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Questioning Whether NEOD001 is Efficacious

Company: Prothena Corp PLC	**Stock Price:** $55.15
Ticker: PRTA US	**Market Cap:** 2.1 billion
Industry: Biotechnology	**Float:** 100%
Report Date: June 29, 2017	**Average Volume (90-day):** 270,000 shares

We are short PRTA. The publicly-available data, in our opinion, does not show that NEOD001 is efficacious. Our impression appears to run contrary to that of the sell-side. We believe that perceived positive responses to the drug are quite possibly – if not likely – due to previous plasma cell directed ("PCD") therapy, and also to the manner in which some early trial data has been presented. Further, NEOD001's proposed mechanism of action is not proven.

AL amyloidosis is a horrible disease. We would be happy to be wrong about our reading of the data. However, even if NEOD001 were to be approved, we see the Street's peak annual sales estimates generally of over $1.5 billion as unrealistic. The patient population is small, and we believe most payers are unlikely to reimburse for this drug if it were priced at a level sufficient to put the peak annual sales estimates within reach.

We note that insiders hold virtually no shares, immediately sell substantially all stock received through option exercises; and, that PRTA raised an additional $155.3 million gross in an equity offering in March 2017.[1] A recent investor conversation with PRTA's CFO led him to take a tone described as defensive when asked pointed questions about the trial data.[2] These observations lead us to believe that management might share our concern about the efficacy of NEOD001. We also find it noteworthy that PRTA presently plans not to release interim data from its Phase 3.

We Conclude Publicly Available Trial Data Does Not Support that NEOD001 is Efficacious

The publicly-available data from the Phase 1/2 trial conducted on NEOD001 do not, in our view, support a conclusion that NEOD001 is efficacious. The main issue we see is that patients' improvements in biomarker levels are quite possibly – if not likely – to have been caused by

[1] http://ir.prothena.com/releasedetail.cfm?ReleaseID=1015749
[2] A transcript of the relevant portion of the conversation is infra.

previous plasma cell directed ("PCD") treatments. In contrast to the conclusions Liedtke et al presented at American Society of Hematology ("ASH") 2016, *we see the timing of patients' organ responses as consistent with responses from PCD treatments*, which often consist of chemotherapeutic agents.[3] We see in the data a lack of correlation between cardiac responses and the depths of hematologic responses, which casts doubt on NEOD001's efficacy. The NEOD001 "Best Response Analysis" is misleading in our view as to efficacy, and we further believe it has led to undue optimism about the drug.

Between 2013 and 2016, PRTA conducted a Phase 1/2 trial on 69 patients with AL Amyloidosis. The first 27 patients were part of the dose escalation and 42 additional patients were added to the expansion cohort. Patient discontinuation in the dose escalation part of the study was substantial, 10 patients did not complete the study and one patient died.[4] All patients had previously undergone PCD treatment, generally consisting of various combination of chemotherapy alkylating agent, protesome inhibitor, steroid and some patients had autologous transplantation. The trial was not placebo controlled, which of itself makes the data of questionable value without a control arm. (The current Phase 2B and Phase 3 trials are placebo-controlled.)

The publicly-available data trail shows biomarker responses that we believe are consistent with improvements expected from PCD therapy. The current treatment standard for AL amyloidosis seeks to improve end-organ function – i.e., achieve a very good partial to complete organ response – through PCD therapy that eliminates the precursor protein of the amyloid that is depositing in the body. Research shows better hematologic responses improves the chances of organ responses, and significantly impact overall survival.

There are a number of PCD treatments that are effective in generating hematologic responses.[5] These treatments include combinations of dexamethasone, oral melphalan, oral cyclophosphamide and the proteasome-inhibitor bortezomib (Velcade). Many of these medications are authorized for multiple myeloma, and are often used off label for the treatment of AL amyloidosis. Two independent retrospective studies of hematologic response rates show the combination therapy of cyclophosphamide-bortezomib-dexamethasone (CyBorD) is highly efficacious. One study reported a hematologic response rate of 94% and a complete hematologic response rate of 71%, while the other reported a 81% hematologic response rate and 42% complete hematologic response rate.[6,7]

Timing of Organ Responses versus Hematologic Responses

Liedtke et al presented slides at ASH that appear to suggest that NEOD001 trial patients' organ responses were likely due to the drug. We do not agree with that interpretation. One of the key slides is below. The graph on the left, showing the cumulative probability of an organ response following nFLCr (normalization of the free light chain ratio, a surrogate for hematologic

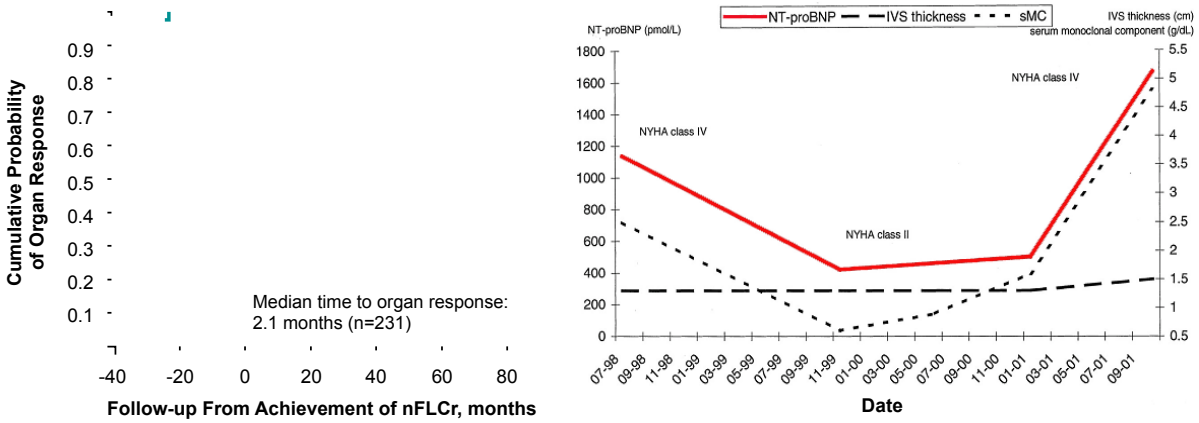
[3] Liedtke et al. Presented at the 58th ASH Annual Meeting & Exposition; San Diego, CA: December 3-6, 2016. Abstract 647.
[4] Gertz et al. J Clin Oncol 34:1097-1103
[5] see Palladini et al 2012.
[6] Mikhael et al Blood 2012. 119(19): 4391-4394
[7] Venner et al Blood 2012. 119(19): 4387-4390

complete response) following chemotherapy, states that the median time to organ response is only 2.1 months. (This data is drawn from Kaufman et al[8]) Because Liedtke et al point out that the median time in the NEOD001 study from the last PCD treatment was 5.8 months, the implication is that the organ responses observed are likely due to NEOD001 because PCD treatments may have already manifested any organ responses by the commencement of NEOD001 treatment. However, closer examination of the Kaufman et al data belies this conclusion, and emphasizes that *there was no wash out period in these trials to control for lingering effects of PCD treatments*.

[8] Kaufman et al. Am. J. Hematol. 90:181-186, 2015

Liedtke et al slide presenting Kaufman et al data:

Background: If Organ Response Occurs After Hematologic Response (HR), It Is Generally Rapid



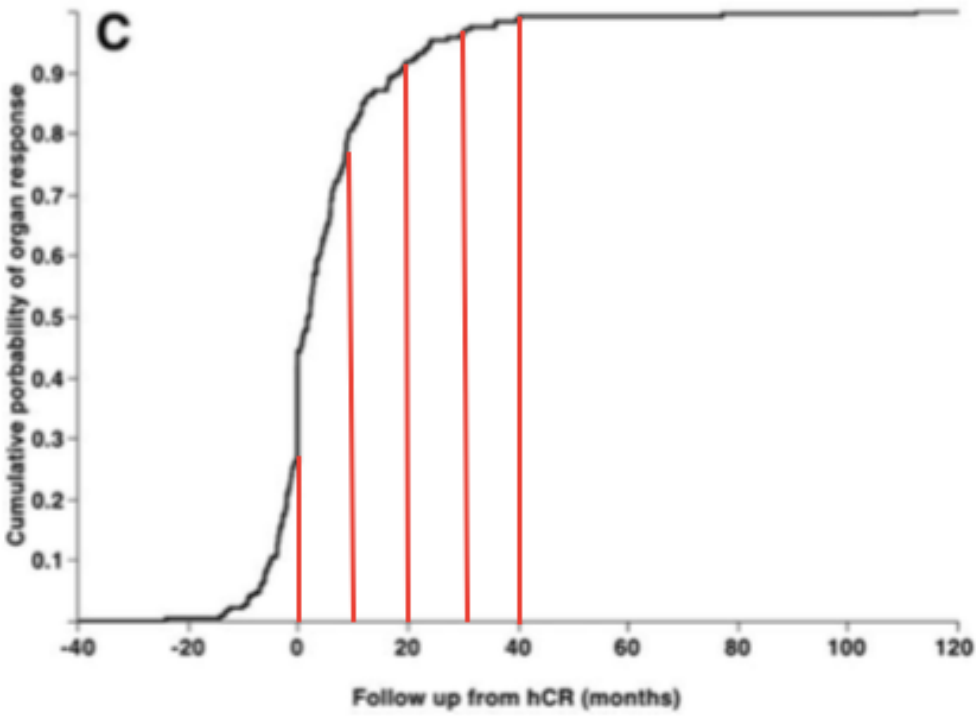
- **FLC reduction is paralleled by simultaneous NT-proBNP reduction and clinical improvement**

6 FLC, free light chain; IVS, interventricular septum; nFLCr, normal ratio of involved and uninvolved free light chains; NYHA, New York Heart Association; sMC, serum monoclonal component.

Modified with permission from Kaufman GP et al. *Am J Hematol.* 2015;90:181-186.

Modified with permission from Palladini G et al. *Circulation* 2003;107:2440-2445.

A close look at the cumulative probability of an organ response yields makes a contrary point (red lines added to Kaufman et al graph):



When we add lines to the graph at approximately zero, 10, 20, 30, and 40 months, *we see that organ responses have been observed up to approximately 40 months after hematologic responses*. Note also that *close to 30% of the patients had an organ response before a hematologic response*. The organ response preceding hematologic response would seem to impact the 2.1 month-median response time that Liedtke et al cite.

Kaufman et al shows the below rates of eventual organ responders achieving an organ response within six and 12 months from nFLCr, which was the surrogate for a complete hematologic resposne:[9]

Organ	**Six Months from nFLCr**	**12 Months from nFLCr**
Heart	75%	87%
Kidney	64%	84%
Liver	71%	87%
Nerve	63%	75%

The above table shows that shows that if an eventual organ responder did not achieve an organ response within six months from nFLCr, *he had an approximately 50% chance of achieving it within next six months without NEOD001*.

We calculated the months 6-12 response rates from the Kaufman et al data in the following manner: (12-month rate – six month rate) / (1 – six month rate):

Organ	Formula	**Months 6-12 OR Rate**
Heart	(87%-75%) / (1-75%)	**48%**
Kidney	(84%-64%) / (1-64%)	**56%**
Liver	(87%-71%) / (1-71%)	**55%**
Nerve	(75%-63%) / (1-63%)	**32%**

The NEOD001 studies only enrolled patients who had already had a HR.[10,11] Based on the foregoing, we therefore conclude the NEOD001 patients' median time since the last PCD treatment of 5.8 months to be unpersuasive with respect to the drug's efficacy. We suspect that the improvements in biomarker levels could be attributable to PCD therapy, rather than NEOD001.

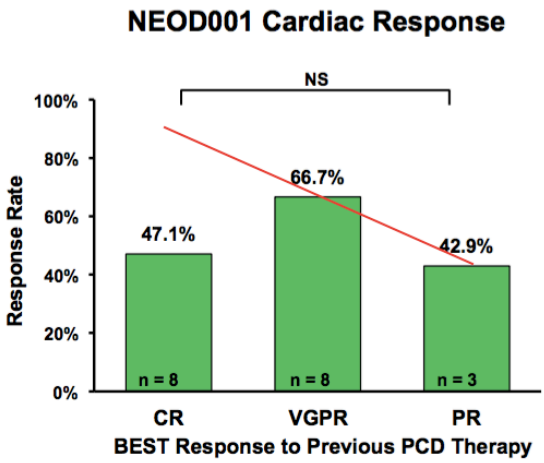
We urge PRTA to release data by individual patient so that investors can better analyze the timing of organ responses, and have a better basis to judge efficacy.

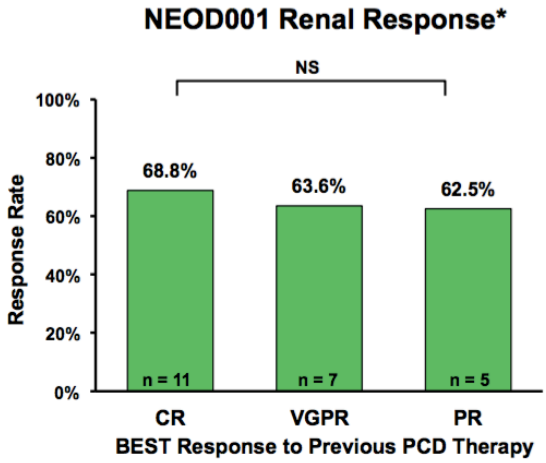
[9] Kaufman et al. Am. J. Hematol. 90:181-186, 2015
[10] Gertz et al. Presented at the 58th ASH Annual Meeting & Exposition; San Diego, CA: December 3-6, 2016. Abstract 644
[11] Liedtke et al. Presented at the 58th ASH Annual Meeting & Exposition; San Diego, CA: December 3-6, 2016. Abstract 647

Cardiac Responses versus Depths of Hematologic Responses

We see in the data a lack of correlation between cardiac responses and the depth of hematologic responses, which casts doubt on NEOD001's efficacy. Kaufman et al's analysis establishes that there should be a relationship between the depth of hematologic responses and organ responses. The Liedtke et al slides below show the cardiac and renal response rates on the Y axes, versus the depths of the hematologic responses on the X axes (best and last, respectively). The hematologic responses are categorized as CR (complete response), VGPR (very good partial response), and PR (partial response). The renal response tables show the trend one would expect: A deeper hematologic response seems to lead to a greater likelihood of organ response. However, the cardiac response breaks from that pattern – we inserted red trend lines based on the VGPR and PR to illustrate the seeming underperformance of the CR category. The criticism of this comparison is of course the small sample size; however, small sample size is an inherent problem in the NEOD001 trial data to date.

Depth of Patients' Best HR Did Not Impact NEOD001 Organ Response



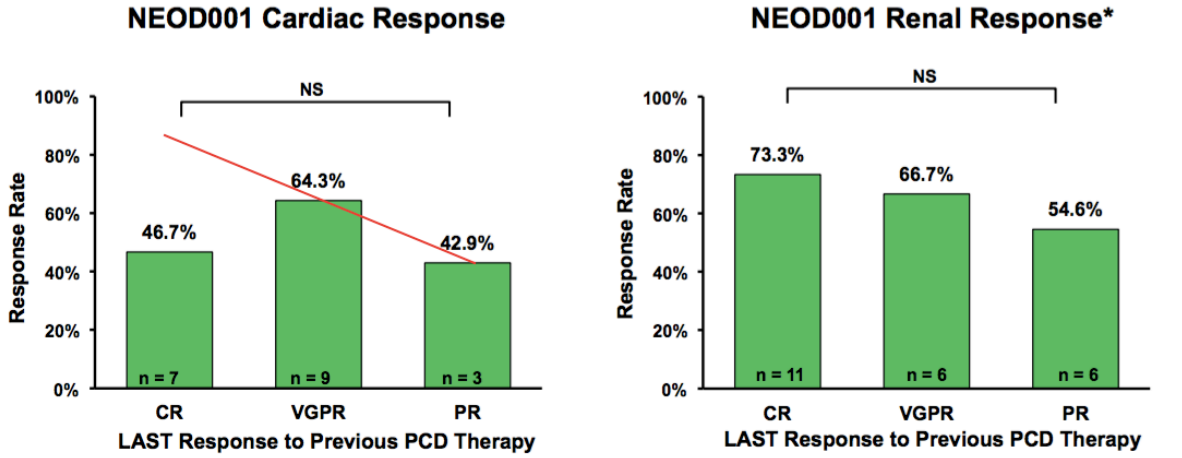


10

NS, not significant, Responder vs Stable for each category

*1 patient excluded as depth of HR known to be greater than PR but otherwise unconfirmed. Groups compared using 2-sided Fisher exact test ($P < 0.05$).

Depth of Patients' Last HR Did Not Impact NEOD001 Organ Response



11

NS, not significant, Responder vs Stable for each category

*1 patient excluded as depth of HR known to be greater than PR but otherwise unconfirmed. Groups compared using 2-sided Fisher exact test ($P < 0.05$).

One possible explanation for the apparent lack of correlation is that enrolled patients had multifactorial congestive heart failure. If this is the case, it points again to weaknesses in the trial data in terms of establishing efficacy.

NEOD001 Best Response Analysis is Seemingly Misleading

The NEO001 "Best Response Analysis" is misleading in our view as to efficacy, and we further believe it has led to undue optimism about the drug. The below slide shows a "Best Response Analysis" for NEOD001, and appears to show 47% of the patients were stable, and 53% responded. We view this presentation of data as questionable with regard to establishing efficacy.

First, this presentation measures the largest biomarker improvement (if any) a patient had during the trial – in our view, it does not establish that the patient's biomarkers consistently improved, nor that the patient had a positive overall outcome. The corollary to this issue is that it is showing changes in NT-proBNP levels, and as we discuss infra, NT-proBNP can change substantially from day-to-day for these patients due various factors.[12,13,14] We think of the Best Response Analysis as akin to extrapolating that former Major League Baseball journeyman Mark Whiten should be inducted into the Hall of Fame based on the one game in which he hit four home runs and 12 RBIs.[15] To help investors gauge efficacy, PRTA should release NT-proBNP levels for each patient in the cohort over the life of the study.

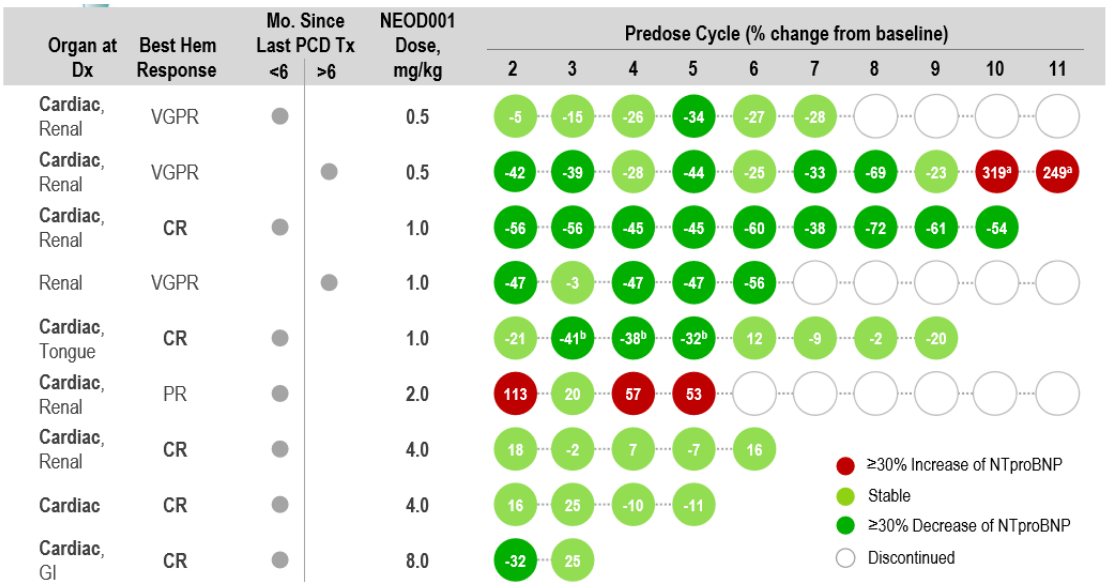
[12] Bonfils et al. Eur J Heart Fail. 2010
[13] www.acep.org/Clinical---Practice-Management/Focus-On--Brain-Natriuretic-Peptide/
[14] O'Hanlon et al. J Cardiac Fail; 2007; 13:50-55
[15] https://en.wikipedia.org/wiki/Mark_Whiten

The second problem with the NEOD001 Best Response Analysis is that it excluded patients with progressive renal dysfunction. It is widely accepted that an improvement in renal function is associated with lower NT-proBNP levels, and that progressive renal dysfunction negatively impacts NT-proBNP levels.[16] Therefore, by excluding patients with progressive renal dysfunction from this analysis, a) the cohort does not match what the real world patient population would look like, and b) the NT-proBNP measurements would seem to be favorably skewed, thereby likely overstating efficacy.

In the Phase 1/2 dose escalation study 10 patients were discontinued in the study and 1 patient died.

Lack of Correlation Between Doses and Responses in 2014 Sample Patients

We understand that PRTA published the below graph in 2014. However, it appears to no longer be available on PRTA's website. The graph shows data that we believe belies the notion that NEOD001 is efficacious. It shows that eight patients in the Phase 1/2 study received doses that ranged from 0.5 mg / kg to 4.0 mg / kg. Our interpretation of this graph is that there was no correlation between response and dose size – if anything, the relationship appears to be almost inversely correlated in that the patients at lower dosages seem to have responded better than the patients at higher dosages. (It should be noted though that the ninth patient, at 8.0 mg / kg only had only two data points, the first of which evidenced a 30% or greater decrease of NT-proBNP.)



The Phase 3 dose is 24 mg / kg, which implies that PRTA views 0.5 mg / kg to 4.0 mg / kg doses as sub-therapeutic; however, 50% (four out of eight) patients at these doses experienced organ responses, which calls into question whether the responses were due to PCD treatments or NEOD001.

[16] Palladini et al. J Clinical Oncology; 2012

Also, if we look at the six patients who each had at least six cycles of therapy, we see that while five out of six each had a response at some point in time (a Best Response Rate of 83%), at most points in time the response rate was 50% - if nothing else, this shows how a Best Response Analysis overstates the results of the trial.

Cycle	2	3	4	5	6
Rate	50%	50%	50%	83%	33%

It appears PRTA has not published any dose-specific data since 2014, nor does it appear to have published dose-specific data on doses between 8.0 mg / kg and the Phase 3 dose of 24 mg / kg.

Other Criticisms About Concluding NEOD001 is Efficacious from the Trial Data

Investors who think that NEOD001 is likely to be efficacious based on the trial data to date are also overlooking other issues in the studies:

- There have been no control arms. As we have argued, patients experiencing a hematologic response, which was a criterion to enroll, have a significant chance of experiencing an organ response. A control arm in the earlier NEOD001 studies would have made them a better basis for judging its efficacy.
- Based on what we understand of the trial, it seems one patient could be counted as a responder multiple times. PRTA defined cardiac responses as 30% and greater than 300 pg / ml reductions in NT-proBNP levels from baseline.[17] It is not clear that PRTA did not count the same patients' organ responses multiple times. As with our other questions surrounding the trial data, PRTA releasing the data on an individual patient basis would go a long way toward understanding this.

Even if the FDA Approves NEOD001, it is Unclear to us how it will Achieve Analysts' Expectations for Peak Annual Sales

The Street seems to expect NEOD001's peak annual sales will approximate $1.5 billion or more. We see these estimates as extremely optimistic because AL amyloidosis is a rare disease, with approximately 4,500 new cases diagnosed in the U.S. per year. With a small addressable market, we have seen sell side analysts assuming per patient treatment will total $200,000 to close to $300,000. At those levels, we see widespread reimbursement for NEOD001 as unlikely. First, existing PCD therapies are fairly effective, and NEOD001 would be additive. Second, the disease usually affects people aged 50 or older, whom we see as relatively more subject to increased payer constraints.

Insiders Have Near Zero Share Ownership

We repeatedly state throughout this report that seeing data on an individual patient level would go a long way to allowing investors to sort out whether improvements in biomarker levels were

[17] Gertz et al. J Clin Oncol 34:1097-1103, 2016

due to PCD treatments or NEOD001. We expect that PRTA insiders though generally have access to much richer data than does the public.

Insiders seem to have voted on PRTA with their feet. Bloomberg shows that insiders currently own 0.04% of the shares (in addition to options). Also according to Bloomberg, since June 1, 2014, insiders have exercised options for 485,542 shares, and on the same days sold 478,876 of those shares. It is therefore fair to ask whether investors are far more bullish than insiders are.

Defensive Tone and Statements by CFO Support Our Concerns

An investor who recently spoke with PRTA's CFO found his tone in response to questions about releasing the individual patient trial data defensive, which could be an indicator that PRTA senior management is concerned about whether the data shows efficacy. Below is the exchange:

> Q: Okay. You know, we worked the data also and looking at the presentations of mean, like certainly made this kind of harder to really work out. Would you guys be able to provide data on a patient-by-patient basis, you know, with the response to the PCD therapy?
>
> Mr. Nguyen: No. We haven't disclosed that information yet. We think we've shown it here. But I hear what you're saying, but we're not going to show that.
>
> Q: Okay. Why?
>
> Mr. Nguyen: Because we're -- at this point, we would either show that in a publication -- you know, the KOLs and us worked it out. I don't personally know why the answer to that is, but we're not prepared to show it.

When combining this reaction to PRTA insiders' consistent share selling (down to effectively no ownership) and the March 2017 equity issuance, we suspect insiders lack confidence in NEOD001's approval prospects.