Proteostasis Therapeutics, Inc. (PTI)
Don't Hold Your Breath

We are short shares of Proteostasis Therapeutics, a clinical-stage biopharmaceutical company whose lead drug, PTI-428, aims to treat the genetic disorder cystic fibrosis. Proteostasis claims that the drug works in a unique way, by somehow increasing the levels of messenger RNA and protein corresponding to the so-called CFTR gene that is dysfunctionally mutated in people with the disease and that gives rise to its ultimately fatal symptoms.

In December, Proteostasis released results from a small Phase 2 proof-of-concept clinical trial, supposedly showing that PTI-428 meaningfully improved lung function relative to placebo. On the back of these results, the company announced last week that the FDA had granted it "breakthrough therapy" designation, a relatively minor development that nonetheless sparked a ~100% spike in the company's stock price. Over the following five trading days, Proteostasis's entire share count turned over more than twice, strongly suggesting an influx of new and potentially uninformed investors. The company quickly capitalized on this surge by announcing a nine-million share public offering last night – apparently as eager to sell shares at recent prices as we are.

Contrary to Proteostasis's hype, we believe that its Phase 2 results are far less meaningful than they appear. The main reason that PTI-428 looks good is not that patients who received it performed unusually well but that the *four* placebo patients to whom they were compared performed unusually poorly. Judged by a more reasonable benchmark, PTI-428 seems to do little – echoing an earlier, more obviously disappointing Phase 1 trial in which the drug yielded no statistically significant improvement in lung function.

While Proteostasis touts changes in CFTR mRNA and protein levels as key signals that PTI-428 is working as intended, closer inspection reveals a wide range of data-quality problems and red flags, such as the absence of consistent dose-response relationships. Given the scarcity of CFTR mRNA and protein even in the airway epithelium, we doubt that Proteostasis can reliably measure its favored biomarkers, calling into question its fundamental understanding of its own drug. Indeed, we find it difficult to trust the company's data, given its tendency to gloss over potentially negative facts. For instance, while a group of partially independent researchers have recently found that, in one *in vitro* model, PTI-428 failed to increase CFTR protein levels or functionality to a statistically significant degree, either on its own or when added to standard-of-care drugs, Proteostasis management has ignored the unpleasant results, even though three Proteostasis employees were co-authors on the paper.

With an ineffective lead drug and unpromising pipeline, Proteostasis has little value; we estimate 70-90% downside, based on cash per share. There is little value in PTI's misleadingly spun data, bizarrely noisy biomarkers, and selectively disclosed results. Alas, it's far easier to inflate weak data than it is to inflate ailing lungs.

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I. Investment Highlights

Clinical data show that Proteostasis's lead drug is ineffective. The apparent success of PTI-428 in its small Phase 2 proof-of-concept trial stems almost entirely from the anomalously bad performance of the 4-person placebo group, while, on average, patients taking PTI-428 barely improved. With larger, more representative placebo groups in future trials, we believe the illusion of PTI-428's efficacy will disappear; after all, the drug already failed to deliver statistically significant efficacy results in an earlier trial. Beyond measures of lung function, PTI-428, unlike effective cystic-fibrosis drugs, has failed to meaningfully improve sweat-chloride concentrations. Meanwhile, other clinical measures that Proteostasis at one point planned to study, like patient-reported health satisfaction, have mysteriously vanished from the discussion, perhaps because the company didn't like the results it got.

Proteostasis claims that its drug works by increasing levels of CFTR mRNA and protein, but its attempts to directly measure changes in these scarce substances have yielded extremely noisy and unreliable data, replete with inverted or nonsensical dose-response relationships (i.e., low-dose or even placebo patients experiencing greater "improvements" in these metrics than high-dose patients). The company has also alluded to problems with biomarker quality control and the need to discard "outlier" values for unexplained reasons, raising serious questions about just how much investors should trust any of its results.

The case of the missing trial and other data mysteries. We believe Proteostasis has a habit of sweeping unpleasant or confusing findings under the rug. Suspiciously, a 14-day, 16-patient trial of PTI-428 combined with another cystic-fibrosis drug, originally projected to read out in 3Q 2017, was quietly shifted to 1Q 2018, only to disappear from the company's recent investor presentations and earnings releases as the first quarter draws to a close. What happened to this trial, and why hasn't the company already explained it?

Similarly, Proteostasis has failed to reckon with the unsettlingly weak results of a recent *in vitro* study of PTI-428 conducted by a semi-independent team of researchers. These researchers found that, in a cell-culture model of cystic fibrosis, PTI-428 only increased CFTR mRNA to a "modest degree" and did *not* appear to increase CFTR protein; even when combined with standard-of-care drugs, PTI-428 did not confer a statistically significant improvement in CFTR protein quantity or channel function. These null results fly in the face of Proteostasis's claims about how its drug ought to work but support our view that, whatever it might do in the company's labs, the drug does little of value in the real world.

II. Company Overview

Proteostasis Therapeutics: Capitalization and Financial Results						
Capitalization			**Financial results ($ mm)**			
				2015	2016	2017
Share price ($)		$6.99				
Fully diluted shares (mm):			Revenue	$ 4	$ 8	$ 5
Shares outstanding		34.5	Net income	(25)	(37)	(59)
Dilutive impact of options		0.5	Free cash flow	(20)	(42)	(53)
Total		34.9	Capital raised*	27	125	46
Fully diluted market cap ($mm)	$	244	Cash†	14	86	74

Source: company filings, Kerrisdale analysis
* "Capital raised" includes gross proceeds from 2015 issuance of convertible preferred stock and convertible promissory notes and 2016-17 issuance of common equity.
† "Cash" includes cash and cash equivalents and short-term investments.

Founded in 2006, Proteostasis began as a broad effort to develop drugs to combat dysfunctional protein processing and regulation. After years of largely fruitless effort, in 2013 the company made what it now regards as a "breakthrough discovery": a novel type of treatment for cystic fibrosis.[1]

Cystic fibrosis is a genetic disease in which people harboring certain mutations of a single gene produce misfolded or otherwise defective forms of a protein known as CFTR, a chloride channel that, among other things, allows the mucus in the airway to remain properly hydrated. Defective CFTR molecules give rise to thick mucus that fosters the growth of pathogens, triggers chronic inflammation, and severely damages the lungs, ultimately leading to death. A rare disease (with only 70,000 victims worldwide), cystic fibrosis defied attempts at addressing its root cause until the advent of Vertex Pharmaceuticals' drug ivacaftor, a small molecule that enables some forms of mutant CFTR to work better once they're embedded in the cell membrane. Unfortunately, patients with the most common form of cystic fibrosis, caused by having two copies of the F508del allele,[2] don't have much membrane-bound CFTR to work with, because the misfolded F508del protein is recognized as faulty by quality-control machinery in the cell and quickly destroyed before it can make its way to the membrane. Thus ivacaftor, on its own, only benefits a very small minority of cystic-fibrosis patients.

However, Vertex went on to develop a second drug, lumacaftor, that helps the F508del-CFTR protein escape destruction and reach the membrane, where ivacaftor can then enhance its (still impaired) ability to act as a chloride channel. This combination of lumacaftor and ivacaftor, marketed under the name Orkambi, is now the standard of care in cystic fibrosis, although some complain about its high cost and modest efficacy (1).

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[1] Proteostasis investor presentation, August 2016, slide 4.
[2] Referred to in some sources as Phe508del or ΔF508.

While several companies, including Vertex itself, are hard at work developing new and improved versions of drugs like ivacaftor (known as potentiators), drugs like lumacaftor (known as correctors), and complex combinations thereof, Proteostasis claims to have created something entirely different: an amplifier. In the company's own words, "[a]mplifiers, which include [its lead drug] PTI-428, are CFTR modulators that selectively increase the amount of newly synthesized unfolded form of CFTR protein, thereby providing additional substrate for other CFTR modulators, such as correctors and potentiators, to act upon."[3] Based initially on its own *in vitro* studies, Proteostasis says that its amplifier drug causes CFTR mRNA and protein to proliferate, supplying enough fuel that, when added to, say, Orkambi, it might fully return patients' lung function to normal.

That's the theory, at least – and it was enough to get Proteostasis's IPO done in February 2016, albeit at a share price 38% lower than initially projected. After a series of clinical-trial delays and disappointing data points, though, Proteostasis lost much of its market value by late 2017, as its share price dipped below $2 (75% less than the IPO level). In December, however, seemingly positive results from a Phase 2 proof-of-concept trial temporarily revitalized the stock, taking it back up to a price of ~$6 – but only briefly, as disappointment appeared to gradually creep back in, driving the price once more toward $2. Last week, however, Proteostasis enjoyed an experience of déjà vu, as its announcement that it won the FDA's "breakthrough therapy" designation, itself the result of the same Phase 2 data from December, led to another price spike. The market is evidently regaining its faith in Proteostasis's approach. But a close look at what the company has actually reported – as opposed to the stories it has told – reveals that its entire "amplifier" concept – the linchpin of its valuation – is likely bogus.

III.   Clinical Data Show that Proteostasis's Lead Drug Is Ineffective

Standard Endpoints

When Proteostasis disclosed results from its Phase 2 study of the "amplifier" PTI-428, the focus was on a standard measure of lung function: percentage of predicted FEV_1, or $ppFEV_1$. "FEV_1" refers to forced expiratory volume over the course of one second, i.e. the quantity of air one can exhale during a forced breath lasting that long. Using standard benchmarks, doctors can establish predicted FEV_1 based on factors like age and height. Dividing a patient's actual measured FEV_1 by his or her predicted FEV_1 yields the standardized metric $ppFEV_1$, which eases comparison across patients. Since cystic-fibrosis patients suffer from progressive lung deterioration that impairs their ability to exhale relative to healthy people, their $ppFEV_1$ values fall well below 100%, typically in the range of 40-70%. Recent high-profile cystic-fibrosis clinical trials have largely aimed to demonstrate improvements in $ppFEV_1$, which can themselves be

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[3] Proteostasis 2017 10-K, p. 1.

quantified in two ways: absolute changes expressed in percentage *points* or relative changes expressed in percentages. For example, a patient whose ppFEV$_1$ goes from 65% to 70% has improved by 5 percentage points in absolute terms and ~7.7% (= 70/65 − 1) in relative terms.
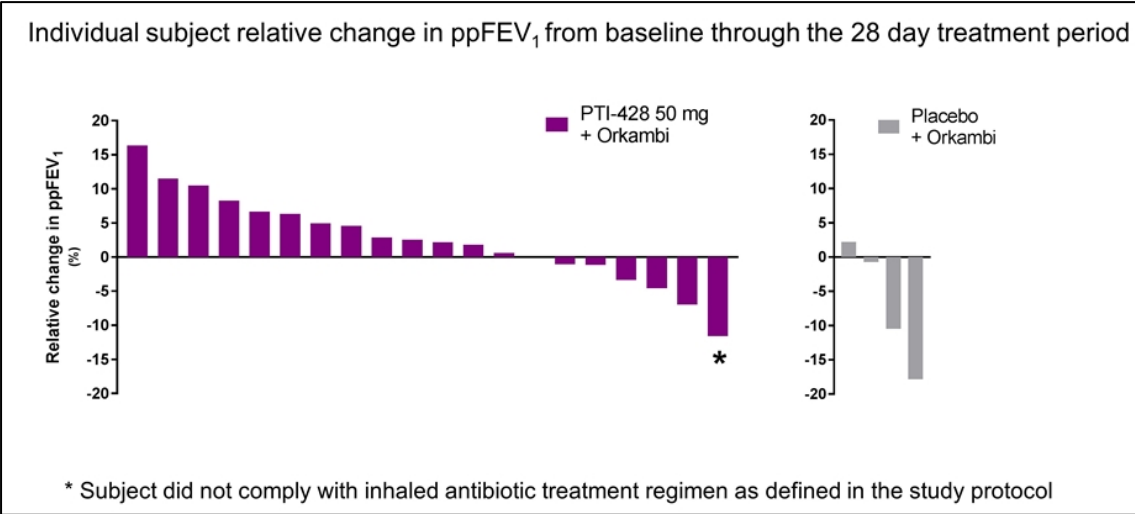
With this terminology in mind, we turn to Proteostasis's results. In a 28-day trial enrolling cystic-fibrosis patients already taking Orkambi (and staying on it), Proteostasis compared 20 patients who added the "amplifier" PTI-428 to their regimen with 4 – yes, 4 – patients who added placebo. Proteostasis summarized the main efficacy endpoint as follows:

> The addition of PTI-428 to Orkambi® demonstrated mean absolute improvements in ppFEV1 of 5.2 percentage points from baseline compared to placebo (p<0.05), with mean relative improvements of 9.2 percent (p<0.05). This treatment effect was achieved by day 14 and sustained through 28 days of dosing.

Though a 5-percentage-point change may not sound like much, it would constitute a meaningful improvement, especially on top of a drug like Orkambi that is already known to work; moreover, Proteostasis claims it was statistically significant at the 5% level. Notwithstanding the usual caveats about small sample sizes, Proteostasis thus treated this 5-point improvement as a decisive vindication of PTI-428, and the market has followed along.

But, to our knowledge, Proteostasis has only directly stated the observed improvement of PTI-428 patients *relative to placebo patients;* it has not separately stated how well each group did on its own. However, individual patient data that the company has only disclosed in graphical form enables us to do the math ourselves, uncovering a much less inspiring picture. Below we reproduce Proteostasis's graph of *relative* changes in ppFEV$_1$, followed by our estimates of the underlying numbers. On average, we calculate that the PTI-428 group improved by just 2.5%, while the (4-person) placebo group *worsened* by 6.7% – exactly replicating Proteostasis's stated placebo-adjusted relative improvement of 9.2%. In terms of absolute changes, we estimate that the PTI-428 group improved on average by just 1 percentage point, while the placebo group *worsened* by 4 percentage points. While this reconciles to the same net 5-point improvement reported by the company, the breakdown puts the data in a different light. The PTI-428 group didn't see its ppFEV$_1$ values noticeably increase; an average 1-point move across 20 patients is negligible. Instead, the unlucky 4-person placebo group saw its average tank, driven by just 2 individuals. The results that the market has celebrated don't show a highly effective drug; they show an anomalously bad placebo. But this fluke is unlikely to repeat in future, larger trials, suggesting that the illusion of PTI-428's efficacy will eventually vanish.

PTI-428 Phase 2 Data:
Appearance of Superiority Driven by Anomalously Poor Placebo Group

Individual subject relative change in ppFEV$_1$ from baseline through the 28 day treatment period

* Subject did not comply with inhaled antibiotic treatment regimen as defined in the study protocol

Kerrisdale estimates of underlying figures

PTI-428 50 mg		Placebo	
	ppFEV$_1$		ppFEV$_1$
Patient #	rel. Δ	Patient #	rel. Δ
1	16.4%	1	2.1%
2	11.5%	2	-0.7%
3	10.4%	3	-10.4%
4	8.2%	4	-17.7%
5	6.7%		
6	6.3%		
7	4.9%		
8	4.5%		
9	2.9%		
10	2.5%		
11	2.1%		
12	1.8%		
13	0.6%		
14	0.1%		
15	-1.1%		
16	-1.1%		
17	-3.4%		
18	-4.6%		
19	-6.9%		
20	-11.6%		
Average	2.5%	Average	-6.7%

Source: Proteostasis December 2017 investor deck, slide 15; Kerrisdale analysis

By contrast, consider several other recent cystic-fibrosis trials that measured changes in $ppFEV_1$. In all the cases shown below, patients in the placebo groups on average experienced only small moves in $ppFEV_1$, typically less than 1 percentage point. Indeed, we have yet to come across a comparable placebo group with worse results than Proteostasis's.

Illustrative Examples of ppFEV₁ Data from Placebo Groups in Cystic-Fibrosis Trials			
	Placebo group		
Trial description	$ppFEV_1$ abs. Δ (% points)	# of patients	Reference
luma+iva in F508del/F508del (pooled data)	-0.3	371	(2)
teza+iva in F508del/F508del	-0.6	256	(3)
cavosonstat in F508del/F508del	+1.0	46	Nivalis press release
GLPG2222+iva in Class III/F508del	-0.8	7	Galapagos press release
Source: Kerrisdale analysis			

Likely anticipating the complaint that PTI-428 only appears effective in comparison to an anomalously bad placebo group, Proteostasis has gone out of its way to emphasize that, even while on Orkambi, cystic-fibrosis patients "continue to experience lung function decline"[4] – perhaps hoping to convince investors that the observed deterioration in the placebo group is meaningful after all, not just noise. However, the long-term study that Proteostasis cites indicated that Orkambi patients experienced ongoing declines in $ppFEV_1$ at a slow rate of just ~1.3 percentage points per year (4). Given that Proteostasis's Phase 2 study took place over just 28 days, or ~0.08 years, the expected background decline in $ppFEV_1$ would be just 0.1 percentage points over the period, again emphasizing the unusualness of Proteostasis's 4-point decline.

With small sample sizes, though, strange things can easily happen. Even for an individual patient, $ppFEV_1$ values can fluctuate substantially from month to month without any apparent change in underlying health. One long-term study of a high-quality registry of 479 Danish cystic-fibrosis patients with 70,448 aggregate monthly $ppFEV_1$ values found "an average [standard deviation] of 6.3% for repeated [$ppFEV_1$] measures on the same individual at short term intervals" (5).[5] As a result,

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[4] See e.g. March 2018 investor deck, slide 15.
[5] Another, even more recent study similarly quoted an estimated standard deviation for 28-day changes in $ppFEV_1$ of 6.5% (6).
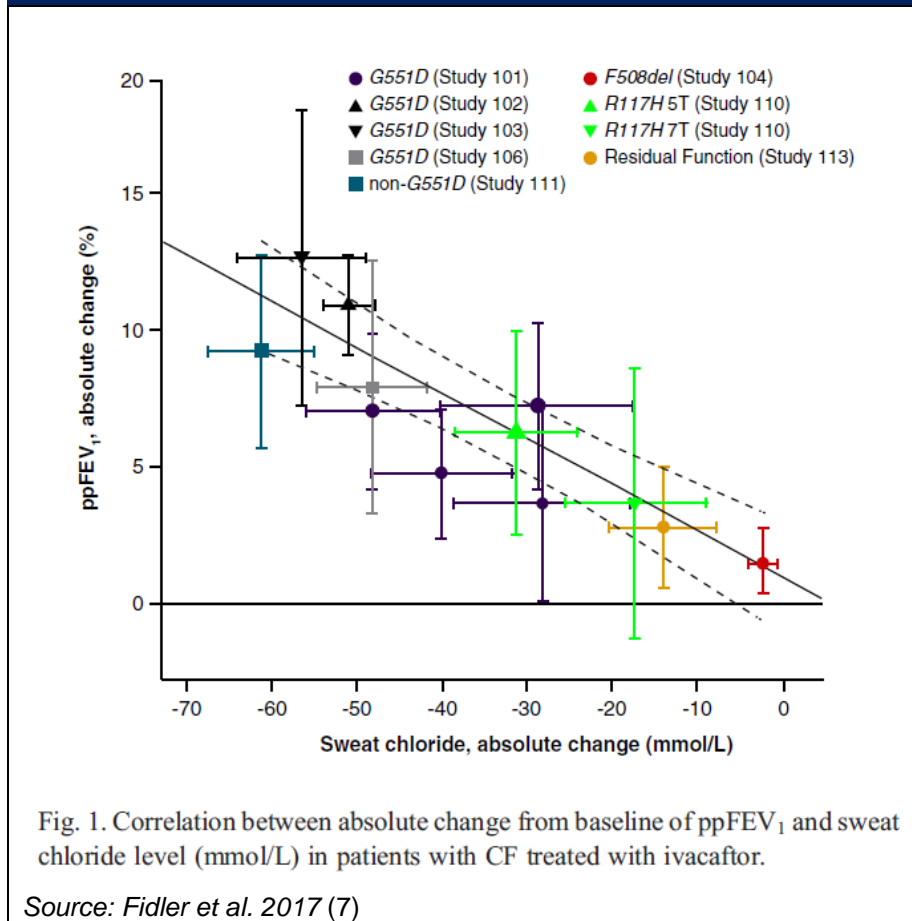
this study implies that on average a change in %FEV_1 of >13% (ie, twice the error SD to give a 95% confidence range) is likely to represent true within-patient variation over time (disease progression), whereas anything less than this could be due to short-term fluctuation, which may recover. (5)

Given that even 13% relative moves in $ppFEV_1$ can easily appear by chance, the small average improvement seen in the 20-person PTI-428 group in the Phase 2 trial is clearly nothing to get excited about, while the unusually large average decline in placebo-group $ppFEV_1$ was probably just pure randomness. Overall, then, the trial results don't depict an effective new add-on to the standard of care, as Proteostasis would have it; rather, they depict a dud that got lucky with an easy comparison.

Moving beyond the likely misleading $ppFEV_1$ data, there is little else to suggest that PTI-428 has much clinical effect at all. Proteostasis has disclosed that, in the Phase 2 trial, changes in the concentration of chloride in patients' sweat – a common indirect measure of cystic-fibrosis disease severity that a group of prominent researchers recently said "may be the most sensitive and best currently available direct biomarker measure for CFTR systemic modulators" (6) – "did not correlate with changes in lung function." While Proteostasis attempts to downplay this null result by pointing to clinical trials of effective cystic-fibrosis drugs that similarly failed to find a correlation between lung-function changes and sweat-chloride changes *at the level of individual patients,* this argument misses the point. Vertex's drugs, for instance, *do* reduce sweat chloride concentrations on average; it's just that, within a given trial, the patients with the largest improvements in sweat chloride are often not the same as those with the largest improvements in lung function. In fact, looking across study populations (as opposed to individual patients), Vertex researchers have recently shown a robust correlation linking sweat chloride to lung function, as shown below. (They also find a statistically significant, albeit modest, correlation at the individual level after pooling patients from multiple studies.)

We suspect that Proteostasis's refusal to disclose the average change in sweat chloride concentration for the PTI-428 and placebo groups in the Phase 2 trial likely means that any change was either negligible or in the wrong direction; if the data made PTI-428 look good, they would probably have reported it from the start rather than talking exclusively about the absence of correlation with lung function. But since, Proteostasis's protests to the contrary, sweat chloride remains a well-regarded signal of cystic-fibrosis treatment efficacy, the apparent absence of this signal for PTI-428 offers more evidence that the drug is ineffective.

Changes in Sweat Chloride and Changes in Lung Function *Are* Correlated across Studies

Fig. 1. Correlation between absolute change from baseline of ppFEV$_1$ and sweat chloride level (mmol/L) in patients with CF treated with ivacaftor.

Source: Fidler et al. 2017 (7)

In fact, it should come as no great surprise that PTI-428 is ineffective; earlier Phase 1 data told a similar story. In a shorter, 7-day trial of PTI-428 plus background Orkambi, Proteostasis admitted that "there was no significant improvement of FEV$_1$ compared to placebo, although there was a numerical increase in FEV$_1$ at day 7."[6] Nor was this non-significant "numerical increase" uniform, let alone large: the company reported that "[a]pproximately 60% of subject on Orkambi who received PTI-428 [i.e. 5-6 out of 9[7]] saw a modest improvement in FEV1."[8] In other words, in Phase 1, PTI-428 plus Orkambi was associated with at best "modest" improvements in lung function in little more than half of the patients, to a non-statistically-significant degree. While the absence of statistical significance might not mean much given the small sample size, the "modest" (and numerically unspecified) nature of the improvements and their narrow reach again suggest a fundamentally unimpressive drug. In addition, "[m]easurements of sweat choride…were used as exploratory biomarkers but the changes were

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[6] Proteostasis 2017 Q2 10-Q, p. 18.

[7] See Proteostasis 2017 Q2 10-Q, p. 18: 11 subjects in the Orkambi + PTI-428 cohort, of which 2 are placebo subjects, leaving 9 PTI-428 subjects.

[8] Proteostasis 2017 Q3 investor presentation, slide 27.

not significant nor correlated with lung function changes."[9] In both Phase 1 and Phase 2, then, once we set aside the hype, we observe the same thing: a supposed "amplifier," pitched as possessing the ability to elevate Orkambi to new heights, instead delivering results that look like more of the same. The only difference is that, in Phase 2, the unlucky placebo group fortuitously allowed Proteostasis to obscure PTI-428's weakness.

A final clue as to the drug's ineffectiveness comes not from what Proteostasis *has* reported but from what it hasn't. Looking at the database record for the Phase 1 and 2 trials on ClinicalTrials.gov reveals a host of secondary and other outcomes that Proteostasis either planned to record but didn't – or recorded and hasn't disclosed. Either way, investors don't have the data. For instance, one such outcome is "change in CFQ-R over time." CFQ-R refers to the Cystic Fibrosis Questionnaire-Revised, a standard instrument for assessing health-related quality of life in cystic-fibrosis patients. At least one of Proteostasis's competitors, ProQR Therapeutics, has tracked a component of CFQ-R as part of its own clinical development program.[10] Looking at its past SEC filings, we see that Proteostasis used to be a believer too. In its 2015 10-K, it said, regarding its then planned Phase 2 clinical trials of PTI-428, "We expect that the secondary endpoints will be to determine the efficacy of PTI-428 including its effect on FEV1, sweat chloride (SC) and **patient reported outcomes (CFQ-R)**" (emphasis added).[11] The 2016 10-K used identical language,[12] but the 2017 10-K dropped any reference to CFQ-R. What happened to this endpoint?

Similarly, ClinicalTrials.gov lists change in weight over time, change in fecal elastase over time, and change in fecal calprotectin over time as outcomes to be measured in the Phase 1 and 2 trials – all of them potential biomarkers of cystic-fibrosis disease severity that an effective drug would hope to influence. Were these outcomes actually measured? If not, why not? If so, what were the results? In light of what we regard as the company's mishandling of data in other areas, as discussed further below, we find it difficult to have faith that Proteostasis is telling investors the whole story.

Specialized Biomarkers

Beyond standard measures like ppFEV$_1$, Proteostasis has emphasized its own preferred biomarkers – CFTR mRNA and protein levels, as measured in patients' nasal epithelial cells – which it claims reflect PTI-428's unique "amplifier" mechanism of action. If PTI-428 is working as Proteostasis says it should, then it ought to cause increases in CFTR mRNA and CFTR protein that in turn give rise to clinical benefits like improved ppFEV$_1$. In reality, though, Proteostasis's

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[9] Proteostasis 2017 Q2 10-Q, p. 18.
[10] See e.g. "ProQR Announces Positive Top-Line Results from a Phase 1b Study of QR-010 in Subjects with Cystic Fibrosis," September 25, 2017.
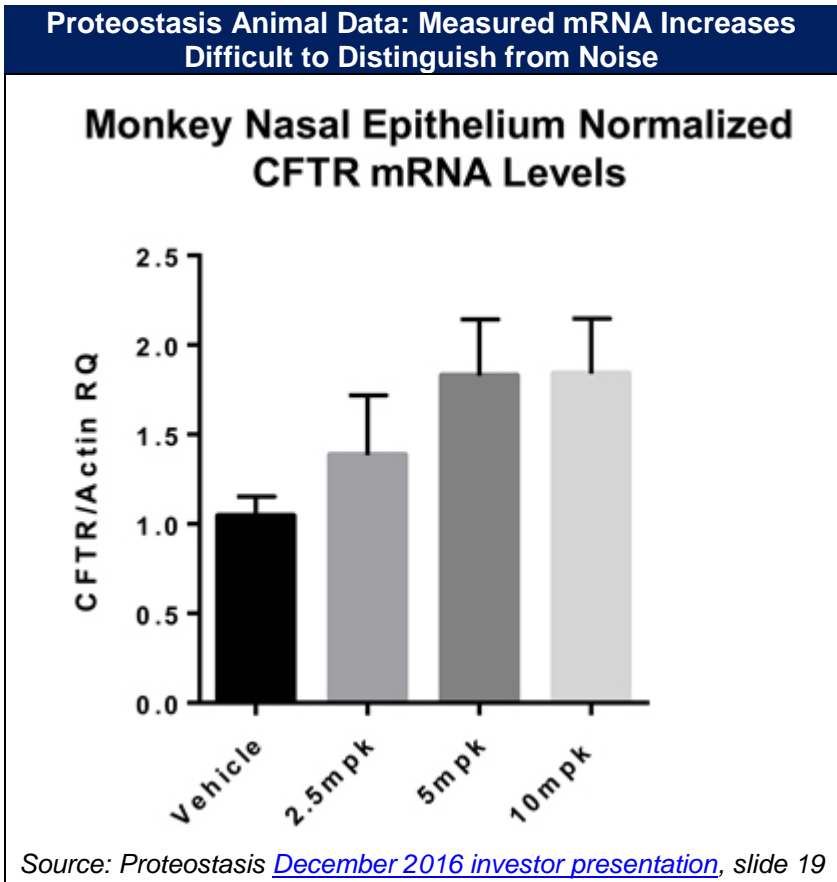[11] Proteostasis 2015 10-K, p. 14.
[12] Proteostasis 2016 10-K, p, 17.

specialized biomarker data are hopelessly garbled, casting further doubt on both PTI-428's efficacy and the reliability of the company's other stated results.

To begin with, it's important to recognize that CFTR protein and mRNA alike are *rare* and thus inherently difficult to measure. A 2014 paper, for instance, highlighted the many shortcomings of the conventional method of quantifying such a "low-abundance" protein, noting that the method's "reproducibility, precision, accuracy, and robustness…are less than ideal" (8). Multiple groups of researchers have made similar remarks about CFTR mRNA. A 1991 paper concluded that "CFTR mRNA transcripts are expressed in nasal, tracheal, and bronchial epithelial cells at ≈1-2 copies per cell," with no difference in expression between healthy individuals and cystic-fibrosis patients (9). Later researchers made similar findings, noting that "*CFTR* mRNA detection and measurement are extremely difficult because of the low to very low levels of its endogenous expression" (10). Indeed, even when analyzing more abundant, less challenging mRNA molecules, researchers often distrust measured changes that are less than two-fold in magnitude, regarding them as likely the product of measurement error and noise.[13] Proteostasis itself began to acknowledge these problems in December 2016, when it added to one of its earlier graphs of mRNA changes over time a large gray bar showing "the noise of the assay" and noted that "an increase in mRNA up to 1.5x considered within the noise of assay" (slide 24). While it's not clear which specific assay the company meant, the problem is that, by this standard – let alone the more stringent two-fold standard adopted by many researchers (see footnote 13) – most of Proteostasis's own mRNA results should be regarded as noise.

Consider, for instance, the company's mRNA animal data. After dosing monkeys with different concentrations of PTI-428 for 24 hours, Proteostasis claimed a modestly positive dose-response relationship, with higher drug concentrations giving rise to more mRNA. However, all the observed changes were less than 2-fold increases, and the company apparently does not even claim that the reported differences across concentration levels are statistically significant. Thus these superficially interesting data might as well be noise.

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[13] For example, on a Research Gate forum thread, one member set off a lively debate by asking "How small of a 'fold-change' in gene expression can be reliably measured by RT-qPCR?...[C]an differences that are less than at least two-fold be taken as credible?" Similarly, a lecture on bioinformatics supplied a simple rule of thumb for analyzing gene expression: a fold change of more than 4 (i.e. >4x increase or decrease) is "very interesting," while a fold change of less than 2 is "not interesting" (slide 7). Most of the changes in mRNA levels that Proteostasis has reported would therefore be categorized, under this scheme, as "not interesting."

Proteostasis Animal Data: Measured mRNA Increases Difficult to Distinguish from Noise

Monkey Nasal Epithelium Normalized CFTR mRNA Levels

Source: Proteostasis December 2016 investor presentation, slide 19

In humans, during the single ascending dose (SAD) portion of the Phase 1 trial (shown below), two of the doses tested never made it outside of "the noise of the assay," while the 100 mg dose (double what was used in the Phase 2 proof-of-concept trial) bizarrely seemed to spike mRNA levels by ~4x within 8 hours, only to drop back to "noise" levels by 24 hours, then supposedly rebound up another ~33% within the next two days, *even as the concentration of PTI-428 in the patient's bloodstream rapidly dwindled to nothing*. This pattern makes no sense: the reason Proteostasis is directing patients to take PTI-428 once a day, after all, is that it believes the drug needs to be continuously present to induce its allegedly positive effects. Large apparent swings up and down in mRNA levels in the absence of meaningful PTI-428 concentrations simply serve to demonstrate how noisy and meaningless these measures can be.

Similarly, while patients on 30 mg of PTI-428 (60% of the Phase 2 dose) saw their CFTR mRNA actually *decline* by 50% within 8 hours, placebo patients taking no drug at all saw their mRNA levels *increase* by 50% – actually rising just above the Proteostasis-defined noise zone. If patients on placebo can "improve" their mRNA levels by >50% just by chance, there's little reason to attribute fluctuations of similar size to the power of PTI-428 as opposed to pure chance. Note that the single-ascending-dose study also examined an even higher dose of 300 mg, other data for which is reported elsewhere[14] – yet, to our knowledge, Proteostasis has

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[14] See Proteostasis investor presentation, January 2017, slide 25, left graph: there is clearly a data point for a 300mg dose.

never reported data on the changes in mRNA levels induced by this high dose. Perhaps, we speculate, the company does not want to disclose such data because they further underscore the murkiness and unreliability of its mRNA measures, possibly by showing smaller increases despite a higher dose.

*Source: Proteostasis December 2016 investor presentation, slide 24*
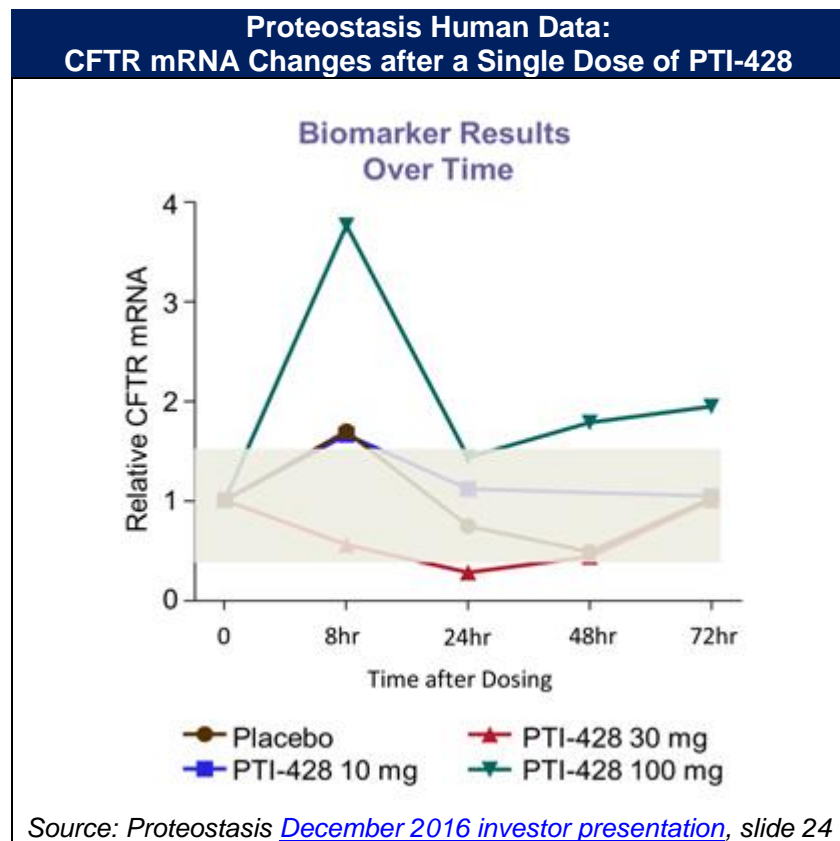
The mRNA problems continued in the multiple-ascending-dose study, in which patients took multiple daily doses of PTI-428 rather than just one. In a presentation of preliminary results, Proteostasis quietly noted that "two outliers [one in the 20mg dose group and one in the 50 mg group] were removed from analysis"[15] without explaining why – another indication of underlying problems with data collection.

When completed results were later released,[16] the pattern again looked strange, as shown below. While the highest dose tested, 150 mg, did appear to increase CFTR mRNA levels, the increase was far slower and far smaller than the 8-hr 4x spike seen with the lower 100 mg in the single-ascending-dose data above. For an effective drug measured in a meaningful way, this would make no sense: how could 100 mg taken just once have a much larger effect than 150 mg *taken once a day for seven days?* Meanwhile, the dose actually used in Proteostasis's supposedly successful Phase 2 study – 50 mg – appeared to *reduce* CFTR mRNA levels by almost 50% and, at day 7, produced worse results than any other groups, including patients on

[15] Proteostasis December 2016 investor presentation, slide 25.
[16] Proteostasis investor presentation, January 2017, slide 24.

placebo, though Proteostasis's difficult-to-read graph makes it somewhat challenging to figure out which group is which.

Proteostasis Human Data:
CFTR mRNA Changes with Multiple Doses of PTI-428

Source: Proteostasis December 2016 investor presentation, slide 24
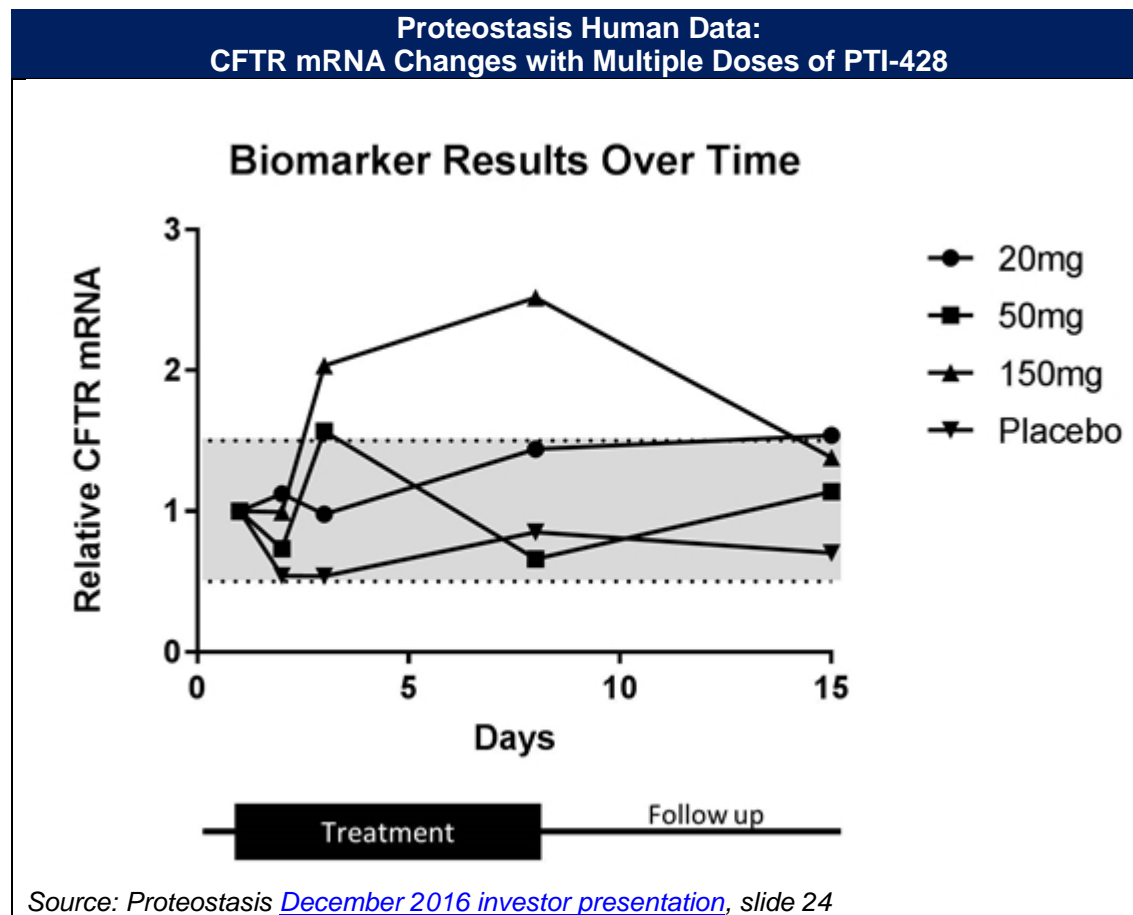
What about the much vaunted Phase 2 trial, in which PTI-428 was supposedly vindicated? Strangely, Proteostasis made no mention of mRNA data in its initial press release disclosing the results, nor in subsequent presentations (except to show *baseline* CFTR mRNA levels, not changes over time). This is a curious omission: after all, Proteostasis is the one insisting that changes in mRNA signal the efficacy of its drug, so why are there no data points to offer? We speculate that the company doesn't want to distract from its seemingly strong ppFEV$_1$ data with yet another noisy and hard-to-interpret mRNA chart, especially if it happens to show an absence of robust increases, let alone an anomalous decline like the 50mg dose previously produced.

Turning from CFTR mRNA to CFTR protein, Proteostasis's data are little better. While the company did disclose some data on protein levels from its Phase 2 trial, they raise more questions than they answer. On average, in Phase 2, the 50mg dose apparently did increase protein levels by 88 ng/mg on average – yet *double the dose,* in an earlier trial, barely moved CFTR protein levels at all, with the average increasing on 19 ng/mg and the median essentially unchanged. In addition, Proteostasis did not report protein levels at specified time points, as the data would normally be presented; instead, it reported the "max response during treatment,"

which would tend to magnify the impact of random fluctuations[17]. It's also interesting to note that, after 28 days on PTI-428 and Orkambi, patients' lung function was still, of course, dramatically below normal, with an average ppFEV$_1$ of ~59%,[18] while, by Proteostasis's measure, their CFTR protein levels were actually *above* the median of a group of healthy volunteers. Indeed, even at *baseline,* the median CFTR protein level in the PTI-428 group in the Phase 2 trial – a group of cystic-fibrosis patients – was almost the same as the median among healthy volunteers. In other words, mere measured protein quantity doesn't seem to convey much useful information about patients' conditions. Having the same amount of CFTR protein as a healthy individual doesn't lead to dramatically improved outcomes, and healthy individuals themselves demonstrate a wide range of protein levels, all apparently consistent with normal lung function. But if higher protein levels don't give rise to substantially improved helath, Proteostasis' entire "amplifier" concept becomes irrelevant.

Earlier Phase 1 protein data are no less befuddling. In fact, as with the mRNA data, the fine print hints at operational problems. One footnote disclosed that the "[b]iomarker analysis is based on **70% nasal samples that met QC criteria** for the CFTR ELISA collected from all 19 CF subjects."[19] This seems to imply that 30% of the samples had to be discarded because they were too low-quality. A separate disclosure, referring to a study in healthy volunteers, noted that "[a]ssessment of CFTR protein changes was not made due to a small number of clinical samples passing the quality control criteria."[20] Proteostasis's fundamental scientific rationale for PTI-428 is that it can help patients by increasing levels of CFTR protein, yet the company cannot even reliably measure this quantity.

Indeed, the Phase 1 protein data that *did* make it through Proteostasis's quality checks are so bizarre that one can only imagine how bad the faulty data was. Tellingly, rather than directly report changes in protein day by day, as one would expect, Proteostasis chose to average the numbers across two separate sub-periods (a 7-day treatment period on PTI-428, PTI-428+Orkambi, or placebo, followed by a 7-day follow-up period), thereby smoothing out and concealing some of the wild fluctuations in this low-quality data. Nonetheless, the stated results make little sense. During the treatment period – the time when they were actually taking the drugs – patients on PTI-428 and Orkambi saw their average CFTR levels *decline* by 20%. Once they *stopped* taking these drugs, they saw their average CFTR levels *increase* by a factor of 5! By contrast, patients on PTI-428 alone were reported to experience an 8-fold increase over the treatment period and an additional 2-fold increase *even once they stopped taking the drug and it left their systems.* Even placebo patients got in on the act, with a 30% increase in average CFTR protein during the "treatment" period and a further 60% increase during follow-up.[21]

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[17] Proteostasis [December 2017 investor deck](),

[18] The ending ppFEV$_1$ average was not directly reported, but we estimate it by increasing the stated baseline level for PTI-428 patients of 57.2% by our estimated average relative change of 2.5%.

[19] Proteostasis [2017 Q3 investor presentation](), slide 26.

[20] Proteostasis [2017 Q4 investor presentation](), slide 26.

[21] Proteostasis [2017 Q4 investor presentation](), slides 27 and 28.

These bizarre fluctuations likely say more about the inaccuracy and shortcomings of Proteostasis's methods of analysis than they do about the benefits of PTI-428. Why would taking PTI-428 with Orkambi – the very treatment that supposedly delivered good lung-function results and CFTR protein increases in Phase 2 – lead to a 20% *reduction* in CFTR protein in a second, similar group of patients? Why would CFTR protein then increase so sharply once the drugs were removed? (Shouldn't the opposite have occurred, if PTI-428 really did what Proteostasis says it does?) Why should *placebo* patients also experience such large "improvements" in protein levels? Why should PTI-428+Orkambi look so different from PTI-428 alone when only the PTI-428 component, shared in common by both treatments, is supposed to influence protein levels? By "creatively" smoothing and framing its data, Proteostasis has tried to keep up appearances, but the cracks are still clearly visible.

In short, whether looking at PTI-428 through the lens of standard clinical measures like $ppFEV_1$ or Proteostasis's hand-picked biomarkers, the results are a confused jumble. Observations drop out because of quality-control problems, important endpoints go missing, dose/response relationships fail to hold, and numbers swing around wildly, even among placebo patients. Of course, that's exactly what one would expect from measuring the impact of an ineffective drug on a set of inherently volatile and often difficult-to-measure metrics: a bunch of noise. In aggregate, PTI-428 has never delivered a strong signal of efficacy outside of Proteostasis's own *in vitro* research, and not for lack of trying; as a result, we believe the drug is wholly ineffective in actual patients, as future trials, especially larger ones, will ultimately reveal.

IV. The Case of the Missing Trial and Other Data Mysteries

As already discussed above, we believe that, like many biopharmaceutical firms, Proteostasis plays games with data presentation, including:

- only directly reporting the placebo-adjusted change in $ppFEV_1$ but not pointing out that it was driven almost entirely by deterioration in the placebo group
- failing to disclose changes in mRNA levels during its Phase 2 trial
- failing to disclose results from the 300mg dose group in the single-ascending-dose study
- not quantifying changes in sweat chloride concentration in any of its trials
- using "maximum response" to inflate measured CFTR protein changes in phase 2 (but not in other places)
- only reporting multi-day averages of CFTR protein changes in phase 1 rather than simply giving day-by-day values

It's only natural to assume that, where results are omitted or glossed over, it's because they create problems for Proteostasis's preferred bullish narrative. Similarly, we are troubled by Proteostasis's recent silence regarding one of its trials: a small, 14-day study of patients on Kalydeco (ivacaftor) who add either PTI-428 or placebo to their regimens. The study has been discussed for at least a year, but the timeline has quietly slipped (emphases added):

- March 30, 2017 (10-K): "We plan to conduct studies in patients on Kalydeco or in those patients who are not taking CFTR modulator therapy in order to assess the therapeutic potential of PTI-428 as Kalydeco add-on therapy or as a monotherapy."
- June 7, 2017 update: "Results from a separate study in a third patient population, where CF patients will receive PTI-428 or placebo in addition to Kalydeco® as background therapy for 14 days, is [*sic*] **expected in the third quarter.**"
- 2017 Q2 10-Q: "We have also initiated and commenced dosing for a study of patients on Kalydeco® who will be dosed with PTI-428 or placebo for 14 days and **currently intend to report preliminary data in the second half of 2017**."
  - The corresponding ClinicalTrials.gov record lists an "estimated primary completion date" of October 2017 and estimated enrollment of only 16 participants
- November 14, 2017 earnings release: "The Company is also conducting a 14 day study of patients on Kalydeco® to receive PTI-428 or placebo for 14 days. The study has commenced dosing and Proteostasis **currently intends to report preliminary data in the first quarter of 2018.**"

In Proteostasis's latest investor deck, however, this trial isn't mentioned at all, nor did it appear in last week's early earnings release. While the company's new 10-K does briefly mention the trial, there is no reference to a timeline for data release, and the language fails to clearly convey whether the trial finished on schedule or whether it's still ongoing:

> We are studying PTI-428 in a 14-day once-a-day, placebo controlled, double blind, dose-range study in patients on background Kalydeco.

While any individual 16-patient trial won't tell us very much on its own, the ClinicalTrials.gov listing promises interesting results that include change in nasal epithelial mRNA and protein expression over time, change in sweat chloride over time, change in FEV_1 over time, and change in weight over time. So where are the data? Why is this small-scale trial, which was supposed to end 5-6 months ago, taking so much time to analyze, and why has Proteostasis suddenly clammed up about it? It's no wonder that one biotech industry observer, who maintains a detailed calendar of upcoming catalysts, complained just last week that Proteostasis is "[o]ne of the most frustrating companies to follow. Timelines always extended, trials disappearing from sight."

Even more under the radar, however, is a very interesting preclinical study (11) published last year in the open-access journal *EMBO Molecular Medicine* – to our knowledge, the only study of PTI-428 (referred to therein by the alternate name of PTI-CH) to include non-Proteostasis employees as co-authors. (Out of 21 named authors, 3 are Proteostasis employees, while the rest are Toronto-based researchers.) Thus, while the study is not *fully* independent, it's closer to independent than any other source of *in vitro* data on the drug, which otherwise all comes straight from Proteostasis. While the results of this study are presented in a sufficiently

sugarcoated manner to *appear* positive, a closer look reveals a host of problems, including some findings that directly contradict Proteostasis's claims about how its drug works.

In the study, the researchers focus on a specific, rare mutation (relatively common in Qatar) that gives rise to a form of cystic fibrosis resembling the most common type. Proteostasis claims that its amplifier is "mutation-agnostic," able to increase the protein and mRNA levels of any version of CFTR and thereby improve chloride-channel function, so it should also be able to work on this mutation too. The results in this study, however, tell a far murkier story.
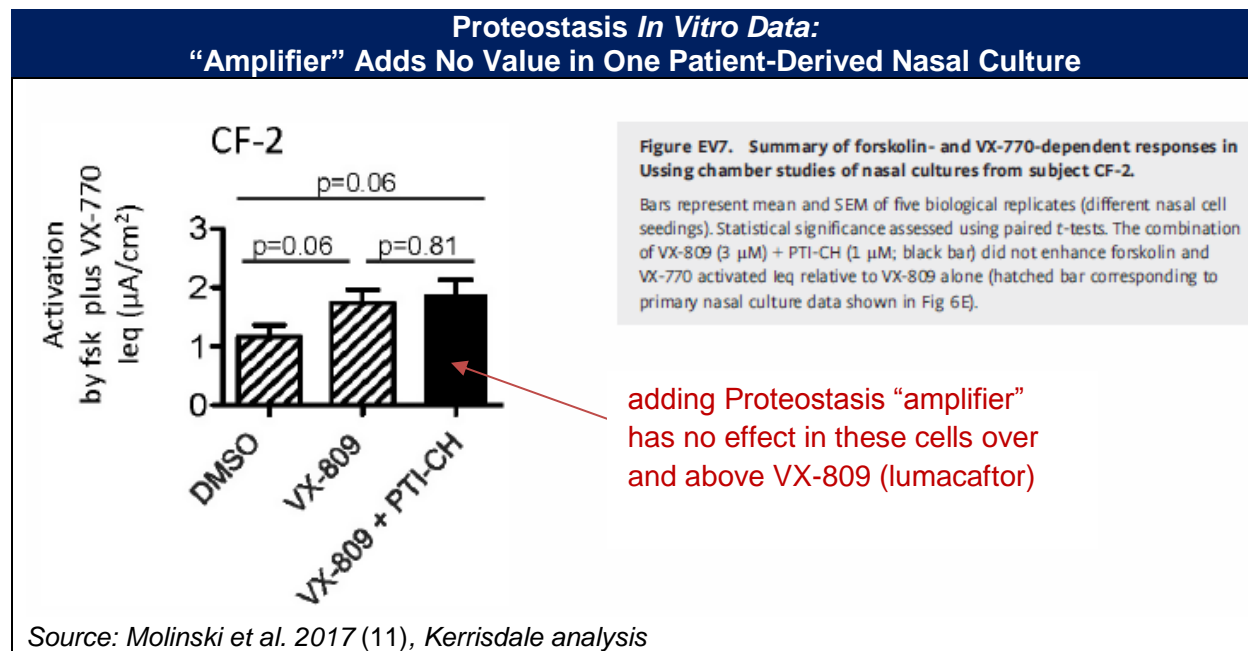
First, the researchers used CRISPR/Cas9 gene editing to engineer human bronchial epithelial (HBE) cells harboring the rare CFTR mutation in question. After treating these cells with PTI-428, they did observe what they describe as a "increase in mRNA abundance," but it was "modest" – a roughly 25% increase, well below the 50-100% thresholds cited in the mRNA discussion above. Furthermore, this "modest increase in mRNA abundance following PTI-CH treatment **did not translate to a significant increase in mutant protein on its own**" (emphasis added). The entire concept of Proteostasis's "amplifier" is that it can ultimately engender higher levels of CFTR protein – yet in this semi-independent study, the drug failed to do so.

While the researchers went on to claim that the drug, though largely ineffective at increasing CFTR mRNA and protein on its own, can enhance the effects of Vertex's drug lumacaftor, their own data doesn't fully support the claim: while lumacaftor does seem to increase CFTR protein levels, the difference between the increase conferred by lumacaftor alone and the increase conferred by lumacaftor plus PTI-428 appears small and is not statistically similar. Similarly, when measuring chloride-channel activity directly in these gene-edited cells, the researchers fail to even say whether PTI-428 on its own confers a benefit, suggesting that it likely doesn't. While Orkambi alone and Orkambi plus PTI-428 both improve chloride-channel activity, the difference between the two is again small and not statistically significant – another sign, in this cell model, that PTI-428 is ineffective.

The researchers then went on to obtain and culture nasal epithelial cells from two patients – siblings – who harbor the rare mutation. What effect did Proteostasis's drug have on these patient-derived nasal culture? Again, in many cases important metrics are simply not directly reported. Did PTI-428, alone or in combination with Orkambi, increase CFTR mRNA in these cultures? We aren't told. Did it increase CFTR protein levels? In *one* of the two cultures, while the authors claim an "increased appearance of band B [immature protein] and band C [mature protein] as studied by Western blotting," the actual images they present are unconvincing, and they neither quantify this "increased appearance" nor claim that it's statistically significant in magnitude, even as they do in other cases in the same paper – leading us to believe that the results are not significant. For the second of the two cultures, they report nothing about protein levels – again, we suspect, because Proteostasis's drug did little to nothing.

The researchers do show, however, that – in one of the two patient-derived cultures – adding PTI-428 to Orkambi confers a statistical significant, though not dramatic, increase in chloride

channel function. Yet in the *second* patient-derived culture – the one created using cells from the other sibling with the same mutation – adding PTI-428 *does nothing at all,* as shown in the graph below. Amusingly, this null result is buried in a supplement, while only the more optimistic data point from the other of the two cultures is included in the main body of the paper.

Proteostasis *In Vitro* Data:
"Amplifier" Adds No Value in One Patient-Derived Nasal Culture

Figure EV7. Summary of forskolin- and VX-770-dependent responses in Ussing chamber studies of nasal cultures from subject CF-2.

Bars represent mean and SEM of five biological replicates (different nasal cell seedings). Statistical significance assessed using paired t-tests. The combination of VX-809 (3 μM) + PTI-CH (1 μM; black bar) did not enhance forskolin and VX-770 activated Ieq relative to VX-809 alone (hatched bar corresponding to primary nasal culture data shown in Fig 6E).

adding Proteostasis "amplifier" has no effect in these cells over and above VX-809 (lumacaftor)

Source: Molinski et al. 2017 (11)*, Kerrisdale analysis*

Overall, then, this semi-independent clinical paper reinforces the evidence from Proteostasis's clinical data that PTI-428 is broadly ineffective: it does little to nothing to increase CFTR mRNA and protein in cultured epithelial cells (despite the fact that achieving such increases is its entire raison d'être), and, in two out of three cultures studied (gene-edited HBE cells and the second sibling's nasal cells) it failed to enhance Orkambi's impact on chloride-channel activity to a statistically significant degree. Yet, just as Proteostasis has gone quiet on its Kalydeco trial, it also fails to mention any of these troublesome data points in its communications with investors, sticking instead to its own internal (and largely unpublished) *in vitro* results. So much of Proteostasis's potential value hinges on the validity and reproducibility of such results, but, when a company routinely minimizes and conceals negative findings, does it really deserve the benefit of the doubt?

V.   Proteostasis's Earlier-Stage Pipeline Is Irrelevant in a Fiercely Competitive Market

Beyond Proteostasis's lead drug, the amplifier PTI-428, the company is also in the early stages of developing its own potentiator and corrector compounds – analogues of Vertex's ivacaftor and lumacaftor, respectively. The company's stated ambition is to create its own proprietary triple combination, bringing amplifier, potentiator, and corrector together for the first time.

Without any meaningful efficacy results to consider, it's difficult to assess the quality of Proteostasis's pipeline compounds, though it's somewhat amusing to note that, at least in the case of its potentiator, it doesn't even claim to outperform the existing therapy – just to deliver "comparable" *in vitro* efficacy.[22] However, the reality is that Proteostasis is late to the party. Vertex and Galápagos, the clear leaders in this space, will already be deep into full-fledged Phase 2 and Phase 3 clinical trials of their own new and improved combination therapies, which have already produced clinical data, by the time Proteostasis is hoping to complete its own small-scale "proof of concept" trials[23] – and, given the company's track record with deadlines, it's a safe bet that those trials will take longer than management currently expects. Indeed, part of the company's challenge in enrolling its past studies was competing with numerous other ongoing cystic-fibrosis trials for patients. In a rapidly advancing field, there is little reason to believe that Proteostasis's me-too pipeline will deliver anything more impressive than PTI-428.

To the contrary, there is a risk that PTI-428 might sabotage Proteostasis's other efforts. Management has at times indicated that having an "amplifier" enabled it to detect new correctors and potentiators that traditional compound screening would have overlooked, implying that, in the absence of "amplification," these correctors and potentiators wouldn't work well. Yet, as we detailed above, Proteostasis's amplifier seems to do far less in the real world than the company's preclinical results would indicate. That in turn suggests that any correctors or potentiators that rely on "amplification" to function properly will falter in the clinic. Ultimately, everything comes back to PTI-428. If it fails – as we believe it will – Proteostasis will go with it.

VI.   Valuation and Conclusion

Given our view that Proteostasis's lead drug is ineffective, we believe the company is worth nothing more than its current cash per share of roughly $2, or 70% below the current price. Of course, the company is likely to continue to burn cash for at least another year to further develop its bogus compounds, implying that a more realistic valuation would be forward cash per share of ~$0.63, 91% below the current price.[24]

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[22] Proteostasis 2017 Q3 investor presentation, slide 15.
[23] See Proteostasis January 2018 investor deck, slide 8.
[24] Forward cash per share is calculated as current cash less the 2017 run rate of negative free cash flow.

References

1. *Lumacaftor/ivacaftor for patients homozygous for Phe508del-CFTR: should we curb our enthusiasm?* **Jones, Andrew M and Barry, Peter J.** 2015, Thorax, Vol. 70, pp. 615-616.

2. *Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR.* **Wainwright, C.E., et al.** 3, 2015, New England Journal of Medicine, Vol. 373, pp. 220-231.

3. *Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del.* **Taylor-Cousar, Jennifer L., et al.** 21, 2017, New England Journal of Medicine, Vol. 377, pp. 2013-2023.

4. *Assessment of safety and effi cacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fi brosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study.* **Konstan, Michael W., et al.** 2016, Lancet Respir Med.

5. *Understanding the natural progression in %FEV1 decline in patients with cystic fibrosis: a longitudinal study.* **Taylor-Robinson, David, et al.** 2012, Thorax, Vol. 67, pp. 860-866.

6. *Advancing clinical development pathways for new CFTR modulators in cystic fibrosis.* **Mayer-Hamblett, Nicole, Boyle, Michael and VanDevanter, Donald.** 2016, Thorax, Vol. 71, pp. 454-461.

7. *Correlation of sweat chloride and percent predicted FEV1 in cystic fibrosis patients treated with ivacaftor.* **Fidler, Meredith C., et al.** 2017, Journal of Cystic Fibrosis, Vol. 16, pp. 41-44.

8. *Targeted Proteomic Quantitation of the Absolute Expression and Turnover of Cystic Fibrosis Transmembrane Conductance Regulator in the Apical Plasma Membrane.* **McShane, Adam J., et al.** 11, November 7, 2014, Journal of Proteom Research, Vol. 13, pp. 4676-4685.

9. *Expression of the cystic fibrosis transmembrane conductance regulator gene in the respiratory tract of normal individuals and individuals with cystic fibrosis.* **Trapnell, Bruce C., et al.** August 6565-6569, 1991, Proc. Natl. Acad. Sci. USA, Vol. 88.

10. *Non-PCR methods for the analysis of CFTR transcripts.* **Trezise, Ann E.O., et al.** August 2004, Journal of Cystic Fibrosis, Vol. 3, pp. 25-28.

11. *Orkambi® and amplifier co-therapy improves function from a rare CFTR mutation in gene-edited cells and patient tissue.* **Molinski, Steven V, et al.** 2017, EMBO Mol Med, Vol. 9, pp. 1224-1243.

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