KerrisdaleCapital

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Prothena Corp. PLC (PRTA)

The Next Big Biotech Blow-Up

Prothena Corp. PLC (NASDAQ:PRTA) is a $2.4bn development-stage biotechnology company whose stock has climbed over 700% since its spin-off from Elan in December 2012. We are certain that its lead asset, NEOD001, will fail its ongoing Phase 2b and Phase 3 trials.

NEOD001 is a monoclonal antibody designed to treat **a**myloid **l**ight chain amyloidosis (AL amyloidosis). AL amyloidosis is a condition caused by light chain proteins misfolding, which then leads to the light chains sticking together and forming amyloid structures. These amyloids are then deposited within tissues and organs of the body where they interfere with organ function, and can potentially lead to organ failure/death. NEOD001 is intended to bind to and induce the removal of amyloid deposits.

While this sounds good in theory, all clinical and scientific evidence points to disappointment. In the Phase 1/2 trial, NEOD001 failed to achieve meaningful clinical response, durable response, dose response, control over catastrophic events, or any apparent benefit at all.

The Phase 2b and Phase 3 trials will be no different. The imminent failure of NEOD001 comes as no surprise to amyloidosis researchers; in the words of one amyloid antibody co-inventor, the probability of NEOD001 succeeding in its Phase 3 trial is “almost zero.” Another co-inventor believes that NEOD001 “is just not going to work.” Antibodies targeting AL amyloidosis have been around since at least 2000 but have performed poorly in practice. The principal issue is that AL amyloid deposits are far too heterogeneous for a single antibody to work consistently among patients. On top of the heterogeneity, researchers believe that organ-specific occlusion and amyloid proteolyzation could further contribute to the inability of AL amyloid antibodies to bind to their target epitopes and achieve meaningful responses. Radioimaging studies for other AL amyloid antibodies have shown that even in situations where investigators have achieved binding between antibodies and amyloid deposits in patients, there is virtually no effect on amyloid deposits in the heart or kidneys — the key targets in Prothena’s trials. Prothena conspicuously opted against publishing such a radioimaging study for NEOD001.

In its Phase 1/2 trial, Prothena declares any patient who achieves a decline in NT-proBNP of ≥30% from baseline at any single point during its trial to be a responder. But NT-proBNP has been shown to have a week-to-week clinical variance of 35% — so seeing 53% of patients temporarily achieve a ≥30% decline in NT-proBNP at one point over a median of 12+ monthly measurements tells investors nothing. Using best response also masks patients who see their condition worsening because it only reflects the single best change in NT-proBNP. For instance, one patient saw his NT-proBNP levels skyrocket by 300% at which point he quit the trial, and another patient died during the trial. Both patients were recorded as “responders” under Prothena’s hollow best response endpoint — but this will still not translate to statistically significant results in the placebo-controlled Phase 2b and Phase 3 trials because precedent published data shows that a control group can be expected to achieve a comparable NT-proBNP response rate. Prothena’s purported cure is nothing but a deception to prop up its stock.

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I. Investment Highlights

Kerrisdale Capital: *What would you guess the probability is that their [Prothena's] Phase 3 trial will be successful? That they will get statistically significant results?*

Amyloid antibody co-inventor #1*: Almost zero.*

Amyloid antibody co-inventor #2: *This disease [AL amyloidosis] is so heterogeneous that you cannot treat them like a population, you have to treat them like individuals… The way it [AL amyloidosis] presents and the way it works, it [NEOD001] is just not going to work. You cannot do it.*

The experts agree — NEOD001 does not work. We spoke with numerous amyloidosis experts who were familiar with NEOD001 and its reported results, including researchers specializing in AL amyloidosis and amyloid antibodies and principal investigators involved with Prothena's Phase 1/2, Phase 2b, and Phase 3 trials. Most, including ones involved with Prothena's trials, were skeptical that NEOD001 actually works.

The data agrees — NEOD001 does not work. Prothena's "positive" data presented to investors and analysts is distorted and misleading for the following reasons:

- Prothena's initial Phase 1/2 data lacks all elements of a successful trial. There is no dose response, there is no duration benefit, and the drug does not appear to have any influence on catastrophic cardiac events. Prothena subsequently stopped publishing a patient-stratified NT-proBNP time series and switched to exclusively providing best response data — indicating that the initial poor results did not improve later.

- Prothena's "best response" is an uninformative measure that substitutes variance for efficacy, and Prothena provides this in lieu of meaningful data because NEOD001 does not work. Prothena makes misleading apples-to-oranges comparisons with other publications, comparing their best response rates with responses over fixed durations to try to show that NEOD001 is efficacious. The average patient was in the NEOD001 Phase 1/2 trial for 12.8 treatment cycles as of the final results presentation. Prothena is cherry-picking the best data point out of those ~12 data points, and then comparing it to studies using a single data point at the end of a pre-specified length of time. Prothena's outcome names ("responders" and "stable") imply much better outcomes than were actually observed because they are purely based off of the single best data point for each patient.

    - One patient saw NT-proBNP skyrocket by more than 300% from baseline while on NEOD001 and subsequently stopped taking the drug — yet still falls under Prothena's definition of "best responder" since he saw NT-proBNP decline by more than 30% before it shot up.

  - One "responder" saw an NT-proBNP best response of -58% — but later died during the Phase 1/2 trial, illustrating the fact that best response is primarily driven by variance and is useless as a clinical endpoint. This patient was counted as a successful responder anyway.

- Prothena repeatedly makes a misleading apples-to-oranges comparison between its 53% best response rate and the 26.5% response rate in Comenzo et al 2012 to convince investors that NEOD001 will succeed in Phase 3 — but Comenzo 2012 measures cardiac response rate based on the **final** change in NT-proBNP six months after baseline, not the cherry-picked **best** monthly measurement over a 12 month period. We can however triangulate the fixed duration response rates (response rates at the end of a specific number of months as opposed to best response rate) from Prothena's Phase 1/2 trial based on responder data provided by the company and make an appropriate comparison with Comenzo 2012. As we show in this report, we see that Prothena's month-to-month cardiac response rates are in the 20-30% range and in-line with what should be expected from a control group in the upcoming Phase 2b trial.

- The 53% cardiac best response rate achieved in Prothena's Phase 1/2 trial is also in-line with what investors should expect from the control group in Prothena's current Phase 2b and 3 trials. In the study Jaccard et al 2014, the authors carved out a subgroup of patients who had survived for at least three months after starting therapy. This subgroup is a good comparator to Prothena's results and of the patients in Jaccard 2014's >3 month survival cohort, cardiac best responses were documented in 45% (19/42).

- The change in best response rates over the course of the NEOD001 trial indicates that NEOD001 does not work. Initial data published in 2014 showed a best response rate of 56%, with the majority of responders being treated with ≤1 mg/kg of NEOD001. Prothena's final results presentation showed a 53% response rate when all patients were titrated up to the maximum dose (24 mg/kg) and average duration increased significantly. Increased doses and administrations (and therefore potential best-response data points) should be linked to higher best response rates — instead, Prothena saw the rates decline. **This would be a highly improbable event if NEOD001 actually worked.**

- Even Prothena's best-response rates are an artifact of the efficacy of prior treatments rather than the efficacy of NEOD001. The median time since last PCD treatment in Prothena's trial was approximately 6 months.[1] However, it is well-known that chemotherapy causes a transient increase in NT-proBNP which subsequently reverses.

  Gibbs et al 2009 showed that there is a transient increase in NT-proBNP levels following chemotherapy in AL amyloidosis patients, with a median increase of 83% six months

[1] 5.8 months in presentation of the final Phase 1/2 results

following diagnosis which naturally reverses afterwards in nearly all patients. The study showed that 92% of patients saw subsequent declines in NT-proBNP levels at twelve months, with the median decline being nearly 50% -- bringing NT-proBNP to approximately where it was prior to chemotherapy.

The science agrees — NEOD001 does not work. Prothena claims that NEOD001 works by binding with a cryptic epitope. A cryptic epitope is a targeted binding site revealed under specific circumstances; in the case of NEOD001, the target is revealed in misfolded light chain proteins forming amyloid deposits but not in ordinary light chain proteins, allowing for NEOD001 to treat amyloidosis without interfering with healthy light chains or having its effects diluted. However, as we confirmed with researchers in the field, this is impossible-- there are simply too many variations in amyloidogenic proteins that cause AL amyloidosis. The proteins and amyloid structures vary between patients and even among amyloid deposits within a single patient far too much for a single cryptic epitope to work with any consistency. On top of the heterogeneity, researchers believe that organ-specific occlusion and amyloid proteolyzation could further contribute to the inability of AL amyloid antibodies to bind to their target epitopes and achieve meaningful responses.

- Even when antibodies showed affinity to some amyloid deposits in some patients, there was still **no** evidence of efficacy in the heart (the principal target for Prothena's Phase 2b and Phase 3 trials). This problem has affected the two predecessor AL amyloidosis antibodies (11-1F4 and GSK2398852), and Prothena has provided absolutely no evidence or even theory to explain why NEOD001 would be an exception.

- Failure to reliably bind to AL amyloid fibrils has been a recurrent theme in AL amyloidosis, even *in vitro*. For instance, in Misdiagnosis of Hereditary Amyloidosis as AL (Primary) Amyloidosis, Lachmann et al reveal that even antibody staining of in vitro biopsies worked less than half of the time.

- Prothena could have refuted this by publishing a radioimaging study showing that NEOD001 **does** bind to amyloid deposits — but either didn't complete a study, or completed such a study but decided against publishing the results. Precedent radioimaging studies for similar antibodies designed to bind with amyloid deposits showed poor binding reliability, with complete failure to bind to amyloid in the heart.

Amyloid deposits, Prothena's alleged "incurable target", resolve naturally once the root cause (plasma dyscrasia) is reduced/eliminated through conventional therapy. Even if NEOD001 did work, it would be extraordinarily hard to show any meaningful clinical benefit.

- It has been known since at least 1928[2] that amyloid deposits regress naturally once serum free light chains are normalized. This was conclusively shown to be true in

[2] Waldenström, Henning. "On the formation and disappearance of amyloid in man." Acta Chir Scand 63 (1928): 479-530.

Gameren et al 2009, a study which showed that significant natural declines in amyloid deposits were seen in patients, with approximately 50% of the complete responders group showing significant declines in amyloid deposits within one year after the start of chemotherapy and nearly all patients seeing significant declines in amyloid deposits within 3 years.

Our discussions with physicians treating amyloidosis patients also confirmed this. Consensus is that once patients get free light chain (FLC) levels under control through chemotherapy, amyloid deposits typically resolve naturally within six months to two years.

Neil Woodford has bid the price up but history shows the Woodford effect does not last

- Investors should beware when no notable healthcare hedge funds are involved in a multi-billion dollar name, and the largest investor has made repeated large mistakes in the biotech sector.

- Within biotechnology, Woodford is best known for buying a 28% stake in Northwest Biotherapeutics, a company alleged to have engaged in a paid stock-promotion scheme and currently under SEC investigation. The stock has declined by more than 95% and Woodford's stake, originally purchased for >$150mm, is now virtually worthless.

- Woodford also holds 28% of Allied Minds, a publicly-traded venture capital firm primarily owning stakes in healthcare companies. We previously published negative views on Allied Minds in September 2015, and the stock has since declined more than 60%.

II. Company Overview

Prothena Corporation PLC: Capitalization and Financial Results

($ in mm except share price)

Capitalization	
Price per share	$60.96
Fully diluted shares	40.1
Market capitalization	$2,443

Financial Results	2016	2017†	2018†
Net income	$ (160)	$ (169)	$ (212)
Free cash flow	$ (134)	$ (171)	$ (195)

Source: company filings, Capital IQ, Kerrisdale analysis
†Consensus estimates via Capital IQ.

Prothena Corporation PLC is an antibody-focused biotechnology company. Sell-side analysts ascribe the bulk of Prothena's value to its principal asset, NEOD001. NEOD001 is an antibody designed to treat amyloid deposits in patients with AL amyloidosis. AL amyloidosis, also known as primary amyloidosis and systemic amyloidosis, is a disease characterized by formation and accumulation of amyloid in organs and tissue.

It is estimated that 1 out of every 100,000 US residents suffer from AL amyloidosis, with approximately 4,500 new cases per year. Amyloids are misfolded proteins, and in the case of AL amyloidosis, the specific proteins are antibody light chains produced by malignant plasma cells. In other types of amyloidosis, amyloids are formed from other proteins: for instance, in the case of AA amyloidosis, the amyloids are primarily composed of serum amyloid A protein fragments. Light chains themselves are normally soluble, but in patients with AL amyloidosis, the misfolded light chains tend to clump together and form amyloid fibrils, which are insoluble and not easily removed naturally by the body. Amyloid fibril build-up can interfere with organ function, causing adverse events and potentially death. Cardiac involvement is the leading cause of death in AL amyloidosis patients.

Prothena filed an Investigational New Drug application for NEOD001 in September 2012. NEOD001 is designed to bind to amyloid fibrils and trigger their removal. In December 2012, Prothena was spun off from Elan Corporation, an Irish pharmaceutical company. As part of the spin-off, Elan invested $26.0mm in Prothena in exchange for an 18% stake, valuing the equity at approximately $144mm and enterprise value at just $19mm. Prothena closed its first day of trading (December 21, 2012) at $7.20/share with 17.7mm shares outstanding for a market capitalization of $127mm and enterprise value of nearly zero.

The first patient was dosed in Prothena's Phase 1/2 trial for NEOD001 in April 2013. Prothena published a positive press release with initial clinical data on NEOD001 on April 23, 2014 and presented the data at the International Symposium on Amyloidosis, claiming that "eight of nine evaluable patients with AL amyloidosis with cardiac involvement either achieved responses

(N=5) or were considered stable (N=3)." In the press release, Prothena also guided to initiating a Phase 2/3 trial of NEOD001 in Q4 2014. Prothena's stock rallied 10% that day. But then on April 29, 2014, Prothena published its poster for NEOD001 which provided a more granular look at the initial Phase 1/2 data,[3] and Prothena's stock plummeted 31% and an additional 16% the next day. The poster is extremely troubling because it shows no discernible trends suggesting efficacy. It includes a time series graph (which we provide on p. 10 of this report) where patients' NT-proBNP levels are clearly gravitating around baseline levels rather than improving over time, and increasing dose and duration of treatment did not appear to have any effect.

In subsequent press releases and presentations, Prothena switched away from providing complete data from the NEOD001 Phase 1/2 trial and has only provided best response data and scatterplots that exclude non-responders. Since then, the stock has tripled to $61/share with a market capitalization of $2.4bn.

III. NEOD001 Has No Chance For Success

Prothena is suppressing negative NEOD001 results

Prothena's valuation implies a high probability that NEOD001 will succeed in its Phase 2b and Phase 3 trials. This optimistic outlook is driven by management's guidance that the drug's Phase 1/2 results as presented to investors, specifically the cardiac best response rate, are far better than would be expected from a placebo group and proof that NEOD001 works.

We strongly disagree with this assessment. Prothena's cardiac best response rate is merely a byproduct of well-documented natural variance, and we believe there is no chance of NEOD001 producing statistically significant results in its current Phase 2b and Phase 3 trials.

Cardiac best response rate is determined by looking at the single greatest decline in NT-proBNP for each patient. So, if a patient showed an NT-proBNP measure of 1000 ng/L at baseline, 650 ng/L after one month of treatment, 1100 ng/L after two months of treatment, 1400 ng/L after three months of treatment, and died during the fourth month, the patient would be counted as a cardiac best responder.

This best response endpoint does nothing to demonstrate that NEOD001 works. Illogical clinical endpoints are typically the result of data mining following the failure of a drug to show actual efficacy. We believe the decision to use cardiac best response in lieu of the typical fixed-duration response — response as measured over a pre-specified period (6 months, a year, 18 months, etc.) — is a product of the fact that the fixed-duration responses in Phase 1/2 were not meaningfully different from what one would expect to see from a control group.

[3] (Abstract #PB-48) Preliminary cardiac biomarker responses demonstrated in an ongoing phase 1 study of NEOD001 in patients with AL amyloidosis and persistent organ dysfunction

Prothena's "best response" endpoint does nothing to demonstrate that NEOD001 works. In fact, it does the exact opposite: it makes it clear that Prothena has diverted investors' attention to its manufactured endpoint because the fixed-duration response rate is poor.

While the ideal endpoint for trials evaluating drugs like NEOD001 would be overall survival, we recognize that this is not practical for a Phase 1/2 trial because of the long horizon required for survival trials. That said, investigators still want to see evidence of efficacy — in the case of NEOD001, they should be looking for sustained decline in NT-proBNP, a key biomarker for measuring the degree of heart failure in patients. We know that Prothena is collecting NT-proBNP data regularly, and there are various ways it could be displayed in posters — patient-by-patient chronological data, median change in NT-proBNP for the entire patient pool by months since beginning NEOD001 treatment, etc.

However, instead of providing any kind of chronological data showing the impact of NEOD001 on patients' biomarkers, Prothena has only provided its "best response" smokescreen, which takes the best response for each patient over duration of treatment and ignores all other data points. The problem with using a best response endpoint is that it is well-known that there is significant variance in the biomarker among the patient population. Rather than demonstrating efficacy, Prothena is just confirming that variance is high and calling it success. Prothena has all the data on month-to-month changes in biomarkers — but chose not to publish it. The only logical explanation is that NEOD001 failed to show any meaningful, sustained response.

This should be no surprise to investors who have been following Prothena since its initial NEOD001 poster in 2014. The granular patient-by-patient data displayed on the poster showed that NEOD001 had no effect on patients. The lack of subsequent comparable data only confirms that nothing changed as the trial progressed. Prothena has since compared its "best response" data to data from other trials measured over a set time period in an apples-to-oranges comparison. Precedent trials measure change over time and produce a single data point for each patient; Prothena collects as many as two dozen data points for each patient and then cherry-picks the best data point for each patient. When we triangulate Prothena's actual response rates over fixed durations, we find that they are well-within the range one would expect from a control group.

Academic and clinical researchers we spoke with were skeptical of the efficacy of NEOD001 based on both the mechanism of action and the publicly-available clinical data. Creating successful antibodies for treating amyloid deposits is far more complicated than Prothena portrays it to be in investor presentations. Misfolded light chain antibodies (the root cause of AL amyloidosis) and the fibrils formed by them are incredibly heterogeneous. Prothena either neglected to complete or neglected to publish proof-of-concept radioimaging studies showing that NEOD001 actually binds to AL amyloid deposits in humans.

However, we can look at human radioimaging studies performed with other amyloid antibodies as precedent. Binding has been unreliable among different patients and even among different organs within the same patient, with no apparent affinity for amyloid fibrils found in the heart in

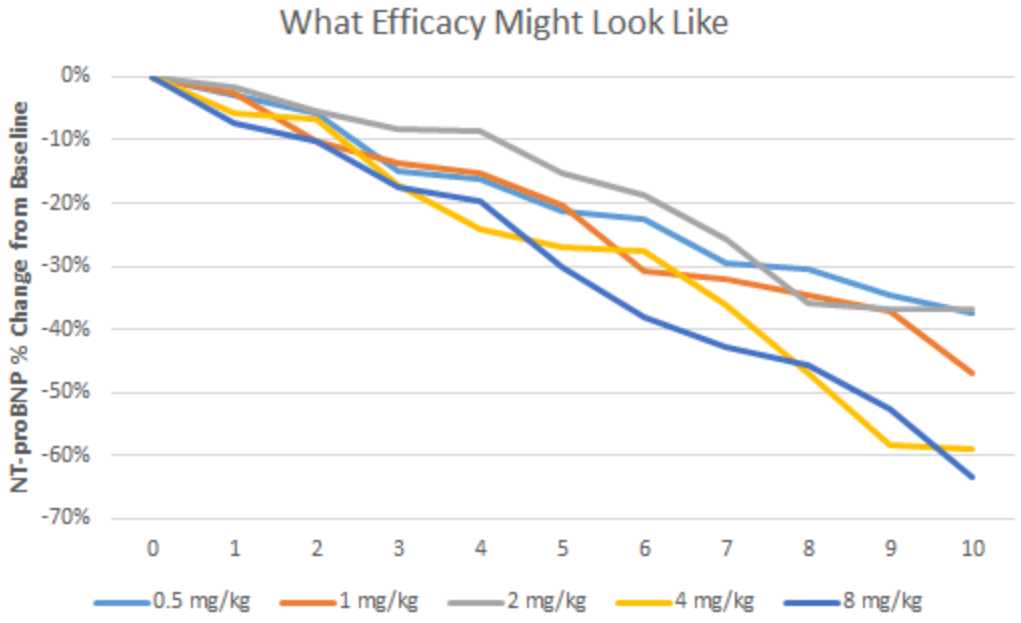
particular — which does not bode well for Prothena's Phase 2b and Phase 3 trial where change in NT-proBNP and mortality/hospitalization are the primary endpoints.

As we show in this report, NEOD001 checks all the wrong boxes for clinical success:

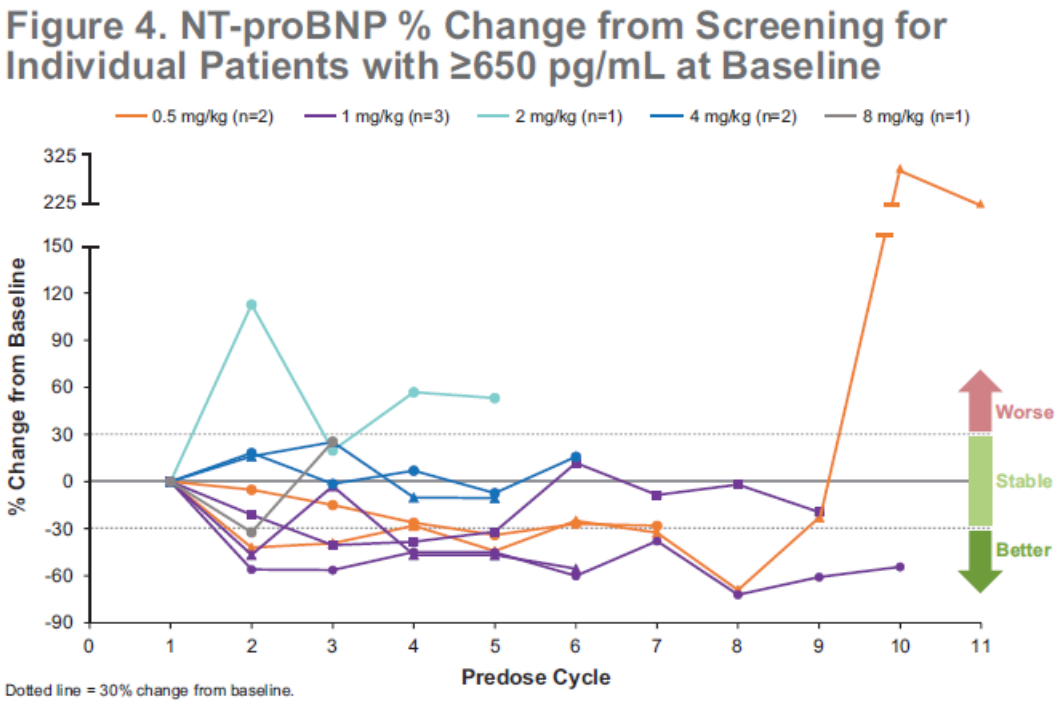
Why We Think NEOD001 Will Fail		
	Yes	No
NEOD001 can be reasonably expected to work based on:		
Mechanism of action		x
Precedent drugs in same class		x
Published data		x
Published data shows:		
Substantive response		x
Durable response		x
Dose response		x
Control over catastrophic events		x
Benefit compared to historical studies		x

Initial patient-stratified Phase 1/2 results show NEOD001 does not work

If NEOD001 worked, you might see changes in NT-proBNP levels that look something like this, as the treatment removes amyloid deposits from heart tissue:



This is what Prothena's preliminary data looked like:



Prothena Poster at 2014 International Symposium on Amyloidosis

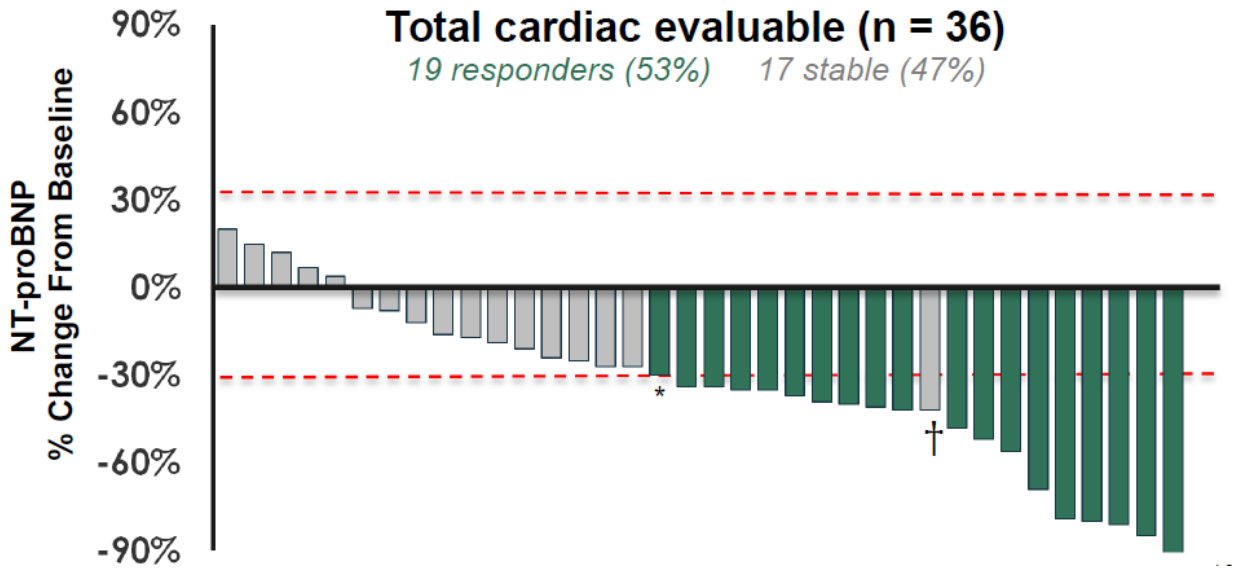
Note that there is no pattern of increasing change over time (or even sustained change) and more than half of the "best response" responders were in the two **lowest** doses — 0.5 mg/kg and 1.0 mg/kg — the opposite of dose response.

Predictably, investor response to this data was poor. The poster was presented at the 2014 International Symposium on Amyloidosis (April 27 – May 1, 2014) and between April 28 and April 30, 2014, Prothena's stock dropped by over 40%. To stem the bleeding, Prothena scheduled a special call to discuss the interim data for May 2, 2014.

During the special call, Prothena management reframed the data to focus on "best response": dodging discussion of the lack of sustained response, dose response, or any other kind of meaningful response. Using its best response criteria, Prothena claimed that five of the nine evaluable patients were responders. Prothena lauded the results and then-CEO Dale Schenk guided analysts to compare the then-56% best response rate with a 15-30% for conventional patients: "It should be noted that somewhere between 15% to 30% of patients are known to be able to show a response on this type of cardiac biomarker following plasma cell-directed therapy."[4]

[4] https://seekingalpha.com/article/2188233-prothenas-ceo-presents-at-neod001-interim-phase-1-data-conference-transcript?part=single

Prothena subsequently switched to exclusively providing updated data on patients' best responses. Below is Prothena's final waterfall chart of best responses to NEOD001, taken from the final Phase 1/2 results presentation:



Source: Prothena Presentation at ASH 2016

Generally, drugs that work show dose response, so one would expect to see improved efficacy with a higher median dose. Even if the drug doesn't work, increasing the duration of treatment (and therefore the number of measurements taken) must increase the probability of the single greatest decline for each patient being greater than 30% because Prothena effectively has more shots on the goal. The data showed the opposite — the best response rate declined, with the final best response rate from the Phase 1/2 trial being 53%, down from the initial 56%. **This outcome would be highly improbable if the drug worked.**

When investigators are measuring the impact a drug has on a specific endpoint for patients, they typically measure this based on change in that endpoint over a predetermined length of time, or in the case of overall survival, they measure the time until a change in that endpoint. Prothena could easily have provided this kind of data to investors — specifically, change in NT-proBNP over a period of six or twelve months. Instead, Prothena has elected not to disclose median change, and to instead provide the percent of patients who, at one point or another, saw a decline of over 30% in NT-proBNP levels.

Prothena's "best response" endpoint masks lack of efficacy with measure-to-measure variance

> *There are challenges in interpretation of NT-proBNP. The challenges are, at what time point are you measuring it, and are you measuring it as best response, because the best*

response could be a 30% reduction, and tomorrow if you measure it, it will be a 25% increase, and then the next day it's progression…I can tell you this from clinical practice that this happens all the time.

— NEOD001 Principal Investigator

Primary endpoints using biomarkers are most often measured as either change from baseline in a specific endpoint at a predefined point in time or as a function of that change; e.g., the percent of patients who saw a change greater or less than a predefined level. Prothena is measuring the percent of patients with "best responses" greater than 30% decline in NT-proBNP.

During discussions with practitioners and clinical investigators in the NEOD001 trials, we were told repeatedly that variance in month-to-month NT-proBNP is very high and strongly influenced by factors that have nothing to do with amyloid deposits, such as diuretics or salt intake. Published data also confirms this.

Wu et al 2003 showed that clinical variation in NT-proBNP in healthy patients over an eight-week period was 33%. Bruins et al 2004 showed that week-to-week clinical variation in NT-proBNP in stable CHF patients was 35%. In Schou et al 2007, researchers found that median year-to-year clinical variance in stable CHF patients was 30%. Bruins concluded that "The high CV_is hamper interpretation of changes in BNP and NT-proBNP concentrations and may partly explain their poor diagnostic values in chronic heart failure." This prompted significant discussion of the utility of NT-proBNP as a diagnostic factor. In response to Bruins et al 2004, Fokkema et al 2006 suggested using a lognormal approach to adjust for skewness in changes in NT-proBNP — but even with this methodology, Fokkema found that the declines required to show any clinical meaning within-day, day-to-day, and week-to-week were -22%, -42%, and -61%, respectively. See below for a summary of published figures regarding variance in individuals' NT-proBNP levels:

NT-proBNP Variance in Individuals

Study	Published	N	Patient Type	Time Between Samples	Median Intraindividual Clinical Variance	Intraindividual Critical Difference/RCV[3]
Wu	2003	8	Healthy	Two Weeks	33%	92%
Bruins	2004	43	Stable CHF	2 hours	9%	25%
				24 hours	20%	55%
				One week	35%	98%
Schou	2007	78	Stable CHF	One year	30%	NA
O'Hanlon	2007	45	Stable CHF	One hour	7%	NA
				One week	21%	50%
Melzi d'Eril[1]	2003	15	Healthy	3-4 Days[2]	9%	26%

Note:

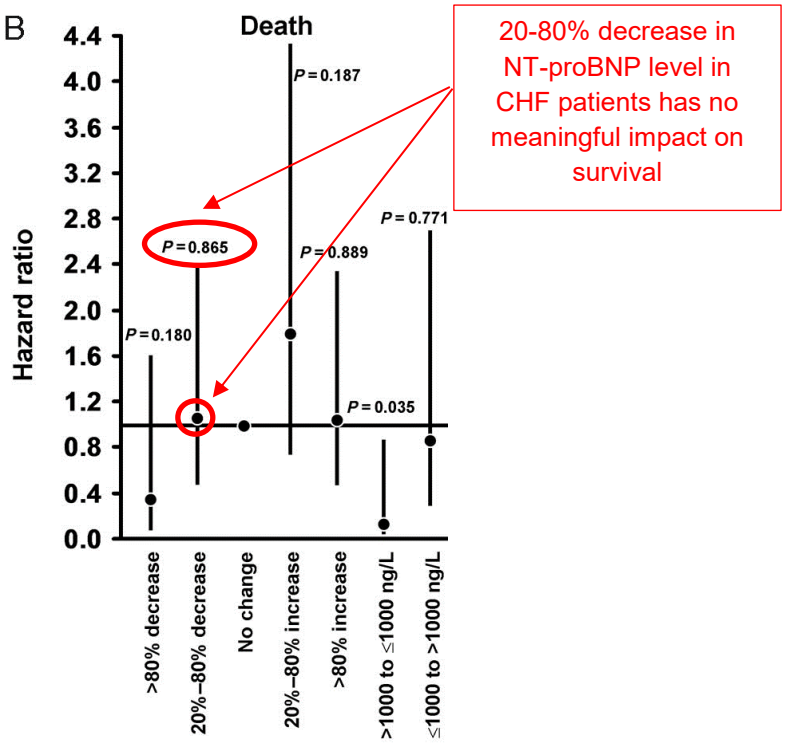
1 Data was log-transformed, hence much lower clinical variance

2 Samples taken 2x/week for 17 days

3 CD (Critical Difference) and RCV (Reference Change Value) are calculated by the authors as the percent change in NT-proBNP required to show any clinical difference in a given patient

Even if it were not just measuring variance, the 30% declines in NT-proBNP would not be sufficient to show a difference in survival.

The 172 patient, two-year trial Miller et al 2009 (appropriately titled *Only Large Reductions in Concentrations of Natriuretic Peptides (BNP and NT-proBNP) Are Associated with Improved Outcome in Ambulatory Patients with Chronic Heart Failure)* confirmed that a substantial and sustained change in NT-proBNP is required to produce any benefit for patients: the study showed that, when measuring mortality risk, a 20-80% decline in NT-proBNP produced a p-value of 0.865 with a hazard ratio that was paradoxically slightly **higher** than 1:



Source: Miller et al 2009

We also reiterate that this is a baseline-to-final-measure change in NT-proBNP, **not** best response, further trivializing Prothena's endpoint. As we argued earlier, Prothena's best response measure is useless because it measures variance rather than sustained response. Miller et al 2009 shows that even if Prothena's data points had been reflective of sustained response, they would not translate to increased overall survival. Miller et al shows that it takes a >80% decline in NT-proBNP levels to produce a meaningful hazard ratio (approximately 0.4), but few patients in Prothena's trial saw declines that high even when measuring on a best response basis.

NEOD001 compared to historical precedent

As we showed in the prior section, Prothena's best response measure is a poor indicator of efficacy because it measures the maximum response in any month over a duration rather than the ultimate change over the duration and is influenced far more by the variance in the measured biomarkers than by efficacy. Yet in communications to the market, Prothena management regularly compares its best response endpoint with published data that relies on a single measurement to determine cardiac responder/non-responder status in blatant apples-to-oranges comparisons. For instance, the following statement was made in a Prothena press release from June 2015 about its clinical data:[5]

> *The 57.1% cardiac best response rate is more than double the expected cardiac best response rate of 26.5% from historical data in patients treated solely with off-label standard of care (Comenzo, et al., Leukemia. 2012;26:2317-2325).*

In this comparison, Prothena is taking its best response data and comparing it with fixed-duration data from Comenzo et al 2012. The 26.5% response rate is calculated based on the percent of patients who saw a decline in NT-proBNP of at least 30% and 300 ng/mL at six months, **not** the percent of patients who saw a maximum response of at least 30% and 300 ng/mL at one time point out of twelve months.

Below is the relevant section of Comenzo et al 2012 that Prothena is referencing:

[5] http://ir.prothena.com/releasedetail.cfm?releaseid=917683

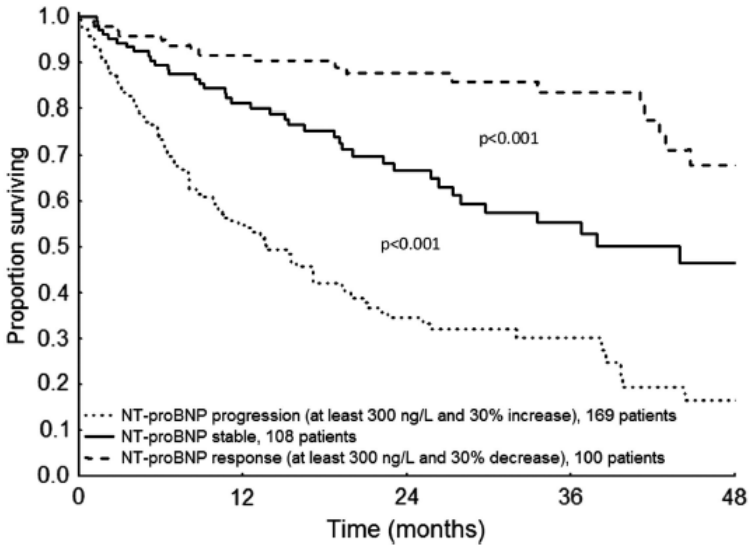


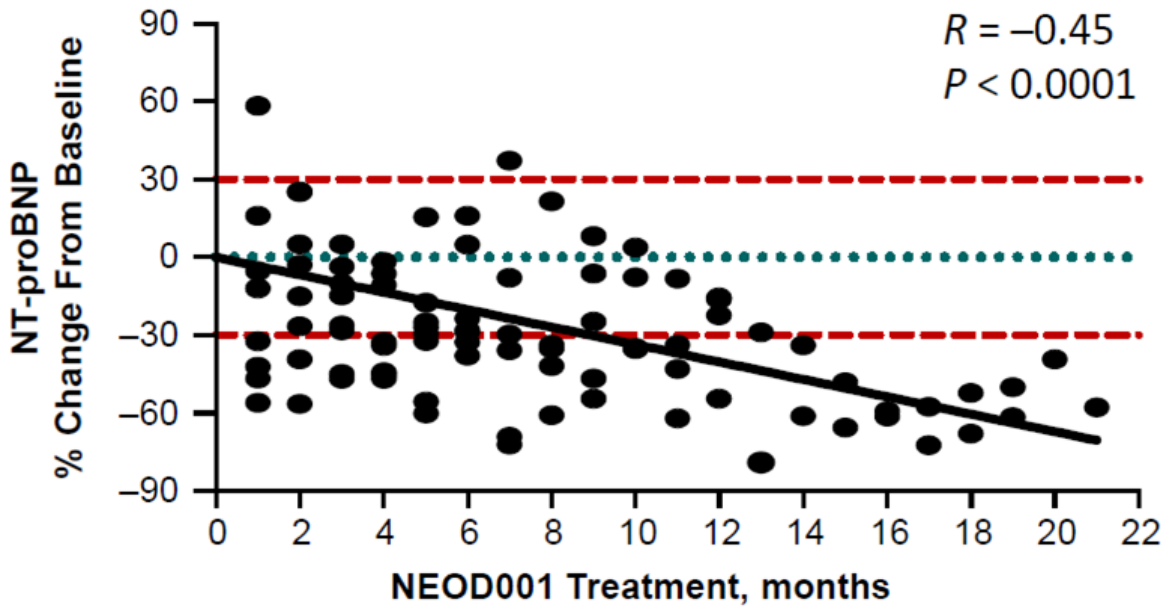
Figure 2. In the international series of 816 patients from 7 centers, staging cardiac biomarkers were available for 53% (432/816). Of these, 24% were stage 1 (both NT-proBNP ⩽332 ng/l and cardiac troponin T (cTnT) ⩽0.035 ng/ml or cTnI ⩽0.1 ng/ml), 52% stage 2 (NT-proBNP >332 ng/l or cTnT >0.035 ng/ml or cTnI >0.1 ng/ml), and 24% stage 3 (both NT-proBNP >332 ng/l and cTnT >0.035 ng/ml or cTnI >0.1 ng/ml). In these survival curves, results for 377 patients with baseline NT-proBNP greater than or equal to 650 ng/l are shown according to NT-proBNP response or progression at 6 months.[20]

Prothena arrives at 26.5% by dividing the 100 patients from the *NT-proBNP response* survival curve by the 377 total patients.[6] However, these are **not** best responses — these are responses at six months from treatment-naïve patients who were evaluated at two time points: treatment initiation and six months following treatment initiation.

The appropriate comparison with the data from Comenzo et al 2012 would be between fixed duration rates using Prothena's drug. Prothena does not provide these directly to investors — but we were able to extrapolate them based on publicly available data, and we found that the 26.5% Prothena points to falls squarely in the middle of the range achieved by Prothena during its trial.

We triangulated the response rate for each month in Prothena's Phase 1/2 trial from graphical data provided by the company in a 2015 presentation. Our conclusions demonstrate that NEOD001 will not outperform the control group in its Phase 2b & Phase 3 trials. Prothena provided a scatterplot of patient NT-proBNP changes in its Phase 1/2 trial as of 2/28/15. See below:

[6] 100 / (169+108+100) = 100 / 377 = 26.5%



Source: Prothena EHA 2015 Presentation

From the scatterplot, we can see how many patients achieved 30% or greater declines in NT-proBNP from baseline at specific points in time. All non-responders were excluded from the graph — and by definition, the non-responders did not see a response of >30% decline and 300 pg/mL at any point, so therefore at every time point on the graph, the non-responders would have been failures. We made a table showing our estimates of the response rates at each point in time based on Prothena's EHA 2015 data:

Fixed Duration Cardiac Response Rates to NEOD001

	Months of Treatment											
	1	2	3	4	5	6	7	8	9	10	11	12
Responders at Specific Month[1]	4	2	2	3	3	2	3	3	2	1	3	1
Total Best Responders[2]	8	7	8	6	7	6	6	4	5	3	4	3
Total Never-Responders[3]	6	6	6	6	5	5	4	4	3	3	2	2
Total Patients[4]	14	13	14	12	12	11	10	8	8	6	6	5
Response Rate among Total Patients	28.6%	15.4%	14.3%	25.0%	25.0%	18.2%	30.0%	37.5%	25.0%	16.7%	50.0%	20.0%

Notes:

1 "Responders at Specific Month" defined as patients who saw a >30% decline in NT-proBNP at a given month

2 "Best Responders" defined as patients who saw a >30% and >300 pg/mL decline in NT-proBNP from baseline at least one time during the trial

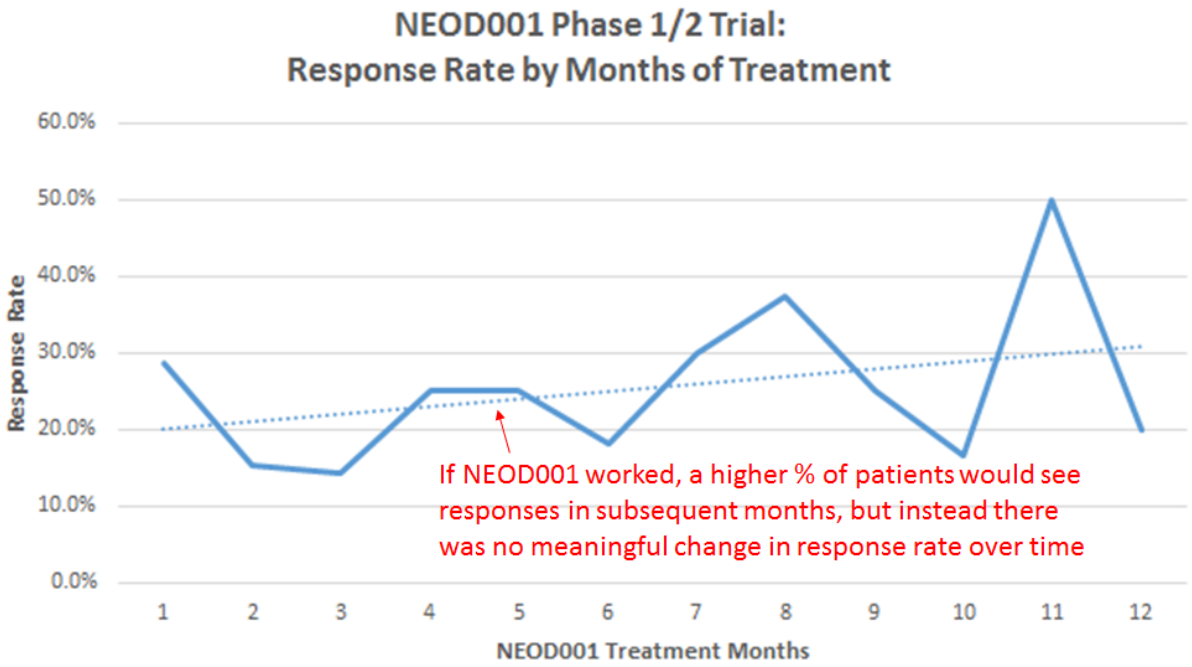
3 "Never-Responders" defined as patients who did not achieve a >30% and >300 pg/mL decline in NT-proBNP from baseline during the trial. Total non-responders were not provided for any given month, however, we know that as of the time this data was presented, all patients included had received at least four months of treatment with median treatment duration of 12 months, and that there were a total of six cardiac non-responders. We used this information along with the attrition rate among responders to estimate the number of non-responders at each point in time

4 "Total Patients" = "Total Best Responders" + "Total Never-Responders"

As stated in the footnotes to the table, non-responder data was not provided by month, but we do know that all patients were treated for at least four months and that the median treatment duration was 12 months as of the presentation. We conservatively assumed that non-responders had a significantly shorter average treatment duration than the general population, and reduced the patient count to five patients after four months, from five to four patients after six months, four to three after 8 months, and three to two after 10 months — an overall decline of 50% after 8 months despite the median duration of treatment for the overall patient population

being disclosed as 12 months at the cut-off date (February 2015) for the final data. Even if you make wildly aggressive assumptions about the dropout rate for never-responders, you cannot get to a meaningfully differentiated response rate — assuming 100% of never-responders dropped out of the trial after 4 months (which is clearly not true), you still have a median monthly response rate of 33% through 12 months (compared to 25% based on our estimates). This 33% is not significantly higher than the 26.5% in Comenzo et al, and it is overstated due to 1) excluding never-responders from months 5-12 and 2) survivorship bias in later months — patients seeing improvement are more likely to stay on therapy regardless of whether the therapy is actually helping them.

The lack of change in response rate over time based on the monthly data demonstrates that NEOD001 does not work. If NEOD001 did work, you would expect a steady increase in the number of patients who responded each month over time. Instead, Prothena saw no such snowballing of response rate:



Looking at the first twelve months of data, the response rate is between 15% and 30% at 10/12 monthly time points with a median response rate of 25%, and this remarkably does not change significantly throughout the trial despite survivorship bias,[7] with the linear trend line sloping

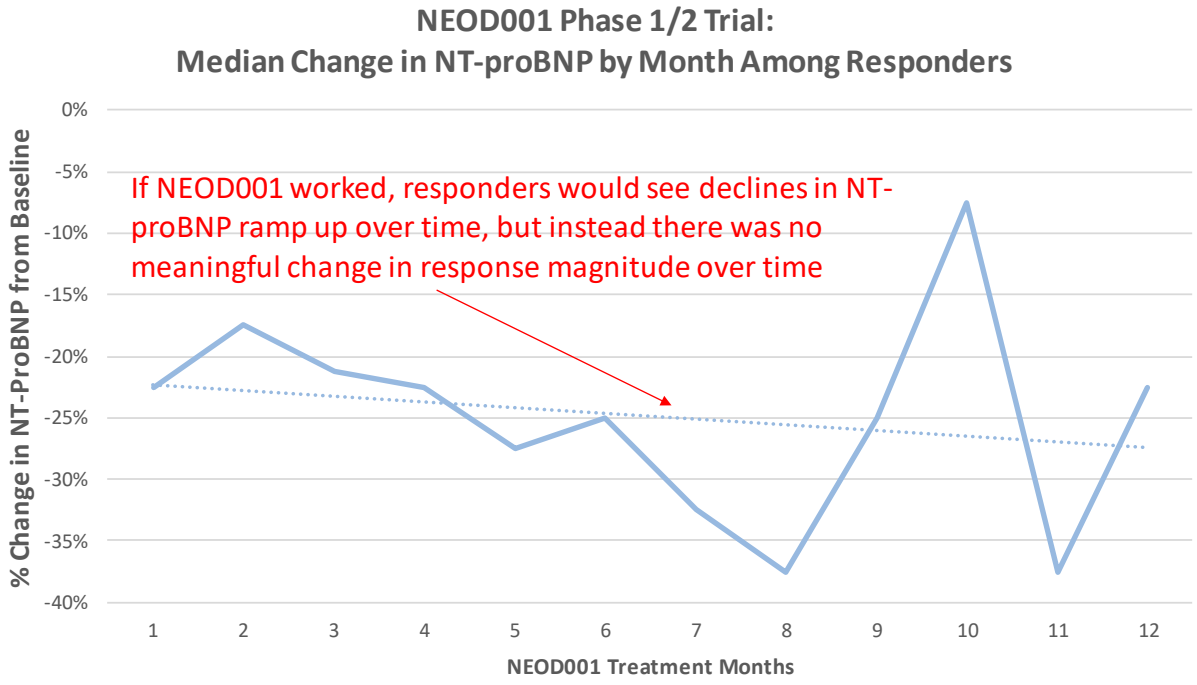
[7] The further out you go, the less indicative the data is of what the response rate would be for a larger trial because the patients who are most likely to drop out are patients who were not seeing positive changes in biomarkers (regardless of whether those changes were driven by the experimental drug or not). While Prothena stopped disclosing discontinuation rates, Prothena previously disclosed that of the first six patients in the Phase 1 study, three discontinued by seven months, which may have inflated later response rates

upwards at a rate of less than 1%/month — in such a small group of patients, this all but guarantees that there is no duration benefit to the treatment. Prothena also disclosed in its "final results" presentation at ASH 2016 that the median time to initial cardiac response was **two months**. This combined with the lack of snowballing in response rate means that responses were fleeting and merely caused by chance — if there were a sustained response, you would see the response rate clearly increasing over time, rather than bouncing around in the 15-30% range.

Perhaps realizing that overall monthly response rates could be triangulated from the scatterplot data, Prothena also stopped providing the scatterplot. It was conspicuously absent from the slide deck Prothena presented at ASH 2016, which focused exclusively on the best response waterfall.

The final best response rate was nearly the same as the response rate at the time of the last scatterplot, suggesting that the cardiac response rates did not increase from the ~20-30% seen in the interim data despite increased duration.

Plotting the median data from Prothena's scatterplot without including any non-responder data, we also see that the median cardiac response to NEOD001 (measured as decline in NT-proBNP) did not improve measurably throughout the trial. Like response rate, this should have been measurably impacted by survivorship bias as well as any duration response. See below:



Additionally, Prothena's scatterplot appears to intentionally exclude unfavorable data even among its so-called responders. There was a patient who saw NT-proBNP increase by 319%

from baseline while on NEOD001, at which point he discontinued treatment. This would clearly be considered by most to fall under the scope of "progression" but Prothena recorded this patient as a responder as well (confirmed with a co-author of Prothena's Phase 1/2 results presentation). Somehow, the final data points showing massive increases from baseline in NT-proBNP for this patient (318.7% and 249.0%) did not make it into the scatterplot provided to investors.

While Prothena regularly compares its best response results to the responses over a predetermined duration in other studies, we can look at other published data to conduct a more apples-to-apples comparison.

In the study Jaccard et al 2014, the authors carved out a subgroup of patients who had survived for at least three months after starting therapy. This subgroup is a good comparator to Prothena's results because Prothena's trials are only enrolling patients who were at least able to stabilize the production of misfolded light chains and survive beyond the conclusion of chemotherapy.

Of the patients in this cohort, cardiac responses were documented in 45% (19/42). We believe the small difference between these patients and those in Prothena's reported 53% best response rate is likely due to the fact that Prothena's patient population had better hematologic responses (ie. Prothena's population had lower FLC levels due to a better response to chemotherapy) compared to the patients in the Jaccard trial. In Jaccard et al 2014, 24% of patients in the >3 month survival subgroup had achieved complete responses, 33% achieved very good partial response, 29% achieved partial response, and 14% achieved no response, compared to Prothena's population, where for the patients for whom their most recent hematologic response was documented, 52% were complete responders, 22% were very good partial responders, 17% were partial responders, and 9% were non-responders.

Other studies show a wide range of NT-proBNP responses, and confirm that Prothena's response rate is anything but exceptional. Palladini et al 2010 measured patients' NT-proBNP levels at baseline and six months after initiating treatment. In this study, investigators found that the cardiac response rate measured six months after initiating treatment was 38% (43/113). In Palladini et al 2006, researchers found that cardiac response rate measured after three cycles of chemotherapy was 39%, with a median decline of 48% in NBT-proBNP among patients who saw a hematologic response. This is not surprising — as we show in this report, amyloid deposits resolve naturally once the source of the problem (malignant plasma cells producing misfolded FLC) is resolved and FLC levels are controlled. This is typically achieved through chemotherapy targeting the plasma cells.

Precedent radioimaging studies show that antibodies cannot treat amyloid deposits in the heart

> *What matters now, the biggest thing, is what happens in the heart and kidneys. If that epitope is present in the heart and kidneys, then that antibody that can image that or bind that is going to be the best therapeutic [option]. For our imaging study…if we knew they had amyloid in the heart or kidney…11-1F4 didn't image that. 11-1F4 didn't image cardiac amyloid. And that's not surprising to us — you might ask why, that's counterintuitive and strange, but when you think of the SAP imaging system, they can't image the heart. Again, you have this anomaly, this SAP agent that binds all amyloid in the body, it's in every deposit, but when you radiolabel it, you get beautiful images of the spleen, adrenals, liver, maybe a little kidney, but never the heart.*
>
> — Amyloidosis Researcher

> *SAP imaging has been around since the early 80's, and nobody knows why [SAP doesn't bind in the heart]…but when you take amyloid out of the heart, from a patient at autopsy, it's got SAP in it — so the ligand is there. It [amyloid antibody development] is complicated by the fact that there is no universality at all.*
>
> — Amyloidosis Researcher

NEOD001 is the third antibody designed to bind to amyloid deposits, and like its predecessors, we believe it has no effect on amyloid in the heart.

Radiolabeling is the process of labeling a substance (in this case, an antibody) with a radioactive tracer. In the case of amyloidosis, radiolabeling tells investigators if and where the antibody is binding to amyloid deposits. This is especially critical for developing antibodies for amyloidosis because, short of a placebo-controlled trial, it is the only way to know whether or not an antibody is hitting its targets.

Prothena has failed to publish any radiolabeling results — either because Prothena did not conduct a radiolabeling study or because the study yielded poor results. Like its Phase 1/2 trial results, the key information for investors is the data that Prothena has failed to give them. However, when looking at precedent antibodies that bind to amyloid deposits, we see that amyloid fibrils present a unique challenge that those antibodies failed to successfully address. As we show in a later section, there are likely multiple causes for this failure, and merely trying a different cryptic epitope (as Prothena is doing) does nothing to address any of them. Just as it is highly unlikely that Prothena has opted to keep positive trial results secret, it is also improbable that Prothena discreetly fixed this complex, multi-faceted problem and opted to not publicize or patent its discoveries.

There are two other amyloid antibodies for treating AL amyloidosis: 11-1F4 and GSK2398852. 11-1F4 is a chimeric antibody that targets a cryptic epitope (like NEOD001) and dates back to the late 1990's. GSK2398852 is an antibody that binds to serum amyloid P component ("SAP"),

a universal component of amyloid deposits and dates back to 1984. Published data has shown that neither of these antibodies are capable of binding to and removing cardiac amyloid deposits.

In 2010, a study was published on 11-1F4 (Wall et al 2010) showing that, while there was significant uptake of the drug in certain places, there was no apparent effect on the heart or kidneys:

> *Among 9 of 18 subjects, there was striking uptake of the reagent in liver, lymph nodes, bone marrow, intestine, or, unexpectedly, spleen (but not kidneys or heart)… those with cardiac or renal amyloid had no demonstrable uptake in these sites.*

In a 1990 NEJM publication (Hawkins et al 1990), researchers found that GSK2398852 (then referred to as an SAP antibody) uptake in the heart and kidneys was minimal. In one patient who died hours after imaging, 0.2% of the SAP antibody was found in the patient's heart. Given that the patient died from a pulmonary embolism, it seems highly probable that there was significant cardiac involvement. While renal involvement for this patient is not clear, the radiolabeled SAP antibody showed similar affinity to amyloid deposits there, with 0.26% of injected antibody found in the kidneys.

In a subsequent 2006 study (Bouke et al 2006), the investigators conducted another radiolabeled study of SAP antibody, where they enrolled 60 patients with AA amyloidosis, 80 patients with AL amyloidosis, and 27 patients with hereditary aTTR amyloidosis. There was no evidence of cardiac uptake of SAP antibody in **any** of those patients:

> *Our findings here further confirm that SAP scintigraphy is not suitable for evaluating myocardial amyloid, which was present clinically in many patients in this series.*

In Misdiagnosis of Hereditary Amyloidosis as AL (Primary) Amyloidosis, Lachmann et al reveal that even *in vitro* antibody staining of biopsies works less than half the time:

> *Immunohistochemistry is usually definitive in identifying or ruling out AA amyloidosis, but it frequently is not diagnostic with respect to AL amyloidosis. In our series, AL fibrils were identified by immunohistochemical staining in only 121 of the 316 patients with confirmed AL disease (38 percent). This reflects the failure of anti–light-chain antibodies to bind to light-chain fragments with an abnormal cross-β amyloid-fibril conformation and also reflects background staining of normal immunoglobulins in the tissues.*

These results are damning for both NEOD001 and Prothena's preclinical PRX004, which would be subject to the same problems with aTTR as NEOD001 is subject to with AL amyloidosis. Through discussions with experts and independent research, we believe that amyloidosis antibodies have performed poorly due to three primary factors that we will discuss in the next section. This scientific rationale coupled with the precedent antibody results and NEOD001's poor clinical results to date make us virtually certain that NEOD001 will fail its upcoming trials.

Amyloid fibril heterogeneity driven by light chain variation, organ-specific polymorphisms/occlusion, and proteolyzation combine to make clinical success impossible for NEOD001

> *There's one important thing to remember about primary amyloid disease, and I beat my medical students over the head with this…basically everyone who has light chain amyloid disease has a different underlying light chain. These clones are made randomly — so they don't have the same disease. They are molecularly unique. I'm not trying to second guess their [Prothena's] work although I'm pretty cynical about some of these studies. It's easy to measure light chain in the blood, but we can't tell you if it's a bad light chain or a good light chain, or if this light chain is going to give you kidney damage or that light chain is going to cause nerve damage…These primary amyloid people can have a host of manifestations because they are making different proteins. On a molecular, amino-acid basis, they are all different.*
>
> — Clinician/Amyloidosis Researcher

> *Amyloid is not just amyloid fibrils, there are lots of other proteins in amyloid deposits and they are contributed by the organ that the fibrils are in. So each amyloid deposit has organ-specific things added to it, and so when we take an antibody that stains kappa light chains and we have tissue from a patient that had amyloid systemically and we look at the liver, the spleen, the heart, the kidneys and they had the same amyloid in every organ from the same patient. We stained each of those tissues with the same antibody and only some of those tissues will light up. We find that the liver and spleen might light up but the kidney won't stain. Even within an individual, the heterogeneity of the deposits within each organ are remarkable. If you just accept all that as true, then the idea that you can find one drug or one antibody that can hit every amyloid in every patient, in every organ of that patient, statistically the chances of that happening are infinitesimally small.*
>
> — Amyloidosis Researcher

> *The proteolyzed fiber may have a different structure — the cryptic epitope may not be accessible and may not even be there.*
>
> — Biochemist/Amyloidosis Researcher

We have concluded that the principal reasons why NEOD001 will fail its trials are 1) the variation in misfolded light chain, 2) the occlusion of fibrils in organs, and 3) proteolyzation of amyloid deposits. NEOD001 is designed to target a single cryptic epitope which is purportedly revealed through protein misfolding. However, based on our research and discussions with industry experts, we believe that the variation in light chains and light chain folding makes the targeted epitope potentially nonexistent or not revealed, occlusion conceals the targeted epitope, and proteolyzation may degrade the targeted epitope. These explain the poor clinical results for NEOD001 and other antibodies targeting AL amyloid fibrils.

It is known that there is significant variation in amyloid fibrils. This makes targeting a specific antigen/epitope very challenging. Raffen et al 1999 described the diversity:

> *Human antibody light chains originate from a total of 30 to 40 κ and λ variable domain gene segments. Each of these gene segments serves as the progenitor of a family of related light chains that diversify by the accumulation of somatic mutations. Consequently, the primary structures of amyloidogenic and nonamyloidogenic light chains differ at numerous sites, and there is no single amino acid substitution or combination thereof that underlies a pathological propensity.*

Experts we spoke with believed that the heterogeneity in light chains and light chain mutations make AL amyloidosis impossible to successfully treat with a single antibody. One researcher who focuses on amyloidosis and is named on AL amyloid antibody patents had the following to say:

> *This disease is so heterogeneous that you cannot treat them like a population, you have to treat them like individuals…The way it presents and the way it works, it's [NEOD001 is] just not going to work. You cannot do it. One thing will not cure everyone.*

Other experts we spoke with agreed, and emphasized that a single antibody was highly unlikely to be able to successfully target the same antigen in AL amyloidosis because of the diverse nature of the amyloids *even in the same individual*.

The second scientific reason for why NEOD001 will not work is potential occlusion of the target epitope. A biochemist/amyloidosis researcher explained this problem:

> *It could be that within the [fibrils], the epitope becomes occluded again. It's not exposed in the native structure of the antibodies…You're probably aware of the phenomenon of amyloid polymorphism, that is, a given sequence of the protein can form a whole bunch of amyloid fibers that differ from one another in structure. The smallest unit of the fiber is called the protofilament, and that consists of two chains. That protofilament like a wire in a cable, can wrap around other protofilaments and there can be different numbers of protofilaments in different fibrils, and that is almost always the case in amyloid, that, you see some fibers are thinner, others are a little bit thicker, some are much thicker, those are amyloid polymorphs. What could be happening is that the epitope in some of these fibrils is now buried in a cable-like structure. It's a real complication in treating amyloid [diseases].*

It is also supported by literature which (as we discussed in the prior section) shows that even in patients where antibodies bound to amyloid fibrils in certain organs, they consistently failed to bind in the heart and kidneys. Based on this data, one could theorize that polymorphisms obstructing the epitope are common in the heart and kidneys — which are the key targets in Prothena's trials.

The third potential reason for why AL amyloidosis antibodies do not work consistently is the proteolyzation of amyloid deposits. While it has been shown that amyloid fibrils can be resistant to proteolysis *in vitro*, there is clearly regression *in vivo* (Tennent et al 1995). On the surface, natural regression of amyloid fibrils would seem like a positive for patients, but it can also make it more difficult or impossible for antibodies to bind to their target epitopes. Even ignoring the potential impact on NEOD001's epitope, we think that the natural regression of amyloid deposits poses a serious barrier to NEOD001 attaining clinical success because it raises the minimum efficacy required to demonstrate clinical success.

NT-proBNP declines following chemotherapy with established regimens and amyloid deposits resolve naturally, making clinical success difficult to attain even without NEOD001's incredible challenges

> *I had a patient with AL amyloidosis with severe cardiac problems. NT-proBNP was 3,000 or 4,000 — it was very, very high. I treated her, I'm not a cardiologist, but I treated her as a cardiologist would and her BNP went way, way down…What I'm trying to say is, you get improvement in BNP through established cardiac regimens. Her BNP went down by about 80%.*
>
> — Clinician/Amyloidosis Researcher

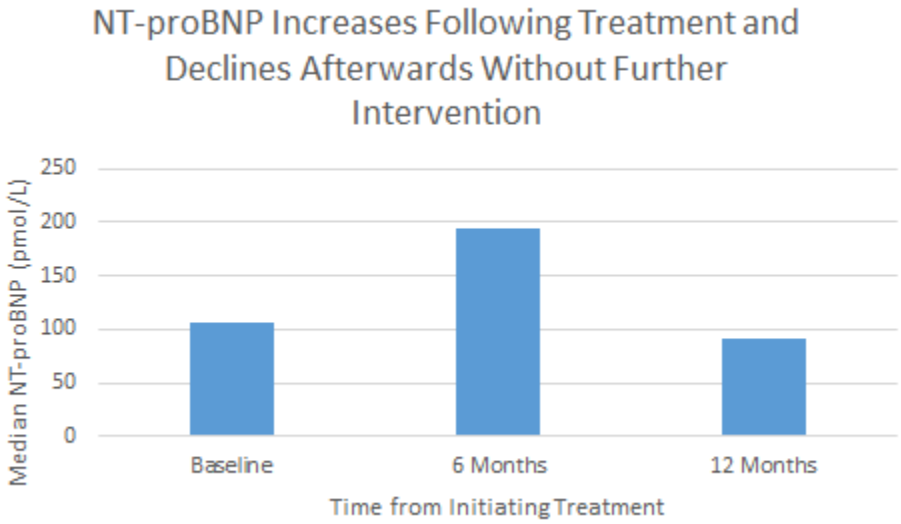
> *NT-proBNP goes up paradoxically with some treatments*
>
> — NEOD001 Principal Investigator

> *If you have a CR [complete response], organs will repair in 70-80% of patients, if you have a hematologic PR [partial response], organs will repair in 30-40% of patients…VGPR [very good partial response] is a new terminology so I don't know the statistics for VGPR. Having said that, the enrollment on the study was after 6 months [following] plasma cell dysplasia treatment…So the median time to enrollment was, I think, 6.5 months, but there were patients who were 2-3 months post chemotherapy regimen who were also enrolled in the trial. So my concern was that we were seeing the leftover effects of plasma cell dysplasia treatment.*
>
> — NEOD001 Principal Investigator

In order to succeed in its ongoing Phase 2b trial, Prothena must produce a statistically significant response rate (measured as a best response of ≥30% decline in NT-proBNP compared to placebo).

Published studies show that there are spikes in NT-proBNP levels following successful chemotherapy treatments for AL amyloidosis, followed by natural declines. These natural declines will pose added difficulty for Prothena in distinguishing its results from the control group. One particular study, Gibbs et al 2009, showed that median NT-proBNP measurements

taken six months after treatment increased by approximately 83%, and after another six months, the NT-proBNP levels declined in 92% of patients to a median value of 92 pmol/L. See below for a graphical representation of the results from Gibbs et al 2009:



Our discussions with practitioners and investigators in the NEOD001 clinical trials confirmed that the increase in NT-proBNP levels during — and decline in NT-proBNP levels following — chemotherapy treatment was a well-known phenomenon among AL amyloidosis patients. Prothena's final Phase 1/2 presentation shows that the median months since last treatment was 5.8 months. We believe that some percent of Prothena's observed best response rate was simply natural decline following the conclusion of chemotherapy.

Further, far from being an incurable condition, amyloid deposits are well-known to naturally resolve once FLC levels have dropped and the source of the problem (errant plasma cells) has been resolved or significantly reduced. It has been known since at least 1928[8] that amyloid deposits regress naturally once serum free light chains are normalized. This was conclusively shown to be true in Gameren et al 2009, a study which showed that significant natural declines in amyloid deposits were seen in patients, with approximately 50% of the complete responders group showing significant declines in amyloid deposits within one year after the start of chemotherapy and nearly all patients seeing significant declines in amyloid deposits within 3 years.[9]

[8] Waldenström, Henning. "On the formation and disappearance of amyloid in man." Acta Chir Scand 63 (1928): 479-530.
[9] Amyloid deposits evaluated on a graded scale

IV. Conclusion

NEOD001 is the most poorly understood “future blockbuster” drug currently pending pivotal results. NEOD001’s best response measure merely confirms what is already well-known: there is high variability in month-to-month NT-proBNP measurements among patients. Investors should ask themselves why a company would be so opaque with its clinical results and avoid releasing more detailed data. We did — and we found out that most who understand the science underpinning the drug are skeptical of Phase 3 success. The heterogeneity of AL amyloidosis combined with organ-specific occlusion and amyloid proteolyzation have made other amyloid antibodies fail to work in practice, and NEOD001 will be no exception. Prothena management’s data smokescreen may have temporarily fooled investors but will not protect anyone from the enormous and inevitable downside from NEOD001’s Phase 2b and Phase 3 failures.

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