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**NPC Research Updates
Conference Call/Webinar
Monday, May 2, 2011**

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Mom of Ty, age 14 (NPC)

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Please Note: The following is not a word-for-word transcript of the conference call, but represents our best attempt to accurately convey the information given by the presenters. This document has been reviewed by the speakers for corrections and accuracy of information. Please refer any questions to the NNPfD Central Office and we will work to obtain the answer. E-mail: nnpdf@nnpdf.org or call: 920-563-0930.

Karen Quandt, Chair of the NNPfD, welcomed everyone to the conference call and thanked the presenters for being willing to share their time and expertise. She introduced the presenters named above.

Dr. Dan Ory – The past several years have seen a number of significant advances in basic science related to NPC disease, laying the foundation for more recent highly collaborative efforts to translate these basic science discoveries into tangible advances in patient care. The goal of this call is to update the NPC community on the progress of these collaborative translational efforts, and specifically on the opportunity to develop a clinical trial for NPC patients.

Topics will include:

- 1) NPC observational study run by Dr. Porter at NIH
- 2) Development of NPC biomarkers
- 3) NIH's NAC biomarker trial
- 4) Advances in NPC diagnosis that relate to biomarkers
- 5) TRND/NIH-sponsored efforts to develop plans for a cyclodextrin trial at NIH

Dr. Denny Porter

- 1) Observational study – started in 2006 – initial purpose was to lay groundwork for a subsequent clinical trial. When the study was started, allopregnanolone was a potential candidate; then the miglustat trial was in the process of being completed, but it was recognized that there was difficulty with identifying reliable outcome measures – a problem that is inherent to NPC due to the variability and the rarity of the disease.

The purpose of the study was to identify clinical and biochemical markers that could be used as outcome measures in a therapeutic trial. First, we wanted to quantify disease progression, we wanted to correlate potential biomarkers with disease status, and then provide a long-term symptom-based outcome measure that could be used to evaluate therapeutic efficacy. We were focused both on biomarkers as tools to try to get relatively quick insight into a therapeutic trial, but also with the recognition that in addition to biomarkers, you need to impact symptoms of the disease. The second goal of the observational study was to try to identify a biochemical marker that could be used for testing or screening. The reason for that, as many of the parents are aware, was the long “diagnostic delay”-- the time between first symptoms and the time at which diagnosis is actually made – which, in our group of patients, is on the order of four to five years. By identifying a simpler test we hope to impact that diagnostic delay. The study was started in 2006 and this past week we enrolled our 56th patient, so for NPC it is a very good-sized cohort of patients.

In addition to following the natural history of the disease, we've also used this study as an opportunity to collect biospecimens. As the parents who are participating know, we collect blood, we collect urine, we establish fibroblast lines on each patient, and we also collect cerebral spinal fluid. Those specimens have been archived and are being studied in multiple laboratories, not only my lab and Dr. Ory's, but in the labs of Drs. Platt, Ioannou, Blennow, Bush, Manner, Maxfield and Lieberman.

One of the goals in establishing this bio-repository was to have a large number of samples that we could arrange to share with outside laboratories who had a good idea, and send it out and in a reasonable length of time get an idea of the behavior of that biomarker in a cross sectional group of NPC patients. With time we are also building a repository of biospecimens collected longitudinally. We have now followed some patients over five years. Because of the variability of NPC, knowing the time course in individual patients, will be the next step with regard to biomarkers, and will be invaluable data in terms of setting up future clinical trials. That really has been the purpose and, to date, the major emphasis of the observational study.

Dr. Dan Ory – As Denny just outlined very nicely, there was a recognition several years ago that NPC biomarkers were needed for several reasons. First, to improve diagnosis of the disease, as almost all participants are aware, the diagnostic delay in NPC is greater than four years, so we are not catching the disease at an early-enough stage.

There was also a need to be able to provide new measures of disease progression, which could be very helpful in terms of clinically treating the disease, but also having such markers would assist us in the development of new therapeutics. Such biomarkers could be used, for instance, as surrogate endpoints which could help us be able to assess therapies in a reasonable amount of time.

The most well-studied of the biomarkers which has emerged from these discovery efforts are the oxysterols, which are the oxidized forms of cholesterol and are studied in Denny's lab and in my lab. As many of you are aware, results of these studies were published last November in *Science Translational Medicine* and more recently online in the *Journal of Lipid Research*. What these studies describe are the oxysterols, which are specifically elevated in the blood of NPC1 patients – we showed that these oxysterols can be used to diagnose NPC1 disease with a greater than 97% sensitivity and 100% specificity – this is far greater than can be achieved with current diagnostic standards -- either filipin staining or even genetic testing. The information provided here is also useful with respect to disease severity, and there's also evidence that the oxysterols might be useful in monitoring response to treatment. We published some data which showed that the oxysterols did modulate in an NPC1 disease model in collaboration with Charles Vite at University of Pennsylvania.

A clinical laboratory test has been developed for the oxysterols and is now being implemented at St. Louis Children's Hospital. We think it is likely that this test, or this marker, will become the new diagnostic standard for NPC1 disease. In addition to oxysterols there have been a number of other efforts to develop biomarkers. Dr. Fran Platt, a member of the NNPfD SAB, has been working on a lysotracker assay in her laboratory and this method involves measurement of lysosomal size, so it's essentially a morphometric assay. Preliminary studies in her laboratory would indicate that it provides some degree of discrimination between NPC1 subjects and controls, particularly in juvenile age groups. There's also been a major effort in terms of using cerebrospinal fluid to develop protein biomarkers. This is work that is currently going on in Denny Porter's laboratory, and also in collaboration with Kaj Blennow in Sweden, whose lab is studying α -beta proteins which are involved in formation of protein aggregates in the brain.

We also are exploring the possibility of using circulating plasma lipids as markers for NPC disease. Similar to what we have done with the oxysterols, we're using mass spectrometry-based approaches to

identify circulating lipid biomarkers in NPC. The focus of these efforts is on complex lipids that are known to accumulate in the tissues of NPC subjects. This represents a collaborative effort between my lab, Denny's lab, and the Porter, Platt and Walkley labs.

Dr. Denny Porter – So I'll pick up with the status of the NAC trials. First of all, the preclinical work is being done in Dr. Ory's lab with the NPC genetic mouse models, in collaboration with Dr. Pavan and my group at the NIH with a new mouse model that's purely liver-based. This work has shown efficacy of NAC, specifically in the genetic mouse model (originally developed by Dr. Laura Liscum's group), in providing functional benefits, and in both the genetic mouse model and what we call the ASO mouse model, in providing reduction of markers of the oxidative stress, including the oxysterols. The NAC trial at the NIH was designed to test the ability of NAC, which is a known antioxidant, to reduce the oxysterol biomarkers. Another purpose of that trial was really to establish the feasibility of doing a relatively rapid trial at the NIH. Did we have the capacity? Were we going to be able to get the recruitment of patients?

We were able to enroll 35 subjects and began the trial in Sept 2009 and completed it in Aug 2010, just under one year. We are still analyzing patient samples, and analyzing the data that we have. We can only start to draw preliminary conclusions. At this point in time, we cannot recommend NAC therapy to patients with NPC, and there actually may be a subgroup of patients in which NAC may cause problems. We're dealing with very small numbers but we're concerned about a subgroup of patients who has a higher than expected degree of liver problems to begin with. Many of our patients have a slight elevation in liver enzymes, one of the blood tests that we checked frequently in the study. This test remained stable for most patients in the study, but there are a few who have a history of significant elevation in these blood tests, and these appear to get worse on the NAC. We understand that everybody would like to have this answer and we're working hard to try to get it, but currently we don't have a definitive answer for the NAC trial. What's clear is that it works in the mice, but as we all know, there are compounds that work in the mice, but in trying to translate them to the kids and young adults, we're dealing with another level of variability. And so what we're trying to do with the NAC trial is to tease out as much information as possible, to figure out if this is worth pursuing in the future.

Dr. Dan Ory -- I'll continue with the work that NIH has been doing along with TRND to help develop plans for a cyclodextrin trial at the NIH, which I know is something many of you want to hear about. A little bit of background -- TRND's involvement goes back to late 2007, when there was a meeting at the NIH between the NPC SOAR group and also the investigators at Chris Austin's facility, the NIH Center for Chemical Genomics. At that time a plan was made to screen patient cells using the NIH Pharmaceutical Collection for Approved Drugs --about 2800 compounds-- and to look for drugs that would decrease lysosomal cholesterol storage. Funding for this project was provided by the Parseghian Foundation. The project led to identification of two compounds that were effective in reducing cholesterol storage. In a collaborative effort involving the Ory, Walkley, Porter and Pavan labs, in vivo testing was begun and is still in progress in terms of evaluating the efficacy of these compounds in the animal model.

In late 2009, TRND selected NPC as one of their pilot projects. Chris Austin can certainly comment on this, but I think the attractiveness of NPC was that we really have superb science in the field, there's

great expertise both in the extramural and intramural communities, and this was also an opportunity for NIH/TRND to consider piloting a repurposing project -- basically taking compounds that would already be approved for human use and redirecting them for use in NPC disease.

I think a very important aspect of the decision to choose NPC as a pilot project was that this community has a very active involvement of patient-driven disease foundations, which is evident by the call today.

In 2010 as a result of a TRND review examining the status of the compounds that emerged from the cell-based assay, and also on the basis of an NIH bench-to-bedside proposal that was submitted by myself, and Denny Porter and Steve Walkley, a decision was made to adopt cyclodextrin as the object of the TRND pilot project. Together with TRND, we've worked to develop a comprehensive program to produce data that would be needed to: 1) be able to see whether or not intravenous cyclodextrin could ameliorate the symptoms and biomarkers of NPC patients; 2) to determine what dose is required and what dose could be maximally tolerated in humans; 3) to determine what pharmacodynamic biomarkers of response could be followed as an indication of response, and this is very important, because in order to determine whether or not the cyclodextrin that's going to be delivered is going to be effective, you need to have some sort of acute measure of the response; and finally, it was important to determine whether cyclodextrin would be safe and effective for treatment of NPC patients as required by the FDA. Of course, the ultimate goal is to be able to obtain approval by the FDA, if indeed, it is safe and effective.

So this project is now ongoing. It's a collaboration that involves, principally, TRND, in fact it is really run through TRND. It involves the Porter laboratory at NIH, my laboratory at Washington University, Steve Walkley's at Albert Einstein, and Bill Pavan's at NHGRI. For this project we set a very ambitious timetable to obtain the necessary preclinical data, and when I say preclinical, I mean essentially in vivo mouse models. We would like to obtain that data within a 12-month period. Concurrent with this preclinical work, the TRND team is now working with regulatory consultants to determine what will be required to file an IND for testing cyclodextrin in a Phase 1/Phase 2 trial at the NIH to be lead by Dr. Porter.

Assuming the cyclodextrin can pass the required benchmarks in preclinical testings, and I point out that that is not at all a certainty, TRND would be ready from a regulatory standpoint to rapidly move the cyclodextrin to a clinical trial. I'll let Denny comment on this, but I think our goal would be to initiate a trial sometime during 2012.

Dr. Denny Porter – My goal, I think the goal of my team here, as well as of all the collaborators, is to set as a challenge initiating the trial within a year, or in 2012. It was interesting because everybody probably saw the AP report, and the reporter had called me and was really pressing me for an answer to that question. It's a hard one -- it's one that we can set goals for, but it's difficult to be certain on the predictions, and some of the difficulty comes in with aspects that we don't control – specifically, getting IRB approval. I've seen protocols hang up in IRBs for months. I think I know my IRB here well, and I think I can anticipate it well, but at the same time, someone may have a question that needs to be answered before we can move forward. The second unknown is the fact that we will have to apply for an IND, or investigational new drug application with the FDA. That definitely is a period of time we cannot accurately predict. They have 30 days to come back to you with a list of what they

want you to do, but that list could be fairly straightforward to deal with, or that list could be fairly complicated.

It was interesting -- I had the same conversation with the reporter, and she kept pressing, "Can you give a time?" and I finally said to her, "This is our goal, and I don't mind talking about a goal, but I want to be realistic with people, and don't want to put false expectations out there. It would be easy for me to set a goal and say we're going to make it, but I think that can be very disappointing to families and patients when they see you not making that goal." My goal is to get it going in 2012, and that's what we're working for, but you have to understand that there are variables there that we will have to deal with as they come up – the variables of the IRB, the variables of the FDA, and as Dan alluded to, we are still doing preclinical work, and there are milestones there, and based on those results, we may have to change what exactly we are going to do. So we have the general outline, and we have a plan, and we have a goal. But I want you to understand that it is a goal – we're committed to trying to get it done in that time, but I think it's important for families to understand that it may take longer.

Dr. Dan Ory – So I think at this point, this represents the initial remarks that Denny and I wanted to make, and I will turn this back over to Nadine and Karen in order to be able to take questions and comments from the participants, which the panel would be very happy to answer.

Nadine Hill – thanked Dr. Ory and Dr. Porter and explained to participants how to enter questions via the Webinar feature. There were also questions submitted prior to the conference call, which were addressed first.

Dr. Denny Porter – First submitted question: "Would cyclodextrin have FDA approval and become available if results of the trial were positive, or would it be something still out of reach as a real treatment for NPC, especially considering the treatment barriers across the blood-brain barrier."

The goal of my group, the TRND group, and all the collaborating laboratories is to do this in a very systematic and scientifically rigorous manner. We want to move this forward so if results were positive they could be used in a new drug application. Because the worst thing would be ending up with a drug that we showed would be effective and patients not be able to get it, or it would be beyond their means to get it. As I think we're all learning with miglustat, if you don't have FDA approval, a lot of insurance companies don't want to cover this drug.

The second question by the same person was: "Has the histone deacetylase inhibitor been tried on neuronal cells outcomes? I believe they cross the blood-brain barrier because they are used in seizure and schizophrenia – was it effective once they cross the blood-brain barrier?"

I [Dr. Porter] actually don't know of them being used on neuronal NPC cells. The source of neuronal cells would be a little bit difficult because the current mouse model is probably not good to be used for testing the histone deacetylase inhibitors based on what their mechanism of action is thought to be. And to get human iPS cells that have residual function of the NPC1 gene, I think multiple labs are working on getting what are called induced pluripotent stem cells. That's very feasible and they exist.

The next step will be can you efficiently differentiate them to specific neuronal cells and get enough of them that you can study?

And then the effective one – they've had multiple effective ones – I know at least one of them does cross the blood-brain barrier that's been used in children, so there is potential here. Again, the histone deacetylases have been shown to be effective in cell culture. They need to be studied further.

One aspect of the natural history study, or the observational trial, is we're making a collection of fibroblasts. Dr. Maxfield's lab is one of the laboratories we are sending fibroblasts to. We literally sent some last week, and have more to send this week. With different defined NPC1 mutations, and based on the type of mutations, you could propose that the histone deacetylases may or may not work in the specific cell lines, so it will be interesting to see what the results are across the panel of cells.

Work is ongoing to really look into whether histone deacetylases can be translated into a therapeutic trial, but again, we're early on in the process and groundwork needs to be done.

Dan, do you want to handle the third question from the first submitter?

Dr. Dan Ory – The first submitter has asked the question of whether we are getting a mouse model that resembles a common NPC1 mutation. The answer is that the field is working towards that. We have developed in our laboratory a mouse that has a knock-in of the NPC1 I1061T mutation, which is the most prevalent mutation in NPC. It affects somewhere between 18 and 20 percent of NPC1 patients. I'm sure if Marie [Dr. Marie Vanier] is listening she would be able to give me the right number.

The NPC I1061T mouse has been generated and it's been put through some preliminary tests in collaboration with Marie Vanier. She has shown that it accumulates the complex sphingolipids that we would anticipate, but it appears to have a less severe phenotype and it lives a bit longer than the NIH NPC1 mouse model.

We are working on getting the mouse back-crossed into a con-genic background, which is required to use this mouse in studies, such as drug studies. I'm hoping that over the next 9-12 months we'll be able to get the mice fully tested and be able to know what their capabilities will be.

There are other point mutation models that exist. There is a point mutation that is available from Jackson Labs. It involves the P1005 residue. That's close to the P1007 residue in the human common mutation. This mouse has been used as a point mutation model to look at the effects of drugs which would require residual NPC1 function. I know that model is being used extensively in Yiannis Ioannou's lab. I also believe there have been some other targeted mutations made. I believe that Brown and Goldstein's lab is going to report on targeted mutations in the NPC1 N-terminal domain that will have cholesterol-binding defects but this is a targeted mutation for experimental purposes and it isn't trying to mimic a specific human mutation.

Dr. Denny Porter – There was a second question submitted – The first part of it gets at the question of a multi-center trial and would this be faster, and specifically is it feasible or practical to do this in the UK and European countries?

The answer is that ultimately, we are going to have to build multi-center trials. This is probably the only feasible way to deal with a patient population that spreads not only across the United States, but across the Atlantic Ocean and in multiple countries – South America, Europe, potentially even Asia, too. With a rare disease, that's going to be essential to build numbers. The question is -- Is it faster at the initial stages?

I have a unique situation here at the NIH in that your tax dollars have already paid for me to set up trials and allow me to bring in patients. So for the initial trials, when I'm thinking what we need to focus on is pharmacokinetics and getting an idea of how do we dose cyclodextrin, in a relatively small number of patients, to figure out where we are, it's probably easier for us to do it here. Each time we involve another institution, we involve another IRB. And each time we involve another country, we involve another FDA-equivalent. So initially, I envision us doing it here. Could other individuals participate? Yes. Obviously, that will come down to the detailed designs of what it will take to participate. The one caveat is that I can only cover travel within the United States itself. I want to get back to, to begin with, it may be easier and faster to initiate it here, but ultimately, it needs to move to a multi-center structure.

In the U.S. a couple of consortiums formed through the Office of Rare Diseases. One includes a number of investigators interested in sterol disorders and I am part of that consortium. The other disease I study is a major part of that consortium, but NPC could fall under it, too. There is also a consortium focused on Lysosomal Storage Disorders. Either would provide an umbrella, and an umbrella that actually has some funding attached to it. That's the other issue when you involve another institution, is that we'd have to figure out how to get funding.

One thing impressive about the NPC community is that you have strong parental-run organizations in multiple countries, and when we get there, that's a resource and an asset that can't be underestimated in terms of trying to arrange for multi-center trials.

There's a question on safety and side effects and concerns remain concerning pulmonary toxicity. The general answer is that anytime I'm thinking about a clinical trial, it is both from the perspective of safety and efficacy. How do we set it up so it is as safe as possible, but also how do we set it up so that if there are untoward effects we catch them early?

I'll use the NAC trial as an example. I would have never, and this is a preliminary result because of small numbers, I would have never predicted that there was going to be a subset of patients that it looks like when you give them NAC, their liver enzymes would actually go up. But that's part of designing a trial, and just as important in my mind as proving efficacy. You want to know that you can do it safely.

There's a question here about intention to begin with IV administration or intrathecal administration into the CSF. Again, coming at it from a safety standpoint, what we want to do is to systematically

study IV administration. Peripheral administration, in both the cat model and the mouse model, has shown some efficacy. I think the first step is to try to show that we can replicate that in patients. I think it's a huge jump in risk-benefit ratio to start to think about intrathecal. Could we get there eventually? Yes, but I think it's important right now to focus on the IV administration which is not without risk itself, and sort out, can we make it effective and to what degree can we make the IV administration effective. Once we start to answer those questions, we can start to say do we need more?

And then there's a question on trial criteria – specifically ages and exclusion criteria. This is starting to get into details about what the trial design would be. IRBs would get very upset if you started recruiting patients before they've approved it. So to try to give you a list of my exclusion criteria at this time would not be appropriate. I would give you certain guidelines: I'm a pediatrician – it would be very unlikely for me to design a trial that doesn't include children.

NPC is a rare disease that's variable – to get numbers, we will have to be very broad in terms of patients that we would be willing to accept. At the same time, young infants present their own issues in terms of how much blood you can collect safely and what you can do. You have to achieve a balance and really, when we get down to exclusion criteria, they're based on safety. What group do we think we can start out with that provides us with the best margin of safety?

I think that's the end of the questions that were initially submitted.

Nadine Hill unmuted the phone lines so participants could ask questions.

Question for Dr. Ory regarding an undiagnosed patient -- Is the new blood test definitive when it is performed, regardless of the type of NPC (adult onset)?

Dr. Dan Ory -- The test has been tested on approximately 110 – 120 NPC patients, so far. The subjects have ranged from very young – the earliest is about 6 months -- to the oldest, probably over 50 years old. There does not appear to be a limitation in terms of the age-- that is, that it can equally detect juvenile onset and adult onset.

The one caveat here with the test is that it's not perfect. It detected over 97 percent of the cases but there are a few cases that it does not detect. So far the types of cases that we would not be able to detect would be the ones where you would have very, very mild or borderline symptoms, or perhaps even be asymptomatic. But I think in aggregate, the test is very good, and certainly better than any of the other modalities that we have. I think that it would make sense to use it as a first line and then if there still is a very strong clinical index of suspicion, and the test still is not registering positive, it makes perfect sense to go on to the next stage, which I think should be genetic testing. But this is going to take some time for us to figure out what exactly is the best algorithm and how to use this. I would certainly welcome comments from Marc Patterson in terms of how he might envision using the assay.

Dr. Marc Patterson—I would agree with Dan – there's no perfect test although the oxysterols are very promising so far. It would seem from the data Dan has described that a negative test would mean

that the likelihood that the diagnosis is being missed is just a couple of percent. The fact is, in difficult cases, which we've dealt with for a long time, I would never suggest relying on one modality, but would use all the diagnostic tools at our disposal.

If you had a negative oxysterol test, a negative filipin test, and if you had negative ultrastructural analysis, in other words, electron microscopy done in a laboratory where people know how to make the diagnosis, and the mutation analysis is negative, then the best that we can say in 2011, is that you don't have NPC. If you have just one of those positive, then you probably have the diagnosis, but there is still a certain degree of uncertainty.

There is no perfect test, and I would caution anyone against relying on one test – you have to look at the complete clinical picture. And I say that, because, in the data Dan and Denny have presented, if you looked at the individual sterols (7-keto sterol and the 'triol'), not the combination where they plotted one level against the other, you had some odd outliers. You always have to take the whole picture into account and I'm very reluctant ever to just rely on a single test. Having said that, the oxysterol test is the most important diagnostic development in many years, and I'm very excited about it.

Dr. Denny Porter – I would put one caveat here – currently the oxysterols are being done as a research test. Until Children's Hospital picks it up, they should not be used for medical decision making. And that's because, until Children's Hospital picks it up as an actual clinical test, Dan's standards won't change at all, but it's not recognized as what's called CLIA-approved. Always keep in mind that when we develop these things in research laboratories, they're not supposed to be used in medical decision making until they're done in a CLIA-approved laboratory.

Participant #1 (speaking of their particular family's case) – We are in that big diagnostic quagmire [without a diagnosis], where the geneticist found faint filipin staining but no mutated NPC1 or NPC2, and yet, the medical doctor insists that it is NPC, that she has all the hallmarks of it. That is why we were so excited to find the press releases on the Internet, not only about the blood tests, about the breakthrough. I realize and understand that the medical requirements not use this as a diagnostic tool but as all of you know, whatever it is she has, is a progressive disorder. Anything we can have that will either say yay or nay, will allow us the opportunity to move forward with the possible treatment and drug therapies which our government in Canada will deny until someone can fill in a diagnosis on the forms.

Dr. Denny Porter – I don't know the Canadian system, but on one level, physicians can make a clinical diagnosis, and Marc can probably back this up, but laboratory testing often is done to confirm and validate that clinical diagnosis.

Dr. Marc Patterson – I would agree. The situation where you have a patient who has what is called variant filipin staining in whom no mutation is identified is uncommon, but not unheard of. It is helpful if you can get ultrastructural proof from electron microscopy of a tissue biopsy.

Dr. Denny Porter – We're happy to help you with this. We actually have a mechanism through which we can get you in here.

Participant #2 – Dr. Porter, if you move forward with a trial of cyclodextrin, how do you think that will affect future trials of, for example, HDAC inhibitors, given that there is such a limited population?

Dr. Denny Porter – I think this is where the biomarkers provide a tool. We're using them as a tool, and say we design this out. What we want to do is say, ok, we have a candidate – if we try this candidate in a short-term trial focused on biomarkers, and we get an answer to say this looks promising and we should move forward and focus on a clinical trial focused on symptoms, which will take time and we don't have the capability to interweave. But at this point in time, I think biomarkers provide a tool that we'll be able to look to try to decide which one is promising to move forward with.

Participant – Basically what I'm hearing is there's no way to effectively conduct two trials at the same time [due to limited number of patients].

Dr. Denny Porter – I don't think we can do two trials focused on symptoms as the outcome measure at the same time. I wouldn't exclude being able to do two biomarker trials at the same time.

Karen Quandt – Question for Dr. Austin and Dr. Patterson – Dr. Austin -- Do you have anything to add from TRND's point of view regarding the cyclodextrin trial?

Dr. Chris Austin – No, the description has been excellent and I think it reflects how closely the team is working together, because of the description of what we're doing and the timeline.

Dr. Patterson – I'm not involved in the study, so I'm just giving a bystander's comment. I think it sounds very good. I think the circumstances are such that some of the pressures and difficulties we had in designing the miglustat trial over a decade ago will be avoided. The problems included having three different sponsors in the course of the study, dealing with regulators in different countries, and a lack of prospective clinical data. In addition, we knew that in designing the miglustat trial that the drug would very likely be approved for a different indication, and become accessible to potential participants. I think cyclodextrin is in a very different situation. We know a lot more about the disease and we have the potential for biomarkers.

Of course, the wild card in all this is what the FDA will and won't accept in the design of a proposed clinical trial. I am involved in a study of a novel therapy for another LSD, which has had the best scientific preparation seen. The clinical trial proposal was just taken to the European authorities who approved going ahead with the trial without any question, and the FDA completely rejected it. So I just think it's important that those who are not involved in this understand that the FDA is unpredictable. You cannot assume that, however carefully you prepare, they will approve what you want to do.

Nadine Hill – Thanked everyone for their participation and invited participants to submit any further questions to the NNPDF. Answers will be sought and posted to the NNPDF Web site – www.nnpdf.org . The recording of this meeting will also be available on the Web site.

Karen Quandt – Thanked the presenters and the participants and closed the meeting.

The following information was not part of the conference call, but the panelists felt it might be helpful, so we are adding it here:

1. Early diagnosis: If oxysterols are included in newborn screening, then the prospect of pre-symptomatic diagnosis and really effective intervention would be opened up. Of course, there are many technical, financial, governmental and ethical challenges in having such screening implemented. If it is part of a metabolic screen, then cases might be picked up earlier by clinicians who would not normally think of the disease, potentially curtailing the usual neurodegenerative disease diagnostic odyssey. If it is just another diagnostic test available through one lab, it might accelerate diagnosis by a few months, because only physicians aware of NPC will order it.
2. Who would supply the cyclodextrin for a trial? There are obvious advantages to studying a drug that is approved for another indication, but the owners of such a drug are not always enthusiastic about having the adverse effects likely to crop up in a clinical trial of a neurodegenerative disease ending up on the package insert for their product.

Answer from Dr. Porter: We will purchase the CD directly and formulate it through NIH Pharmacy Development Service. In comparison to other drugs, it is not that expensive. Eventually any GMP facility should be able to pick it up as a product.