First Take

ProQR Therapeutics N.V. (PRQR)

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Price: $6.45; Market Cap (M): $155; *9/25/2017 Close*

Rating: Buy; Price Target: $40.00

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Believe QR-010 Results Establish POC and Will Likely Trigger Partnership Signing; Reit Buy and $40 PT

Yesterday, ProQR reported topline data from its Phase 1b study of QR-010. The combination SAD (4 cohorts)/ MAD (4 cohorts) trial enrolled 64 homozygous F508del patients. Expectations were appropriately low for observing any efficacy in this safety study in which oligomer delivery was dosed 3x/week for a total of 4 weeks. All patients were either off Orkambi, or had a 12-week washout of Orkambi prior to initiating this study. With respect to safety, QR-010 delivered a very solid and pleasingly unremarkable safety pattern, with no AE's being attributed to drug treatment and only 3 SAE's reported from 2 patients (abdominal discomfort and nausea being reported).

Focus on entry criteria give context to the results. Exploratory efficacy endpoints of the CFQR-R (respiratory domain) and improvement in the absolute ppFEV1 from baseline were also measured. It is important at this juncture to point out that the entry criteria did not include a cap on ppFEV1 values so at baseline the mean ppFEV1 was approximately 86% across all groups. Such a high ppFEV1 value suggests that the patient population in this trial is relatively healthy and had little room to demonstrate a ppFEV1 improvement during this short 4-week study. With that in mind, it was reassuring to observe the following increases in the CFQR-R: placebo decreased 6.5 points, the 6.25 mg group improved 13.0 points, the 12.5 mg group improved 19.2 points, the 25 mg group improved 14.3 points and the 50 mg group improved 3.5 points. In the CFQR-R, an increase of 4 points is typically viewed as having a discernible difference on the patient, thus 3 of the 4 doses reached that level of significance, albeit in somewhat of a bell-shaped curve response.

We believe the trend is suggestive of effect and warrants further investigation. With respect to ppFEV1, the responses were lower, although a similar bell-shaped response could be observed. Based on both CFQR-R and ppFEV1, a dose of 12.5 mg of QR-010 delivered for 4 weeks duration gave a response that we would interpret as influencing lung function in F508del patients. Although the effect is neither robust nor definitive in this study, it clearly suggests a trend that supports further investigation, especially considering the "uncapped entry criteria." When the data set was sub-segmented to sort patients with a <90 or >90 ppFEV1 at baseline, an even greater effect was observed. Patients exposed to 12.5 mg QR-010 who had a <90 ppFEV1 at baseline showed a 10.9 ppFEV1 improvement (P value =0.046). Two other exploratory endpoints, sweat chloride levels and weight gain were unchanged in this study. *In toto* we believe this data continues to support development of QR- 010.

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Dennis isn't the only Rodman that knows how to rebound. Regarding future plans, ProQR has recently added Dr. David Rodman to their management team as the Chief Development Strategy Officer. Dave has a long and prestigious history and is particularly noted, in our opinion, for his ability to design highly informative clinical trials. We expect similar insight and execution for the QR-010 subsequent trials that he will likely design and develop. Dr. Rodman has initially discussed a possible 13-week trial with a 4-week interim analysis that would primarily be used to select 1 or 2 doses that would then be over-enrolled during the final 9 weeks. The reasoning behind this strategy is based on management's belief that the observed "bell-shaped" curve may be due to accumulation of QR-010 in the lung. We are not entirely convinced that this would explain the decreased response at higher doses. If overexpression of CFTR occurs at higher doses of QR-010, it may not result in increases in functional CFTR activity, or a further effect on mucociliary clearance. But it is not clear how that overexpression would result in a decreased effect on ppFEV1. Moreover, there does not appear to be any significant safety signal associated with the increased dosage. We await a more plausible explanation, which may come from a longer trial, or perhaps as Dr. Rodman indicated, a trial design that uses a higher loading dose followed with a lower maintenance dose. With respect to the "better" (larger magnitude) response in CFQR-R vs ppFEV1, we tend to agree with management that this could be due to CFQR-R displaying a response from the whole lung, large and small airways, whereas ppFEV1 may only be sampling from the large airways, especially in relatively mild patients (>85 ppFEV1). Management is considering inclusion of Lung Clearance Index, LCI, in future studies as that may provide a better perspective on effects in the small airways, especially in milder disease patients. Although FEV1 is still the approvable endpoint for the regulators, we note that more companies have been discussing and including LCI in their trial design, and we expect that trend to continue.

We expect that today's results are likely to trigger a partnership signing and believe expansion of CFFT partnership should be viewed as validating. Finally, management clearly discussed their ongoing desire to partner QR-010 for future studies, and we believe this may be driven by the exciting advances being made in their other programs including the recently demonstrated *in vivo* Proof of Concept data for the Axiomer RNA editing platform. Specifically, we can anticipate the ongoing expansion of the ProQR and CFFT partnership to now include targeting of Class I stop mutations. This would satisfy the gap in the CFFT pipeline that occurred following the discontinuation of the PTC Therapeutics' (PTCT; not rated) Ataluren development program. In our assessment, the QR-010 program deserves continued development and could be a salient contributor to what we are now viewing as a broad RNA platform.

Valuation and risks to achievement of target price. Our price target of $40/share is based on a DCF/NPV analysis (discount rate 12.5%, growth rate 2%). Risks to our investment thesis and target price include: (1) failure of QR-010 in clinical studies; (2) failure of QR-010 to secure regulatory approval; (3) failure of QR-010 to achieve peak commercial revenue estimates in our model due to market size, penetration rates, and pricing; and (4) other pipeline failures.

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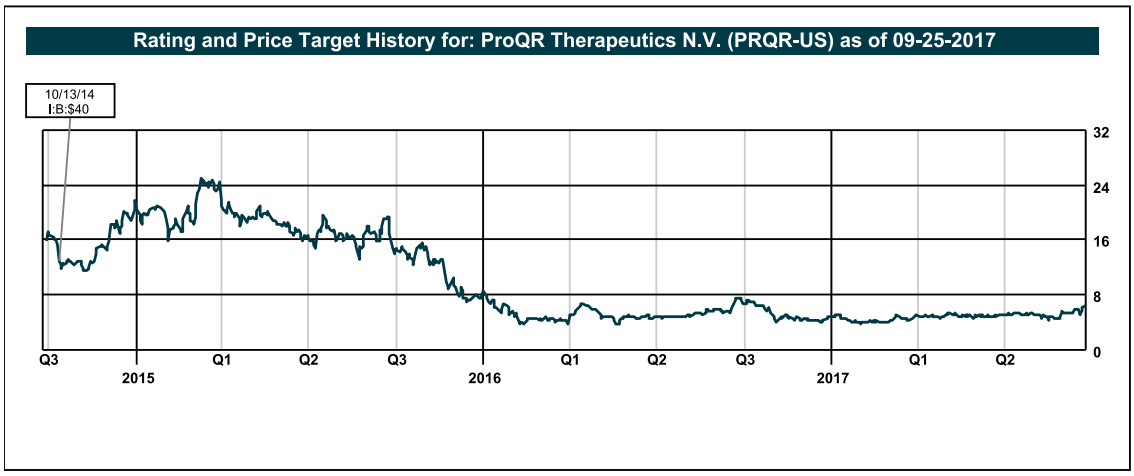

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			IB Service/Past 12 Months	
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Neutral	10	4.00%	0	0.00%
Sell	0	0.00%	0	0.00%
Under Review	18	7.20%	3	16.67%
Total	250	100%	76	30.40%

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