



**Global NPC Community Questions submitted to Mallinckrodt Tues. Nov. 13th, 2018
VTS-270 2b/3 Clinical Trial (VTS301)**

Communication

1. Why weren't the Primary Investigators (PIs) in each country notified of the release beforehand?

As a publicly traded company, there are certain US Government rules governing the timing and extent to which data can be shared with individuals and groups. These rules prevented us from notifying PIs (or anyone) in advance of the public release of this information. We did, however, inform the co-principal investigators for the study prior to the investor call to help us understand the data. The two principal investigators are under a confidentiality agreement and are required to maintain the same standards as Mallinckrodt with regard to release of data. Additionally, we informed the principal investigators and advocacy groups via phone calls and email within one hour of the earnings call and teleconferences were set up for the next day.

2. Why didn't MNK reach out to patients and families to announce their findings immediately afterwards?

There are regulations that prevent us from knowing who the patients are in the trial and communicating with them directly. At the time that we released our top-line findings, we simultaneously reached out to the US and international NPC advocacy groups to share this information. We also communicated with the principal investigators at each site. We did that because they are the advocates for the patients and families and we knew that they would rapidly disseminate the information to the broader NPC community. Since then, we have been in regular communication with the principal investigators and the advocacy community including NNPfD, NPUK, INPDA and others.

3. How does MNK intend to share information going forward, with families, PI's involved with the trial and the broader community?

Our entire team at Mallinckrodt is committed to keeping the lines of communication open. As we continue our work and learn more, we commit to getting the news to you as quickly and transparently, as possible. We are working with the co-principal investigators and many others to review and understand the data and commit to communicate new information through the clinical investigators and the advocacy community as quickly as possible.

4. How will MNK reassure parents and patients that they are committed to the trial and to communicating effectively with the community?

We understand the outcome of this trial can have lasting implications on the lives of patients and their families. As a company focused on our mission of improving lives, we recognize the importance of pursuing this potential treatment for Niemann-Pick Type C, and we thank the families and patients involved in the clinical trials.

Patients, their families, and our patient group partners, should know that all of us at Mallinckrodt remain deeply committed to you and this critical work. We commit to keeping you updated to the fullest extent possible by law. We remain united in our work to pursue potential treatments for severe and critical diseases for underserved patients such as NPC.

Trial Data (VTS-270-301)

5. When will a deeper analysis of the data be completed?

The deeper analysis of this study is well underway. We believe that information beyond the first 52 weeks of treatment will be very helpful. This means that we need to go through the process of getting this data to our statistical team to be able to generate the results from this new data cut. These processes take time and rely on many different groups to handle specific tasks. It will take us several months to gather and analyze this next set of data and will be working with the principle investigators to understand it.

6. Was data collected from every country involved in the trial, for different age groups e.g. paediatric /adult onset of disease and will you include data from those in the sham group (even those who progressed and received treatment early)?

All data from every patient at every site was included in the initial analysis; we are looking at all aspects of the data.

7. Who will evaluate the data?

The data will be reviewed internally, as well as by the co-principal investigators and other external experts.

8. The information shared so far is a statement about the primary endpoint. When will you share the data on the primary endpoint?

The co-PI's and other experts are aware of the data since they are working with us to understand it. At this time we are unsure when we will release the actual data. We are working on a plan to do this.

9. When will you share data on secondary endpoints and other outcome measures / biomarker measurements?

The co-principal investigators and other experts are aware of the secondary endpoints and other outcome measures since they are working with us to understand it. At this time we are unsure when we will release the actual data. We are working on a plan to do this.

Blood and cerebrospinal fluid (or CSF) samples were obtained during the study. At present, there is no known biomarker that is correlated with efficacy or safety. Because the results of the study are inconclusive we have elected to not analyze the biomarkers right now as we only have a small amount for each patient. In discussions with external experts on this matter, it was agreed that it would be premature to analyze these samples. Because of the efficacy results, we do not have any way to make a correlation between some trend that is seen in the biomarker samples and the results of the study.

10. Will you provide a breakdown of differences across the domains of the severity score, any subgroup (based on baseline disease severity) analysis trends - even if not of statistical significance? Are there outlier patients in the placebo group that could be impacting the top line data?

Understanding the individual domains of the NPC-SS scale is important as well as subgroup analyses. This work is underway. The co-PI's and other experts are aware of the data since they are working with us to understand it. We are working on a plan to share the results.

11. What is taken into consideration when evaluating data - only the severity scores or also the "subjective perceptions" of families, especially families of patients on expanded access?

Assessment of how the patient did in the study was done by the family, and in the case of older patients enrolled in the study the patient themselves. This is definitely an important component of our evaluation.

Not only is it important in Study VTS-270-301, it is important in evaluating every patient that is receiving VTS-270, including expanded access protocols or compassionate use programs.

12. If children receiving treatment did not show disease progression, isn't that evidence enough that the treatments helped?

It is true that on average, neither the placebo group, nor the VTS-270 treated group, showed significant disease progression. However, in order for the lack of disease progression in the treatment arm to have meaning, we would need to see significant disease progression in the sham (placebo) arm. This difference between the two arms would support the treatment effect for VTS-270. Unfortunately this difference did not occur. A deeper analysis of this study is important to try to understand this result. We believe that information beyond the first 52 weeks of treatment will be very helpful, as well as information for other clinical studies and the compassionate use programs

13. How will data from the unblinded trial be used?

Mallinckrodt understands that NPC is a devastating disease and that finding a treatment that can benefit patients is important. Our goal is to review all of the data, including this trial, with the global regulatory agencies to understand how to best proceed. The data from Study VTS301 is an important component of any discussion with regulatory agencies.

14. Why has it taken so long for MNK to release the top line data results since the end of the trial?

The last patient completed Part B, the blinded portion of Study VTS301, in March 2018. At that time, Mallinckrodt was still discussing the analysis plan with the FDA, a dialogue that continued into late August. After an agreement on the analysis plan with FDA and prior to unblinding the study, the analysis plan and the protocol itself needed to be amended and submitted to regulatory agencies globally. After the data was unblinded, the statistical team needed time to run the required analyses and fix any glitches prior to sending the data to the clinical team to review and interpret. As we have said, the results were surprising. Because of this, we sought input from some external experts. All of this work took time.

15. Will families be able to access their own data? If so, when, and how will they do this?

We understand the value to families around this data and this is currently under consideration taking into account applicable laws and regulations.

16. Is compassionate use patient data being used in evidence to the FDA? Is the FDA indicating they are willing to look at it as a persuasive factor?

The totality of the data, including compassionate use data, will be important in a discussion with FDA. At a meeting in August the FDA indicated to us that their view on the potential approvability for VTS-270 will be based on the totality of data, not a single study or endpoint.

17. How many patients were on Miglustat in the active and placebo cohort? Can the results provide some information on the efficiency of the combination VTS-270 / Miglustat in humans, on VTS-270 alone and on Miglustat alone?

The overall number of patients in the study is very small (56). While looking at subgroups can provide some information, the applicability of that information beyond the context of the study is not always possible.

Trial Design (VTS-270-301)

18. How is it possible to evaluate the natural history in such a small group of patients evaluated in such a short period of time especially with regard to the different phenotypes and the presumably slowed degeneration due to Miglustat?

We are assessing the data to try to better understand the results.

19. Will the trial design be changed?

The double-blind portion of the study has been completed; this part cannot be changed. At present, there are no planned changes for the patients in Part C.

20. Would you consider lowering the dose for younger patients? Almost all compassionate use children are on lower doses - will you consider changing your protocol?

We understand that a different dosing regimen is used in the compassionate use programs - this is at the physician's discretion. We cannot change the dosing for this study now as all patients still in the study are already receiving VTS-270.

21. How will you tell if the drug is working and shows impact?

We planned on showing a difference in disease progression between the group of patients treated with VTS-270 and the group of patients receiving sham treatment using two tools. These two tools are the Niemann-Pick Type C Severity Scale (NPC-SS) and the Clinician Clinical Global Impression of Change (or Clinician CGIC). The NPC-SS is a scale developed specifically to look at the neurologic symptoms of NPC; while it is a newer scale, it was used in the open-label study with VTS-270. The CGIC scale is used in other progressive neurologic diseases such as spinal muscular atrophy and Alzheimer's disease.

As you know, these scales did not show any difference between the two groups of patients, and more importantly they did not show either treatment group getting worse. This is unexpected and we need to try to understand why this happened. We are working with external experts to help us. We also need to talk to global regulatory agencies, including the FDA and EMA, about what would provide convincing evidence that the drug is working.

22. Are all patients enrolled in the trial now receiving drug?

All patients enrolled in the study who continued in Part C are able to continue on VTS-270.

Future of the VTS-270-301

23. Will the trial continue?

Yes, the study is continuing. All patients that are in the study are receiving VTS-270.

24. What will happen if the FDA/EMA does not approve treatments?

We are continuing our conversation with the various global regulatory agencies to understand the regulatory options for VTS-270 and the appropriate path forward.

25. What stage of the review process is the drug in with the FDA/EMA?

Our last discussion with FDA was prior to unblinding Part A/Part B of Study VTS301, in late August, 2018. Discussions with EMA were even earlier. Before we go again to FDA and EMA, we need to have a proposal for them to consider. The work that we are doing now to further investigate Study VTS301 as well as all of the other clinical data including the compassionate use programs gathered on the impact (good or bad) in patients receiving VTS-270 is a first step to having a proposal to review with FDA and EMA.

26. Is it possible the FDA/EMA may want to see the trial extended and, if so, is MNK willing to do so?

We are continuing our conversation with the various global regulatory entities to understand the regulatory options for VTS-270 and the appropriate path forward. Mallinckrodt believes that long-term data, from Study VTS301, the original clinical study with VTS-270 as well as the ongoing compassionate use programs, is important and may provide valuable information in helping us understand the study results.

27. How long can children in the trial stay on the treatment?

There are no plans to stop Study VTS301 or any of the ongoing sponsored clinical studies or expanded access programs. Mallinckrodt believes that data gathered from the patients who are continuing to receive treatment of VTS-270 in Study VTS301, as well as the compassionate use programs, is important and may provide valuable information in helping us understand the study results.

28. Will VTS-270 remain available for trial and iIND/compassionate use patients? Will new patients have the option of compassionate use?

Yes, the current trials and compassionate use programs will remain in place and new patients will be considered on a case by case basis.

29. If the trial continues, what will be the future frequency of treatment? Could MNK consider provision of local/home care to better support patients and treating physicians?

It's too soon to address this question.

30. Is MNK investigating use of a new port, and if so when might these be introduced?

Evaluation of an alternative way to administer VTS-270 intrathecally was a requirement agreed with the European Medicines Agency (EMA) Pediatric Committee. This evaluation was done in Part C of Study VTS301 in Europe, using an already approved and marketed device. In general, a device to administer medicine intrathecally needs to be surgically placed in the body (usually lower abdominal area near the lower part of the vertebrae or backbone). With this kind of device, there is a closed cup or chamber where medicine is injected (under the skin) and a tube that goes into the spinal canal (intrathecal space). For the specific device that was tested in Study VTS301, we

discovered during the evaluation of the device is that it was not suited for patients with NPC because the tube that went into the intrathecal space frequently moved out of the space. This made the device unusable for administering VTS-270. Mallinckrodt stopped the evaluation of this device in Study VTS301 because it was clear that it was not working for the majority of patients.

Mallinckrodt recognizes that an alternative way to administer VTS-270 into the intrathecal space is important. We do have a team working on identifying options for this. It is being done outside of Study VTS301 because we have to do a lot of work to get to the point of being able to assess the new device in patients.

Trial Data (VTS303)

31. What is the status of the pediatric study (VTS-270-303 – a study in patients with NPC under 4 years old)?

Study VTS-270-303 is a new study that is designed to look at the effects (good and bad) of VTS-270 in patients with NPC under the 4 years old. As this is a very vulnerable population, before making the decision to start Study VTS-270-303, we want to wait until our ongoing assessment from additional data analysis is complete. We are working with NPC physicians to determine potential avenues to support these patients and their families.

As the NPC community is aware, Mallinckrodt is currently evaluating data from its trial of VTS-270 for use in NPC. The efficacy results of Study VTS301 were unexpected. There were no unexpected safety findings in the trial and we believe it is acceptable for those on drug through the trial or compassionate use to continue to receive VTS-270.

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