GSK Q&A For Patient Advocacy Groups: 04 October 2013

For reactive use in response to enquiries from patient groups only

1. **Will assessments and visits continue now that the patients are no longer receiving study treatment?**
    - Yes, while dosing of boys in the ongoing studies (DMD114349, DMD115501 and DMD114673) has been placed on hold, scheduled visits, safety monitoring and relevant assessments will continue. Efforts are underway by GSK to reduce assessments so that the burden to the boys is reduced while maintaining their safety.

2. **Why are the patients who participated in the study still supposed to go for the planned assessments to the study centre?**
    - Although dosing has been placed on hold, the studies are ongoing and it is still important to gather the information according to the study protocols. Drisapersen has a long half-life (how long it takes for the concentration of a medicine to decrease by half in the body), so even though dosing of the medicine has been placed on hold, it will still be present in the body and that is why safety monitoring needs to continue. Efforts are underway by GSK to reduce assessments so that the burden to the boys is reduced while maintaining their safety.

3. **Will study participants be able to complete laboratory work closer to home or will they continue to have to travel to the study sites? (particularly important for people who live far from the closest study site.)**
    - Although it may cause some boys and their parent's difficulties, at present the assessments will continue at the study centres. Efforts are underway by GSK to reduce assessments so that the burden to the boys is reduced while maintaining their safety.

4. **Please ask GSK why can't the boys who want to continue taking drisapersen (as promised as part of the open-label extension phase) if the company would like us to continue being monitored (giving results)? My son, 13 years old, appears to have stabilize while on drisapersen. A video of him still being able to ride his bike has been sent to GSK via Debra Miller at Cure Duchenne. His doctors at the Montreal Children's Hospital were in amazement at his last clinic visit. He has improved on some of the strength tests.I have all 10 of his 6MWTs, and he has been stable for 2 years, while providing results for the company. This drug works for him! I dread the decline in the non dosing months to come as statisticians play with numbers. We will jump through hoops if it means my son (and others) are allowed continued access.**
5. **Why can't they continue the drug while they are analyzing the data?**

6. **If there are no more side effects.... why place the drug on hold. Why not allow the kids to access the drug while they analyse the data.**
7. **Risk Vs Benefit - They have mentioned that the risks outweigh benefits.... how do 'injection site reactions' come across as risks that are so big that they have to put the drug on hold. Is there a side effect they are not telling us?What made GSK decide to stop giving the drug/Drisapersen**
8. ***With regards to GSK, I think our supporters and wider community will not understand their decision to stop dosing. I understand that advice from the DSMB is fundamental, but I wasn't clear from the call exactly how or why this decision was taken. The risk/benefit ratio is a very vague indicator and the exact methodology and statistical analysis needs to be explained. Fundamentally, this was an executive decision by the company and scientifically I can understand why this was a case, but from a parent perspective this is difficult.***
9. **Who decided to stop the medication?**
    - **Combined answer for 4, 5, 6, 7, 8 & 9:**

      The benefit-to-risk profile of any medicine evolves over time as we learn new information. This new information can come from newly completed clinical trials (in this case study DMD114044) or from longer term experience with exposure to the drug (for example, the ongoing extension study outside of the US called DMD114349).

      Study DMD114044 was designed to provide the pivotal evidence for our understanding of the efficacy and safety of drisapersen. The results of DMD114044 study showed that there was not a statistically significant difference in the primary outcome, the 6 Minute Walk Distance (6MWD), with drisapersen compared to placebo after 48 weeks of treatment. Treatment effects were also not seen for key secondary endpoints (North Star Ambulatory Assessment, 4 stair climb velocity, and 10m walk/run).

      Overall, the safety profile of Study DMD114044 is consistent with that seen in the other drisapersen studies. Based on the preclinical and clinical safety profile of drisapersen, adverse events were predictable, yet not trivial. As expected, subclinical proteinuria was one of the most commonly reported adverse events after injection site reactions. Subclinical proteinuria was reported in 57/125 (46%) boys treated with drisapersen and 15/61 (25%) boys treated with placebo. As previously reported, one boy had severe proteinuria requiring hospitalization to facilitate treatment and recovery. This boy fully recovered following

withdrawal of drisapersen and appropriate treatment. No boys had thrombocytopenia during the phase III DMD114044 study, however in tracking participants from other studies with longer term exposure to the medicine some cases of severe thrombocytopenia were seen.

We take into account all findings when understanding the safety profile of a drug and in making the very difficult decision to suspend dosing of a drug while further interrogating the data. This is very important to us, because we take patient safety very seriously and it is important that we take appropriate measures.

Since the primary endpoint of this pivotal phase III study was not met, we need to explore the data in greater detail and will aim to confirm next steps for the program by the end of the year.

10. What does it mean the trial is 'on hold' compared to trial 'stopped'

- The dosing in the studies has been placed on hold pending a full review of the data. If the review shows that certain boys may benefit from treatment with drisapersen then it may be possible to continue dosing for those patients. If the studies were stopped then we could not restart the drug in a timely manner. However we need to further examine the individual cases in the context of the whole population before drawing any conclusions regarding a possible treatment benefit, and the decision to suspend medication will be revisited after completion of the planned analysis.

11. Is there any explanation at this moment why the outcome of this phase 3 trial is so different from the earlier trials.

- The outcome of study DMD114044 was disappointing given the encouraging results from earlier studies. Study DMD114044 was designed to provide the pivotal evidence for our understanding of the efficacy and safety of drisapersen. We need to explore the data in greater detail and conduct additional analyses, including looking at particular sub-groups, before providing any interpretation of why the primary endpoint was not met. Several factors need to be considered including individual patient data.

12. When will we hear more about the data of this trial?

- An abstract of Study DMD114044 has been submitted for presentation at the World Muscle Society scientific congress on the 5th October 2013. The results

will also be presented at the Oligonucleotide Therapeutics Society meeting (8th October 2013) and we will progress plans to submit the results for publication in peer-reviewed scientific journal. We are also working with the advocacy community to present the results in a Webinar format. Currently we are aiming to hold a Webinar on the 15th October 2013.

13. **Is there a chance the children who participated in the trial can go back on the drug soon? And if yes, what is the expected timeline?**
    - Only at the end of the ongoing detailed analysis of all available data with drisapersen, we will be able to confirm next steps for the program. Such analysis is expected to be concluded by the end of this year. The decision to suspend medication will be revisited after completion of the planned analysis.

14. **What further plans do GSK have with Drisapersen?**
    - We need to explore the data in greater detail before determining our next steps for the clinical program.

15. **Were certain groups doing better than others?**
16. **Was there a statistically significant difference in 6 Minute Walk test in patients 9 years old and up?**
    - We are in the process of reviewing the data and performing further sub-analyses and do not have this data available at the moment.

17. **If older patients (9 & older) showed a statistically significant difference in 6 Minute Walk, could GSK/Prosensa ask the FDA for an approval on older patients and keep younger boys in a long term extension trial?**
    - At the end of the ongoing review of all available data with drisapersen, decisions will be taken regarding this programme. These decisions may also involve discussions with regulatory authorities.

18. **Why are they not setting up a War Room or situation room to address the situation, why does it takes so long to analyze the data? I don't see the need of urgency on this matter from GSK.**
    - GSK is doing everything possible to address questions related to the program and analyse the data as quickly as we can.

19. **Why were we not informed in advance that they are facing issues and if they will be unable to resolve the issues then down the line there is a possibility of aborting the**

trials? There is a reason for asking this. I see 6MWT as the sole reason for not showing improvement. If i had known this issue then i would have prepped my son for test as he prepares for his school test. Am sure he can walk/run 30M faster than his present results. (I'll check his timing again tomorrow). Am not influencing the results, it's a matter of sensitizing the kid on importance of subject.

20. **Why didn't think know the trial was failing sooner?**
21. **One more question for GSK. Was it an interim analysis done in phase 3? If not, why not? If yes, why weren't the results made public? Most phase 3 trials have interim analysis.**
    - **Combined Answer for 19-21**: The Phase III Study DMD114044 was a randomised, double-blind, placebo controlled study. GSK were blinded to all key clinical parameters, including the primary endpoint. The Independent Data Monitoring Committee were unblinded to treatment and recommended continuing the study following regular review of the safety data. An interim analysis was not performed on this trial and so we only became aware of the final result once the study had completed and the data had been analysed. Although an interim analysis is sometimes performed on studies because they can give an earlier idea of what is happening in the study, an interim analysis was not considered appropriate for this single pivotal study. The maximum treatment effect was anticipated to be shown after the full 48 weeks of treatment, and hence an analysis of data from boys reaching this time point was considered most appropriate for an assessment of efficacy.

22. **I see 6MWT as the sole reason for not showing improvement. If i had known this issue then i would have prepped my son for test as he prepares for his school test. Am sure he can walk/run 30M faster than his present results. (I'll check his timing again tomorrow). Am not influencing the results, it's a matter of sensitizing the kid on importance of subject.**
23. **GSK question -My son was 5 at the start of trial. He doesn't really understand the 5 minute walk, and gave variable effort at the different test days. Some of this is due to his age, some from cognitive challenges of duchenne. he was unable to really comply with secondary measures, like North Star or pfts. However, he improved physically and cognitively. He has deteriorated at age 6 after 6 months in the washout phase. How can kids that young really be compared in any meaningful way? They are the ones who stand to benefit the most from slowing muscle loss over a longer time, but are the hardest to quantify. There needs to be a different way of measuring in younger boys, or at least continue them on it until they are able to comply. The other 87% of boys who are not eligible make a fine placebo arm.**

- **Combined Answer 22 & 23:** The 6MWD is a validated measure of ambulatory function in boys over 5 years of age and is increasingly used as a primary end-point in clinical studies. It was included as the primary end-point in the drisapersen ambulant clinical program in consultation with regulatory authorities and disease experts. Experts such as Professor Craig McDonald have also published papers indicating the clinical meaningfulness of the 6MWD, with a change of approximately 30m being clinically meaningful. It is important to also note that key secondary endpoints that are distinct from the 6MWD (North Star Ambulatory Assessment, 4 stair climb, 10m walk run) also did not show a difference between drisapersen and placebo.

24. I am wondering if the recent results will have any effect on the upcoming trials of pod45? I mean the start dates for the trials.

- We are unable to comment on trials run by another company.

25. Why was dystrophin data not collected and reported in the phase 3? Don't we need to understand WHY there are improvements in the 6mwt in the phase 2? Don't we have to correlate that with some change in the muscle chemistry? If not, what do we learn?

- Dystrophin data from the phase II study (DMD114117) have been analysed and have been presented at the World Muscle Society Congress in October 2013. The pharmacodynamic data (drug tissue concentration and detection of exon skipping) from the phase III study (DMD114044) is currently being analysed and will be available in the near future. Based on these results we will be able to determine the best analysis plan for dystrophin.

26. How long it will take between the conclusion of the subanalysis and having children back on the drug?

- Only at the end of the ongoing detailed analysis of all available data with drisapersen, we will be able to confirm next steps for the program. Such analysis is expected to be concluded by the end of this year. Restarting dosing will depend on finding a positive risk-benefit profile.

27. **If the drug is not working - what would explain the stability of condition that my son was experiencing while on it?**
28. **What if my child did very well on Drisapersen for more than 4 years? How you expect us to stop now? What if we want to continue? Can we ask for access through a Named Patient program?**
    - We need to carefully evaluate the full benefit-to-risk profile of drisapersen. As we progress, we will continue to keep the advocacy community and the investigators updated. Until we complete that evaluation, we will continue to hold treatment. In reference to a "Named Patient Programme", we need to explore the data in greater detail and will aim to confirm next steps for the program by the end of the year. In the meantime, all dosing has been suspended, even in a compassionate use context.

29. **Parents feel their child will lose ground very rapidly after stopping the trial and for example are planning to change the steroid regime of their son.**
30. **Is there any suggestion how long it will take before the children will lose the effect of Drisapersen**
31. **Do you have any experience in what happens if you stop giving Drisapersen?**
    - **Combined Answer 29 - 31:** Drisapersen has a long half-life (how long it takes for the concentration of a medicine to decrease by half in the body) of approximately 29 days, so even though the drug has been held, it will still be present in the body. Also, within study PRO051-02/DMD114673 (a 12 boy study with an extended treatment phase which is currently still ongoing) subjects had an 8 week treatment interruption (after 72 weeks of weekly treatment) and then moved on to an intermittent dosing (8 weeks on drug / 4 weeks off) and did not have an apparent decline in 6MWD.

32. **Where did the dystrophin go which was evidenced during earlier trials?**
    - We have reported results of all key secondary endpoints that were pre-specified in the statistical analysis plan. The pharmacodynamic data (drug tissue concentration and detection of exon skipping) from Study DMD114044 is currently being analysed and will be available in the near future.

33. What is the best parents can do meanwhile?

(a) Can we start using other drugs?

(b) Can we participate in other trials?

(c) Can we switch from an intermittent steroid regime to daily steroids

- Any patient is a specific case and any intervention or change in care should be carefully evaluated and discussed with an expert. Please contact your treating physician to discuss these matters and seek advice.

34. It is well known that Utrophin levels in younger boys are higher than older boys. Was including younger boys a mistake where the 6 minute walk is the primary end point and not dystrophin production?

- Professor McDonald recently published a paper looking at the reliability, concurrent validity, and minimal clinically important differences in the 6-minute walk test using an international clinical trial enrolling 174 ambulatory males as young as ≥5 years old - the conclusion was that the 6MWD is an optimal primary endpoint for Duchenne muscular dystrophy (DMD) clinical trials that are therapeutically focused on preservation of ambulatory functioning and slowing disease progression. Additionally, clinical primary endpoints are currently the regulatory standard for assessing efficacy in DMD.

35. Is there anything point in looking at specific mutations in the spectrum of those thought to potentially benefit from skipping 51? (I sure hope not, because that will be a real challenge to all of exon skipping)

- We are currently in process of reviewing integrated data across the drisapersen development program.

36. Will the other trials conducted by Prosensa go on hold as well? (we have the statement from Prosensa)

37. How this will affect the trials currently conducted by Prosensa.

38. Another question - we eagerly await an update on eteplirsen progress. We would appreciate any information about whether our son may be allowed to participate in an eteplirsen trial, given that he received drisapersen.

- **Combined Answer 36 – 38:** GSK is unable to comment on trials run by another company.