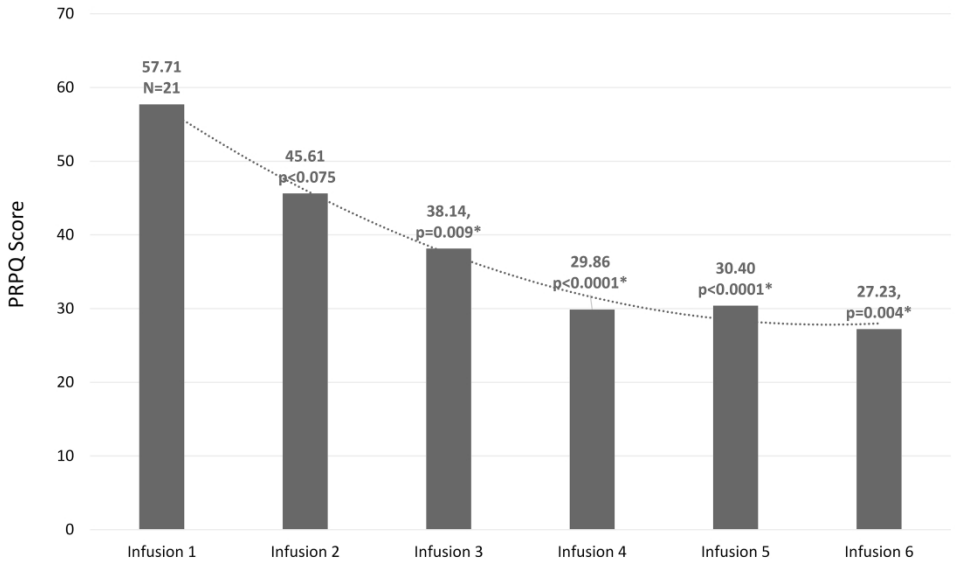


Unadjusted mean scores from infusion 1 to infusion 6 (infusions occurred every 3 weeks) of the Parent-Rated Pediatric Acute-Onset Neuropsychiatric Syndrome Questionnaire (PRPQ)(Appendix 2) (*$p < 0.05$ was considered statistically significant). This questionnaire takes 10-20 minutes to complete and contains 58 items selected as key symptoms of interest for data analysis per the most important PANS characteristics reported in the literature. The importance of this assessment, as compared to the others conducted in this study, is that it demonstrates the efficacy of IVIG following each infusion. Statistically significant reductions in symptoms were noted by the third IVIG infusion.

165x101mm (600 x 600 DPI)

Figure 5. The subject was asked to draw, "self and others." A) Subject's drawing prior to treatment. B) Subject's drawing following IVIG treatment.

Figure 5. The subject was asked to draw, "self and others." A) Subject's drawing prior to treatment. B) Subject's drawing following IVIG treatment.

107x76mm (300 x 300 DPI)

**Table 1. Sociodemographic and Baseline Clinical Characteristics**

| *Characteristic* | *n (%)* | *Mean ± SD* |
|---|---|---|
| Age | 21 (100) | 10.86 ± 2.88 |
| Male sex | 13 (62) | |
| Female sex | 8 (38) | |
| Race | | |
| White | 19 (90) | |
| Asian | 1 (5.0) | |
| Asian/White | 1 (5.0) | |
| Weight (kg) | 20 (95) | 43.83 ± 21.18 |
| PANS Scale OCD Symptom Score (0-25) | 19 (90) | 21.32 ± 5.22 |
| CY-BOCS total (0-40) | 21 (100) | 22.10 ± 7.82 |
| CGI Severity | | 4.67 ± 0.84 |
| Moderate (4) | 10 (48) | |
| Marked (5) | 6 (28) | |
| Severe (6) | 5 (24) | |
| CaMKII | | |
| Serum | 21 (100) | 130.85 ± 25.01 |
| Elevated (> 130) | 7 (33) | |
| Anti-tubulin antibodies | | |
| Serum | 21 (100) | 1880.95 ± 1252.66 |
| Elevated (≥ 1000) | 20 (95) | |

Abbreviations: n=number; SD=standard deviation; PANS Scale: Pediatric Acute Neuropsychiatric Symptoms Scale; OCD=Obsessive compulsive disorder; CY-BOCS=Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS); CGI=Clinical Global Impressions; CaMKII= calcium calmodulin-dependent protein kinase II.

# PEDIATRIC ACUTE NEUROPSYCHIATRIC SYMPTOM SCALE* Parent version

**Date:** **Name:** **Gender: F M**

**Date of birth:**

**Date of onset:**

**Informants:** **Telephone numbers**

**Version:** June 6, 2012

| DOMAIN | One week prior to 1st Onset | Week following 1st Onset | Current (past 7 days) |
|---|---|---|---|
| Date | | | |
| Obsessive-compulsive symptoms (0-25)<br>(5 X the worst of the OC symptoms)** | | | |
| Associated neuropsychiatric (NP) symptoms (0-25)<br>(sum of the 5 (of 7) worst NP domains)*** | | | |
| 1. Anxiety symptoms (0-5) | | | |
| 2. Extreme moodiness and/or depression (0-5) | | | |
| 3. Irritability or aggressive behavior (0-5) | | | |
| 4. Learning/cognitive symptoms, confusion (0-5) | | | |
| 5. Behavioral regression (0-5) | | | |
| 6.A. Sensory symptoms (0-5) | | | |
| 6.B. Hallucinations (0-5) | | | |
| 6.C. Motor symptoms (0-5) | | | |
| 7.A. Urinary symptoms (0-5) | | | |
| 7.B. Sleep disturbance, fatigue (0-5) | | | |
| 7.C. Dilated pupils (0-5) | | | |
| TOTAL SYMPTOMS (0-50) | | | |
| Impairment (0-50) | | | |
| TOTAL SCORE (0-100) | | | |

*Based on the clinical experience of Susan Swedo, M.D., Miroslav Kovacevic, M.D., Beth Latimer, M.D., and James Leckman, M.D., with the help of Diana Pohlman, Keith Moore and many other parents. **Six Obsessive-compulsive symptoms domains are presented. Rate all of them. However, on the above table only enter the score of the most severe domain (times 5; 0-25).***Seven Associated symptom domains are presented. Rate all of them. However, for each domain one or more symptom sets are listed. On the above table, only enter the score of the most severe symptom set for each domain (0-5).

**Date:**

**Name:**

**SYMPTOM SEVERITY RATING SCALE (use these anchor points for each of the symptoms)**

| **Severity** ***(rate each of the symptoms listed on the following pages for the past week)*** | |
|---|---|
| **NONE** No evidence of specific symptoms and behaviors | **0** |
| **MINIMAL** Specific symptoms and/or behaviors are present but are only evident occasionally and not a major source of difficulty. | **1** |
| **MILD** Specific symptoms and/or behaviors are present during the past week, and are episodically a source of some distress and difficulty. | **2** |
| **MODERATE** Specific symptoms and/or behaviors are present every day and are a source of distress and difficulty. | **3** |
| **SEVERE** Specific symptoms and/or behaviors are present every day and are severe resulting in a great deal of distress and difficulty. | **4** |
| **EXTREME** Specific symptoms and/or behaviors are always present and are extremely severe resulting in an extreme degree of distress and difficulty. | **5** |

**If multiple time points will be rated on this form, please use the following indicators:**

"**B**" = Symptom severity one week ***Before*** the onset of the first episode of illness

"**O**" = Symptom severity during the week following the initial ***Onset*** of symptoms

"**C**" = ***Current*** symptom severity during the past week

**Date:**

**Name:**

**Informant:**

**I. CORE Obsessive-compulsive Symptoms (circle and rate ALL symptoms that have been present in the past week). Use the "BOC" indicators if multiple time points are being scored (see p. 2).**

| Obsessive-compulsive symptoms | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Intrusive and persistent obsessional worries (anxieties) about dirt and germs and related washing compulsions (circle obsessions and/or compulsions) | | | | | | |
| Intrusive and persistent obsessional worries (anxieties) about harm to self or others and related compulsions; a need to tell or confess (this symptom domain may be closely related to separation worries, but rate both if both are present | | | | | | |
| Intrusive and persistent obsessional worries (anxieties) about sexual or religious thoughts or behaviors and related rituals and compulsions | | | | | | |
| Intrusive obsessional worries about symmetry and related compulsions: ordering, counting, *or* arranging; a need to touch, tap or rub, or a need for things to feel, look, *or* sound 'just right' | | | | | | |

| Obsessive-compulsive symptoms | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Intrusive and persistent obsessional worries (anxieties) about collecting and hoarding | | | | | | |
| Restrictive and/or avoidant food intake symptoms; Eating or feeding disturbance (including but not limited to apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; or concern about aversive consequences of eating) resulting in a refusal to eat (atypical anorexia) or a marked decrease in food intake | | | | | | |
| Miscellaneous. The need to know or remember; Fear of saying certain things; Fear of not saying just the right thing; Intrusive (non-violent) images; Intrusive sounds, words, music or numbers; Need to repeat activities (e.g. in/out of a doorway, up/down from chair); The need to involve another person (usually a parent) in ritual (e.g. asking a parent to repeatedly answer the same question; Mental rituals other than checking / counting; Excessive list making; Other (describe) _____ _____ | | | | | | |
| **Severity of all the above Obsessive-compulsive symptoms (**over the past week) Five times this rating [0-25] should be entered on p. 1 | | | | | | |

**II. ASSOCIATED SYMPTOMS (circle and rate ALL symptoms that have been present in the past week). Use the "BOC" indicators if multiple time points are being scored (see p. 2).**

| 1. Anxiety symptoms | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Separation anxiety – need to maintain proximity to person, a familiar location, or a thing | | | | | | |
| General anxiety | | | | | | |
| Unfounded irrational fears and/or phobias | | | | | | |
| Panic episodes | | | | | | |

| 2. Emotional lability, depression, | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Emotional lability – mood swings - moodiness | | | | | | |
| Depression with or without suicidal or self-injurious thoughts | | | | | | |

| 3. Increased irritability or aggressive behavior | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Increased irritability; defiant/ irrational demands; reactive aggressive behavior, temper tantrums; rage attacks | | | | | | |

| 4. Behavioral regression | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Behavioral regression ("baby talk," behavior atypical for actual chronological age) | | | | | | |
| Change in personality | | | | | | |

| 5. School performance Concentration/ Learning | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Difficulties in attention, concentration or learning – unable to concentrate or a clear problem with immediate or short term memory | | | | | | |
| Loss of academic skills – especially math or in reading or writing | | | | | | |
| Confusion | | | | | | |

| 6.A. Sensory symptoms | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Heightened sensitivity to light, the way things “feel” (tags or labels) or “sound” or other sensory stimuli – such as smell or taste; a need to touch things in a specific way; how things “look” including spatial distortion (eg, objects appear closer than they actually are) | | | | | | |

| 6.B. Hallucinations. | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Visual or auditory hallucinations | | | | | | |

| 6.C. Motor symptoms | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Dysgraphia (loss of ability to draw, copy figures and/or write letters) | | | | | | |
| Motoric hyperactivity and/or adventitious movements - kicking, spitting, flailing, rolling, or stomping (do not rate tics here); unable to stay still | | | | | | |
| Piano playing finger movements | | | | | | |
| Simple motor tics or vocal tics (grunting, squeaking, etc) | | | | | | |
| Complex motor or vocal tics including; spitting, obscene words or actions, repeating words or actions changes in rate or pitch of speech | | | | | | |

| 7.A. Urinary symptoms | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Urinary frequency or increased urge to urinate; daytime or night; inability to urinate | | | | | | |

| 7.B. Sleep disturbance - Fatigue | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Sleep problems (lengthy bedtime rituals, insomnia, inability to sleep; hypersomnia, nightmares) | | | | | | |
| Extreme tiredness or fatigue | | | | | | |

| 7.C. Dilated pupils | 0 = Absent | 1 = Minimal | 2 = Mild | 3 = Moderate | 4 = Severe | 5 = Extreme |
|---|---|---|---|---|---|---|
| Dilated pupils –"terror stricken look" | | | | | | |

**Name:**

**Informant:**

**III. Impairment Rating**

**Use the "BOC" indicators if multiple time points are being scored (see p. 2).**

| **IMPAIRMENT** ***(past week)*** | | |
|---|---|---|
| **NONE** | **0** | |
| **MINIMAL** Symptoms associated with subtle difficulties in self-esteem, family life, social acceptance, or school or job functioning (infrequent upset or concern about tics *vis a vis* the future, periodic, slight increase in family tensions because of symptoms; friends or acquaintances may occasionally notice or comment about symptoms in an upsetting way). | **10** | |
| **MILD** Symptoms associated with minor difficulties in self-esteem, family life, social acceptance, or school functioning. | **20** | |
| **MODERATE** Symptoms associated with some clear problems in self-esteem family life, social acceptance, or school or job functioning (episodes of dysphoria, periodic distress and upheaval in the family, frequent teasing by peers or episodic social avoidance, periodic interference in school performance because of PANS symptoms. | **30** | |
| **SEVERE** Symptoms associated with major difficulties in self-esteem, family life, social acceptance, or school functioning. | **40** | |
| **EXTREME** Symptoms associated with extreme difficulties in self-esteem, family life, social acceptance, or school functioning (severe depression with suicidal ideation, disruption of the family (separation/divorce, residential placement), disruption of social ties - severely restricted life because of social stigma and social avoidance, removal from school). | **50** | |

## PANS Questionnaire

## Parent-Rated Symptom Severity

Subject Identifier: _____ Date: _____

INSTRUCTIONS:
This form is for you to rate your child's symptoms related to PANS at each study visit as part of the clinical trial. You will be able to review the previous visit to note if there have been any changes in any of the behaviors. The ratings are to show any worsening of the condition or improvement. The column for previous behavior would be checked if the child had this symptom prior to PANS. For example, if your child had attention issues before the diagnosis of PANS, please check the box for previous behavior and then rate the severity.

As well, we would like to capture your ratings of the initial on-set of the PANS symptoms. At the screening visit, please fill out one for the initial onset and one for how they are at the time of the visit. Please check the box if you feel that the symptoms at each visit are 'spiking' (exacerbation) or if the symptoms have reduced to be in more of a 'remission' phase (remission). Feel free to write any added comments or symptoms that are not in the form that you feel are important.

☐Screening ☐Infusion # _____ ☐ End of study

Parent-Rated Syndrome Status:

☐ Initial – historical ☐ Exacerbation ☐ Remission

| Does your child experience: | None | Mild | Moderate | Severe | Extreme | Previous behavior |
|---|---|---|---|---|---|---|
| 1. Separation anxiety | 0 | 1 | 2 | 3 | 4 | |
| 2. Irrational fears or worries | 0 | 1 | 2 | 3 | 4 | |
| 3. Specific phobias - _____ | 0 | 1 | 2 | 3 | 4 | |
| 4. Sleep disturbances | 0 | 1 | 2 | 3 | 4 | |
| 5. Difficulty falling asleep | 0 | 1 | 2 | 3 | 4 | |
| 6. Difficulty staying asleep | 0 | 1 | 2 | 3 | 4 | |
| 7. Waking too early | 0 | 1 | 2 | 3 | 4 | |
| 8. Bedtime fears | 0 | 1 | 2 | 3 | 4 | |
| 9. Nightmares | 0 | 1 | 2 | 3 | 4 | |

## PANS Questionnaire

### Parent-Rated Symptom Severity

Subject Identifier: _____ Date: _____

| Does your child experience: | None | Mild | Moderate | Severe | Extreme | Previous behavior |
|---|---|---|---|---|---|---|
| 10. Increase in frequency of urination | 0 | 1 | 2 | 3 | 4 | |
| 11. Urinary urgency | 0 | 1 | 2 | 3 | 4 | |
| 12. Enuresis - bed wetting | 0 | 1 | 2 | 3 | 4 | |
| 13. Sensory defensiveness | 0 | 1 | 2 | 3 | 4 | |
| 14. Sensitive to light | 0 | 1 | 2 | 3 | 4 | |
| 15. Sensitive to noises | 0 | 1 | 2 | 3 | 4 | |
| 16. Sensitive to smells | 0 | 1 | 2 | 3 | 4 | |
| 17. Sensitive to textures - touch | 0 | 1 | 2 | 3 | 4 | |
| 18. Sensitive to clothing | 0 | 1 | 2 | 3 | 4 | |
| 19. Need to touch (feel) specific items or textures | 0 | 1 | 2 | 3 | 4 | |
| 20. Change in food intake or eating behaviors | 0 | 1 | 2 | 3 | 4 | |
| 21.Anorexic behavior | 0 | 1 | 2 | 3 | 4 | |
| 22.Body-image distortion | 0 | 1 | 2 | 3 | 4 | |
| 23. Sensitive to food texture | 0 | 1 | 2 | 3 | 4 | |
| 24. Fear of choking | 0 | 1 | 2 | 3 | 4 | |
| 25. Fear of contamination | 0 | 1 | 2 | 3 | 4 | |
| 26. Irritability | 0 | 1 | 2 | 3 | 4 | |
| 27. Agitation | 0 | 1 | 2 | 3 | 4 | |
| 28. Depressive state | 0 | 1 | 2 | 3 | 4 | |
| 29. Oppositional behaviors | 0 | 1 | 2 | 3 | 4 | |
| 30. Defiant behavior | 0 | 1 | 2 | 3 | 4 | |
| 31.Aggressive behaviors | 0 | 1 | 2 | 3 | 4 | |
| 32.Fear of harming others | 0 | 1 | 2 | 3 | 4 | |
| 33. Fear of harm to self | 0 | 1 | 2 | 3 | 4 | |
| 34. Self-injurious behaviors | 0 | 1 | 2 | 3 | 4 | |
| 35. Mood swings - emotional lability | 0 | 1 | 2 | 3 | 4 | |
| 36. Obsessive compulsive behaviors (OCD) | 0 | 1 | 2 | 3 | 4 | |
| 37. OCD behaviors at home | 0 | 1 | 2 | 3 | 4 | |
| 38. OCD behaviors in school | 0 | 1 | 2 | 3 | 4 | |
| 39. OCD behaviors with peers | 0 | 1 | 2 | 3 | 4 | |
| 40. Excessive ritualized hand-washing | 0 | 1 | 2 | 3 | 4 | |

## PANS Questionnaire

### Parent-Rated Symptom Severity

Subject Identifier: _____ Date: _____

| Does your child experience: | None | Mild | Moderate | Severe | Extreme | Previous behavior |
|---|---|---|---|---|---|---|
| 41. Excessive cleaning | 0 | 1 | 2 | 3 | 4 | |
| 42. Excessive concern with illness or disease | 0 | 1 | 2 | 3 | 4 | |
| 43. Repeated rituals | 0 | 1 | 2 | 3 | 4 | |
| 44. Checking compulsion | 0 | 1 | 2 | 3 | 4 | |
| 45. Inattention | 0 | 1 | 2 | 3 | 4 | |
| 46. Hyperactivity | 0 | 1 | 2 | 3 | 4 | |
| 47. Impulsivity | 0 | 1 | 2 | 3 | 4 | |
| 48. Motor tics | 0 | 1 | 2 | 3 | 4 | |
| 49. Abnormal hand or finger movements | 0 | 1 | 2 | 3 | 4 | |
| 50. Increase in clumsiness | 0 | 1 | 2 | 3 | 4 | |
| 51. Change in gait | 0 | 1 | 2 | 3 | 4 | |
| 52. Behavioral regression | 0 | 1 | 2 | 3 | 4 | |
| 53. Language regression | 0 | 1 | 2 | 3 | 4 | |
| 54. Decline in handwriting | 0 | 1 | 2 | 3 | 4 | |
| 55. Decline in school performance | 0 | 1 | 2 | 3 | 4 | |
| 56. Loss of math skills | 0 | 1 | 2 | 3 | 4 | |
| 57. Decline in artistic skills | 0 | 1 | 2 | 3 | 4 | |
| 58. Decline in school attendance | 0 | 1 | 2 | 3 | 4 | |

**COMMENTS:**

_____

_____

_____

_____

_____

_____

_____

_____