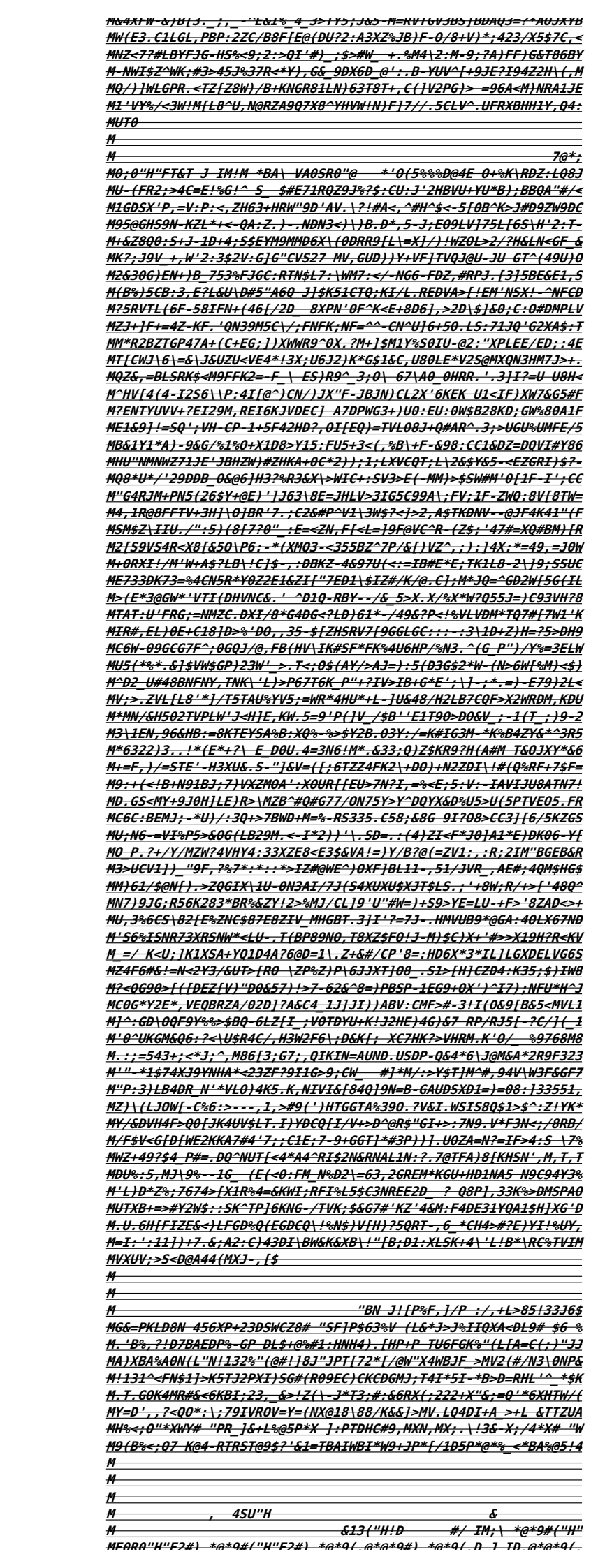

0001104659-24-1276116-K ProQR Therapeutics N.V. 2024121120241211160120160121160121 0 0001104659-24-127611 6-K 80 20241211 20241211 20241211 ProQR Therapeutics N.V. 0001612940 2834 000000000 1231 6-K 34 001-36622 241541492 ZERNIKEDREEF 9 LEIDEN P7 2333 CK 31 88 166 7000 ZERNIKEDREEF 9 LEIDEN P7 2333 CK ProQR Therapeutics B.V. 20140708 6-K 1 tm2430675d1_6k.htm FORM 6-K Â Â UNITED STATES SECURITIES AND EXCHANGE COMMISSION Washington, D.C. 20549 Â FORM 6-K Â Report of Foreign Private Issuer Pursuant to Rule 13a-16 or 15d-16 of the Securities Exchange Act of 1934 Â For the month of December 2024 Â Commission File Number: 001-36622 Â PROQR THERAPEUTICS N.V. Â Zernikedreef 9 2333 CK Leiden The Netherlands Tel: +31 88 166 7000 (Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrantâ€™s Principal Executive Offices) Â Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F. Â Form 20-F x Form 40-F Â¨ Â Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1): Â¨ Â Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7): Â¨ Â Â Â Â Â Â On December 11, 2024, ProQR Therapeutics N.V. (â€œProQRâ€) hosted a virtual analyst and investor event to discuss its proprietary Axiomerâ„¢ ADAR-mediated RNA editing platform, along with updates on its pipeline of development candidates including data updates and next steps on its programs for NTCP and B4GALT1, AX-0810 and AX-1412. A copy of the presentation is attached hereto as Exhibit 99.1 and is incorporated herein by reference. Â ProQR hereby incorporates by reference the information contained herein into ProQRâ€™s registration statements on Form F-3 (File No. 333-282419, File No. 333-270943, and File No. 333-263166). Â Â Â Â SIGNATURES Â Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized. Â Â PROQR THERAPEUTICS N.V. Â Â Date: December 11, 2024 By: /s/ RenÃ© Beukema Â Â RenÃ© Beukema Â Â Chief Corporate Development Officer and General Counsel Â Â Â Â INDEX TO EXHIBITS Â Number Â Description Â Â Â 99.1 Â Presentation of ProQR Therapeutics N.V. for December 11, 2024 Analyst and Investor Event. Â Â Â Â Â EX-99.1 2 tm2430675d1_ex99-1.htm EXHIBIT 99.1 Exhibit 99.1 Â INVESTOR & ANALYST EVENT December 11, 20241. Welcome & Agenda Sarah Kiely 2. Strategy overview Daniel A. de Boer 3. Axiomer Platform Peter Beal, PhD 4. AX -0810 for Cholestatic Diseases Prof. Gideon Hirschfield, MA, MB Bchir, FRCP, PhD Gerard Platenburg 5. AX -2402 for Rett Syndrome Monica Coenraads, MBA Gerard Platenburg ProQR Therapeutics â€“ Investor and Analyst Event 2024 2 Agenda Speakers 6. AX -1412 for CVD Gerard Platenburg 7. AX -2911 for MASH Gerard Platenburg 8. Summary & Milestones Daniel A. de Boer 9. Q&A Daniel A. de Boer Gerard Platenburg RenÃ© Beukema 10. Closing Daniel A. de Boer Monica Coenraads, MBA Founder, CEO at Rett Syndrome Research Trust Prof. Gideon Hirschfield, MA (Oxon) MB BChir (Cantab) FRCP PhD Professor of Gastroenterology and Hepatology, Toronto Centre for Liver Disease Sarah Kiely VP Investor Relations & Corporate Affairs Daniel A. de Boer Founder & CEO Gerard Platenburg Chief Scientific Officer RenÃ© Beukema Chief Corporate Development Officer Peter Beal, PhD Professor, UC Davis; ProQR Chief ADAR Scientist; SAB memberForward-looking statements This presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to", "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. Such forward-looking statements include, but are not limited to, statements regarding our strategy and future operations, statements regarding the potential of and our plans with respect to our technologies and platforms (including Axiomer), our preclinical model data, our pipeline targets, our other programs and business operations, our current and planned partnerships and collaborators and the intended benefits thereof, including the collaboration with Lilly and the intended benefits thereof, including the upfront payment, equity investment, and milestone and royalty payments from commercial product sales, if any, from the products covered by the collaboration, as well as the potential of our technologies and product candidates; our updated strategic plans and the intended benefits thereof, our plans to seek strategic partnerships for our ophthalmology assets, and our financial position and cash runway. Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this presentation. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, without limitation, the risks, uncertainties and other factors in our filings made with the Securities and Exchange Commission, including certain sections of our annual report filed on Form 20-F. These risks and uncertainties include, among others, the cost, timing and results of preclinical studies and other development activities by us and our collaborative partners whose operations and activities may be slowed or halted due to shortage and pressure on supply and logistics on the global market; our reliance on contract manufacturers to supply materials for research and development and the risk of supply interruption from a contract manufacturer; the ability to secure, maintain and realize the intended benefits of collaborations with partners, including the collaboration with Lilly; the possible impairment of, inability to obtain, and costs to obtain intellectual property rights; possible safety or efficacy concerns that could emerge as new data are generated in research and development; general business, operational, financial and accounting risks; and risks related to litigation and disputes with third parties. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future, except as required by law. ProQR Therapeutics â€“ Investor and Analyst Event 2024 3Presenter: Daniel A. de Boer Strategic Overview ProQR Therapeutics â€“ Investor and Analyst Event 2024 4ProQR Therapeutics â€“ Investor and Analyst Event 2024 5 Peter Beal, PhD ProQR Chief ADAR Scientist & SAB member, Professor UC Davis â€¢ Professor in the Department of Chemistry at the University of California at Davis and Director of the NIH-funded UC Davis Chemical Biology Graduate Program â€¢ Advanced understanding of the structures and mechanism of action for the ADAR enzymes responsible for adenosine to inosine RNA editing in humans â€¢ Led in the development of structure-guided methods for optimizing chemically modified oligonucleotides for recruitment of RNA-binding proteins including ADARs â€¢ Teaches organic chemistry at the undergraduate level and several classes in nucleic acids chemistry and chemical biology at the graduate level â€¢ Over 100 peer-reviewed publications in the field of RNA chemical biology and mentored over 50 Ph.D. and M.S. degree students â€¢ ProQR Chief ADAR Scientist, Scientific Advisory BoardAxiomer advancing to value inflection ProQR Therapeutics â€“ Investor and Analyst Event 2024 6 Pipeline with transformative potential for diseases with high unmet medical needs work at root cause Innovative ADAR-enabled RNA editing science driving advancement of Axiomer supported by robust IP estate Experienced team driving execution High impact strategic partnerships Eli Lilly, Rett Syndrome Research Trust Runway into mid 2027 â‚¬89.4 million cash and cash equivalents as of end of Q3, plus $82.1 million gross proceeds from October financing providing runway into mid-2027 â‚¬Driving innovation in the ADAR RNA editing field Axiomer Platform ProQR Therapeutics â€“ Investor and Analyst Event 2024 7 Presenter: Peter Beal, PhDProQR Therapeutics â€“ Investor and Analyst Event 2024 8 Axiomer RNA-editing platform technology ADAR: Adenosine deaminase acting on RNA, mRNA: messenger RNA, miRNA: microRNA, lcRNA: long non-coding RNA Versatile â€¢ Ability to target multiple organs and a wide range of diseases with numerous applications â€¢ Potential to include protective variants â€¢ Designed to target a variety of RNA species (mRNA, miRNA, lncRNA) Safety â€¢ No permanent changes â€¢ No irreversible DNA damages and less risk of permanent side effects High specificity â€¢ Highly targeted therapeutic with potential to minimize off-target effects and reduce the risk of adverse reactions Transient â€¢ Provide a long-lasting therapeutic effect that does not require frequent dosing â€¢ Potential to target diseases for which permanent changes would be deleterious No viral vector â€¢ No risk of immunogenicity or capacity limitation due to the vector â€¢ Efficient development and faster production increase the chance to reach market Endogenous ADARs â€¢ Leverage bodyâ€™s potential to treat disease â€¢ Less risk of off-target effect vs. exogenous ADARs9 ProQRâ€™s Axiomer ADAR journey since 2014 ProQR Therapeutics â€“ Investor and Analyst Event 2024 ADARs: Adenosine deaminases acting on RNA, EONs: Editing oligonucleotides

ProQR and Eli Lilly enter into first 5 target partnership worth $1.25B 2021 ProQR demonstrates >50% editing in CNS and liver in NHP and announces pipeline 2023 ProQR files key patents that protect ADAR mediated RNA editing broadly 2014-2018+ ProQR optimizes the ADAR platform in stealth 2015-2021 ProQR and Eli Lilly expand partnership to 10 targets worth ~$3.9B 2022 2022 ProQR pivots to solely focus on ADAR editing 2014 2023-2024 Key ADAR patents get granted in EU and US 2020-2023 ProQRâ€™s ADAR patents win opposition cases filed by strawmen across the world ProQR invents oligo mediated RNA Editing recruiting endogenous ADAR 2024 â€¢ ProQR first in the field to report a disease relevant biomarker effect using Axiomer in NHP. Initial indication of good safety profile. â€¢ Initial clinical validation of ADAR editingProQR Therapeutics â€“ Investor and Analyst Event 2024 10 What is ADAR editing? Enzyme that performs specific form of natural RNA editing, called A-to-I editing. During A-to-I editing an A nucleotide (adenosine) is changed into an I nucleotide (inosine) ADAR (Adenosine Deaminase Acting on RNA) Inosine Adenosine Natural ADAR editing (A-to-I) RNA Double stranded RNA Double stranded ADAR Inosine AdenosineBy attracting ADARs and allowing highly specific editing ProQR Therapeutics â€“ Investor and Analyst Event 2024 Axiomer EONs unlock cellular machinery potential to treat diseases Natural ADAR editing (A-to-I) ADARs: Adenosine deaminases acting on RNA. RNA Double stranded Adenosine RNA Double stranded ADAR Inosine Editing Oligonucleotide (EON)-directed therapeutic editing (A-to-I) RNA+EON Double stranded EON ADAR Inosine RNA Single stranded Adenosine 11Oligonucleotide-directed RNA editing Reference: Doherty EE, Beal PA. Mol Ther. 2022 Jun 1;30(6):2117-2119. ProQR Therapeutics â€“ Investor and Analyst Event 2024 12 Genetics Phenotype Wild type MECP2 gene Functional MECP2 protein W104X mutation Truncated protein UGG UAG Mutation Guide Oligonucleotide Target transcript with corrective edit Target transcript + 5â€™- -3â€™ 5â€™- -3â€™ 5â€™- -3â€™ 3â€™- -5â€™ ADARProQR Therapeutics â€“ Investor and Analyst Event 2024 13 Driving innovation in the RNA field with Axiomer editing oligonucleotides â€¢ A targeting portion for binding to a target RNA incl. target adenosine â€¢ A recruitment portion (hairpin structure) for recruiting endogenous ADAR to edit the target adenosine EON ADAR Targeting portion Recruitment portion A-to-I edit Target RNA EON Target RNA ADAR A-to-I edit Patents: Granted appeal pending EP 3 234 134 B1; Granted US 10,676,737; Granted US 11,781,134 Patents: Granted US 10,941,402; Granted US 11,851,656; Allowed US 18/296,912 1st Axiomer EONs generation relate to (chemically modified) oligonucleotides that comprise 2ndAxiomer EONs generation relate to oligonucleotides that comprise â€¢ No hairpin structure â€¢ One or more wobbles and/or mismatches, and chemical modifications in the base, ribose sugar and/or linkage to increase activity as well as stability and are still able to recruit endogenous ADAR to edit the target adenosine.No PMe PMe 0 1 2 3 4 Fold-change relative editing % (ddPCR) to no PMe ProQR Therapeutics â€“ Investor and Analyst Event 2024 14 ProQR leading research to optimize editing oligonucleotides for therapeutic use RNA editing of SERPINA1 E366K in A1AD patient hepatocytes Transfection of 100nM EON, N=2, 48 hours hA1AD dC hA1AD dZ 0 2 4 6 8 10 Fold change editing % (ddPCR) relative to dC Adapted from Doherty EE, et al. Nucleic Acids Res. 2022;50(19):10857-10868. Statistical significance between groups was determined using one-way ANOVA with Tukeyâ€™s multiple comparisons test or an unpaired t-test with Welchâ€™s correction; **P < 0.01; ***P < 0.001; ****P < 0.0001. dZ in EER to increase ADAR activity PN and PMe linkages in the ABR to increase stability, EON liver concentration and target engagement Modification of the orphan base In vitro deamination kinetics for ADAR2 and duplex RNAs derived from hMECP2 R255X 100nM ADAR2, 3 technical replicates, mean, SD 3-deaza-dA in EER to increase editing activity in 5â€™G unfavorable context Modification of the base opposite to 5â€™g Linkage modifications in the ABR 14 Phosphoroamidate linkage RNA editing of ActB in liver C57Bl/6J mice, 7d, 3x10mg/kg, SC, N=4, dPCR, mean, SEM Methylphosphonate linkage RNA editing of APP in HepG2 cells Gymnosis, 5d, 5ÂµM single dose, N=2, dPCR, mean, SEM O P O HN O S O O R R = Me: Mesyl-PN PN PMe O P O O Low - Low - High + 0 10 20 30 40 50 Editing (%) âœ± âœ±âœ±âœ±âœ± #PN GalNacSequence optimization enables stable editing oligonucleotides with prolonged PK Learnings from advanced programs inform editing optimization ProQR Therapeutics â€“ Investor and Analyst Event 2024 EON11 concentration in liver of mice disease model Hybridization-HPLC, n=6, 30mg/kg, EON11, SC, GalNAc conjugation, up to 4 weeks 15 0 168 336 504 672 0.01 0.1 1 10 100 1000 Time (hr) Peak Area Ratio Unconjugated EON Metabolite 1 Metabolite 2 Metabolite 3 Metabolite 4 Metabolite 5 Metabolite 6 Sum Total Analytes PAR â€¢ Rapid absorption in the liver and long half-life of EON11 in liver measured â€“ around 80 days â€¢ EON show high stability with no metabolites observed for oligonucleotide itself â€¢ Up to six metabolite were identified and all were the metabolite of the GalNAc entity â€¢ Most represented is linker between EON and GalNAc moiety â€¢ Others were a combination of different cleavages of different GalNAc arms or within the linker EON11 metabolites in liver of mice disease model LC-MS, n=6, 30mg/kg, EON11, SC, GalNAc conjugation, up to 4 weeks Perkins E. 726. Complex Metabolism and Prolonged PK/PD of a GalNAc-Conjugated Editing Oligonucleotide (EON) in Mice. ASGCT 27th Annual Meeting Abstracts; Molecular Therapy, Volume 32, Issue 4, 1 - 889Mutations correction Thousands of G-to-A mutations, many of them described in literature Alter protein function or include protective variants Modified proteins achieving loss- or gain-of-functions that help addressing or preventing diseases Disrupt >400 different types of PTMs Regulate protein activity, change localization, folding, preventing immune escape or slowing down degradation Change protein interactions Changes localization, folding, protein function or prevents immune escape of glycosylated tumor antigens Mutation correction leading to protein recovery Variant resulting in a dominant negative effect Reduction of protein phosphorylation altering protein function Variant impacting protein interaction with sugar ProQR Therapeutics â€“ Investor and Analyst Event 2024 16 Creating a new class of medicines with broad therapeutic potential Correction Protein modulationProQR Therapeutics â€“ Investor and Analyst Event 2024 17 Axiomer RNA editing science translating toward therapeutic applications Science â€¢ Harnessing advanced knowledge of ADAR and oligonucleotide science â€¢ Pioneering the optimization of editing oligonucleotides (EONs) to achieve best-in-class therapeutic solutions Versatile applicability â€¢ Demonstrating proven success in correcting genetic mutations and enabling diverse protein modulation strategies â€¢ Platform with potential to address diverse conditions rooted in human genetics Leadership position â€¢ Driving innovation in the ADAR RNA editing science with Axiomer EONs since 2014 â€¢ Dominant IP position to drive ADAR-mediated RNA editing platform innovationTargeting NTCP to address cholestatic diseases unmet medical need at the root cause AX-0810 Program ProQR Therapeutics â€“ Investor and Analyst Event 2024 18 Presenters: Prof. Gideon Hirschfield, Gerard PlatenburgProQR Therapeutics â€“ Investor and Analyst Event 2024 19 AX-0810 RNA editing therapy targeting NTCP for cholestatic diseases Cholestatic diseases have high unmet medical need. Patients accumulate bile acids in liver leading to fibrosis and ultimately liver failure. Initial indications are Primary Sclerosing Cholangitis affecting adults and Congenital Biliary Atresia affecting pediatrics early in life. Both conditions have no approved therapies and may require liver transplantation.1,2 â€¢ Biliary Atresia is projected to affect ~20,000 pediatric individuals in US and EU. â€¢ Primary Sclerosing Cholangitis is projected to affect more than 80,000 individuals in US and EU. AX-0810 is a unique therapeutic approach leading to a potentially disease modifying therapy by targeting the NTCP channel which is responsible for majority of bile acid re-uptake in liver cells. 1Trivedi PJ, et al. Clin Gastroenterol Hepatol. 2022 Aug;20(8):1687-1700.e4; 2Schreiber RA, et al. J Clin Med. 2022 Feb 14;11(4):999Prof. Gideon Hirschfield MA (Oxon), MB BChir (Cantab), PhD, FRCP Professor of Gastroenterology and Hepatology, Toronto, Ontario, Canada ProQR Therapeutics â€“ Investor and Analyst Event 2024 20 â€¢ Lily and Terry Horner Chair in Autoimmune Liver Disease Research â€¢ Director, The Autoimmune and Rare Liver Disease Programme, Toronto General Hospital â€¢ Professor, Division of Gastroenterology and Hepatology, University of Toronto â€¢ Prof. Gideon M. Hirschfield is an experienced and highly focused clinician-scientist specialising in autoimmune and cholestatic liver diseases. He holds the Lily and Terry Horner Chair in Autoimmune Liver Disease Research at the Toronto Centre for Liver Disease, Toronto General Hospital, and serves as a Professor of Medicine in the Division of Gastroenterology and Hepatology at the University of Toronto. â€¢ Prof. Hirschfield completed undergraduate studies in Medicine from the Universities of Oxford and Cambridge and subsequently was awarded a PhD from the University of London in 2006. He completed specialist training in Internal Medicine, Gastroenterology and Hepatology in London, Cambridge and Toronto. â€¢ An internationally recognised expert, Prof. Hirschfield has published over 350 peer-reviewed articles, including lead authorship in high-impact journals such as the New England Journal of Medicine, The Lancet, and Nature Genetics. â€¢ His research focuses on advancing therapies for autoimmune and cholestatic liver diseases with the clear goal of preventing the need for transplantation alongside improving patient quality of lifeProQR Therapeutics â€“ Investor and Analyst Event 2024 42 AX-0810 RNA editing therapy targeting NTCP for cholestatic diseases Cholestatic diseases have high unmet medical need. Patients accumulate bile acids in liver leading to fibrosis and ultimately liver failure. Initial indications are Primary Sclerosing Cholangitis affecting adults and Congenital Biliary Atresia affecting pediatrics early in life. Both conditions have no approved therapies and may require liver transplantation.1,2 â€¢ Biliary Atresia is projected to affect ~20,000 pediatric individuals in US and EU. â€¢ Primary Sclerosing Cholangitis is projected to affect more than 80,000 individuals in US and EU. AX-0810 is a unique therapeutic approach leading to a potentially disease modifying therapy by targeting the NTCP channel which is responsible for majority of bile acid re-uptake in liver cells. 1Trivedi PJ, et al. Clin Gastroenterol Hepatol. 2022 Aug;20(8):1687-1700.e4; 2Schreiber RA, et al. J Clin Med. 2022 Feb 14;11(4):999ProQR Therapeutics â€“ Investor and Analyst Event 2024 43 NTCP modulation leads to positive effect on different mechanism involved in cholestasis Zeng J, Fan J, Zhou H. Cell Biosci. 2023 Apr 29;13(1):77; Trauner M, Fuchs CD. Gut 2022;71:194â€“209; Halilbasic E, Claudel T, Trauner M. J Hepatol. 2013 Jan;58(1):155-68. Restores Bile Acids Balance Protect hepatocytes by lowering bile acid levels and decrease hepatic bile production through downregulating effects â†‘ Liver bile acids Reduces Inflammation Prevents bile leakage and infiltration, limiting liver cell damage and release of proinflammatory mediators Slows Fibrosis Progression Stops cholangiocyte senescence and proliferation, reducing fibro-inflammatory responses Genetic predisposition environmental insults Failed metabolic homeostasis Cell stress and cell death Inflammation Cholestasis Fibrosis NTCP MODULATIONProQR Therapeutics â€“ Investor and Analyst Event 2024 44 NTCP variants reduced bile acids uptake into liver in health population research Healthy population discovered with NTCP variants that reduces bile acids uptake into liver1-4 1Salhab A, et al. Gut. 2022 Jul;71(7):1373-1385; 2Ho RH, et al. J Biol Chem. 2004 Feb 20;279(8):7213-22; 3Vaz FM, et al. Hepatology. 2015 Jan;61(1):260-7; 4Schneider AL, et al. Clin Res Hepatol Gastroenterol. 2022 Mar;46(3):101824; 5Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069; 6Cai SY, et al. JCI Insight. 2017 Mar 9;2(5):e90780.Bulevirtide Bulevirtide Bulevirtide ProQR Therapeutics â€“ Investor and Analyst Event 2024 NTCP modulation has hepato-protective effects in vivo in disease models Bulevirtide (Hepcludex) is a daily SC injected NTCP inhibitor approved for Hepatitis D. Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069. NTCP inhibition increases plasma bile acids concentrations (2- to 3-fold in mouse models) Reduced bile acid production during cholestasis (expected to decrease intrahepatic bile acids load) Reduced cholestatic liver injury via improvement in liver enzymes 45 3-fold increase in conjugated BA 2-fold increase in conjugated BA Bulevirtide Bulevirtide BulevirtideProQR Therapeutics â€“ Investor and Analyst Event 2024 46 NTCP modulation leads to clinically meaningful impact in patients *NTCP channel is a known transporter for bile acids and hepatitis virus from bloodstream to the liver. Bulevirtide (Hepcludex) is a daily SC injected NTCP inhibitor approved for Hepatitis D. Wedemeyer H, et al. N Engl J Med. 2023 Jul 6;389(1):22-32; Wedemeyer H, J Hepatol. 2024 Oct;81(4):621-629.; Dietz-Fricke C, JHEP Rep. 2023 Mar 15;5(4):100686. NTCP inhibition increases plasma bile acids concentrations in humans (2- to 4-fold) Treatment with NTCP inhibitor led to improvement in liver fibrosis (stiffness and histology) Liver enzyme improvement occur in patients, even without virologic response* 0 1 2 3 4 Bulevirtide Phase 3 10mg W48 Bulevirtide Phase 3 2mg W48 Fold change plasma bile acids vs. control VR: viral responders PR: Partial responders NR: Non responders Bulevirtide 2 mg ALT Normal values 7-56 U/L Bulevirtide 10 mg -5 -4 -3 -2 -1 0 1 2 Bulevirtide 10mg Bulevirtide 2 mg 50 60 70 Histological activity index improvement (N) Liver stiffness CFB W48 (kPa) Improvement direction Reducing liver bile acids toxic overload via NTCP modulation is a key driver for hepatoprotective effectsHigh concentration of bile acids in hepatocytes AX-0810 modifies the NTCP channel to limit bile acids uptake while preserving all other functions of the channel ProQR Therapeutics â€“ Investor and Analyst Event 2024 47 Human genetics validates NTCP modulation as strategy for cholestatic disease â€¢ The AX-0810 program introduces a variant in individuals with cholestatic disease to lower bile acids concentration in hepatocytes by a single A-to-I change â€¢ The AX-0810 program is designed to be a disease modifying treatment â€¢ To alleviate symptoms in PSC and BA â€¢ To limit inflammation and fibrosis linked to bile acid toxicity â€¢ To prevent or delay the development of cirrhosis, organ failure and need for transplant NTCP WT NTCP Q68R EON ADAR Inosine BA, Biliary atresia; PSC, Primary Sclerosing Cholangitis Liver with cholestatic disease AX-0810 strategy for diseased liverProQR Therapeutics â€“ Investor and Analyst Event 2024 48 Q68R NTCP variant leads to modulation of bile acids re-uptake Glutamine Arginine Hydrophobicity Electrostatic potential â€¢ The Q68R variant disrupts some hydrogen bonds and contacts in the Na+ binding pocket. â€¢ Clashes are inevitable since the Arg side chain is buried and likely to be found in one or another unfavorable rotamer state. â€¢ Further assessment of Q68R variant in a bile acids uptake assay showed a near complete inhibition of BAs (specifically Taurocholic Acid or TCA) uptake in vitro, confirming findings from the 3D modeling BAs uptake (TCA) in vitro* n=3, meanÂ±SEM 3D Model of Q68R variant impact on Na+ binding pocket of NTCP NTCP: Na-taurocholate cotransporting polypeptide, *Transiently transfected U2OS cells. Control is WT without TCA. Q68R WT Control NTCP Variants 0 2 4 6 8 10 pmol TCA uptake TCA 10 Î¼MProQR Therapeutics â€“ Investor and Analyst Event 2024 49 Q68R NTCP variant solely affects bile acids re-uptake function Western Blot Analysis Rabbit anti-mFlag Na/K-ATPase** GAPDH* *Loading control for intracellular proteins **Loading control for surface proteins EON: editing oligonucleotide, NTCP: Na-taurocholate cotransporting polypeptide, *transiently transfected U2OS cells. SLC10A1 is the gene that encodes for NTCP protein â€¢ No significant differences in NTCP RNA and protein levels were detected. The plasma membrane location of the Q68R variant was also unaffected. â€¢ The Q68R variant solely affects NTCP bile acids reuptake function making it an approach of interest for Axiomer EON therapeutic application. NTCP protein expression was detected on western blot using the anti-FLAG antibody for all constructs â–® Nuclei â–® Anti-FLAG Parental Q68R WT Empty vector NTCP protein localization in vitro*EON mediated RNA editing leads to NTCP Q68R variant in WT hepatocytes Editing of NTCP RNA modulates bile acids reuptake in a dose dependent fashion ProQR Therapeutics â€“ Investor and Analyst Event 2024 50 NTCP: Na-taurocholate cotransporting polypeptide, BAs mentioned in this experiment are specifically Tauro-nor-THCA-24-DBD. SLC10A1 is the gene that encodes for NTCP protein NTCP-mediated BAs uptake in HepaRG cells with Axiomer EON treatment n=3, 50-100nM, 72 hours, meanÂ±SEM Early generation of EONs induces a dose-response inhibition of bile acids in vitro confirming its modulation by NTCP Early generation of EONs targeting NTCP RNA in PHH Transfection, n=3, 72 hours, meanÂ±SEM, dPCR 0 20 40 60 80 100 0 20 40 60 Concentration (nM) Editing (%) EON A Vehicle 50nM EON A 100nM EON A 0.0 0.1 0.2 0.3 Fluorescence (AU)/protein (mg/mL)ProQR Therapeutics â€“ Investor and Analyst Event 2024 51 EON mediated NTCP editing in NHP has linear correlation with bile acids plasma levels NTCP: Na-taurocholate cotransportingpolypeptide, BAs mentioned in this experiment are specifically Tauro-nor-THCA-24-DBD. SLC10A1 is the gene that encodes for NTCP protein Correlation between change in plasma BAs and editing of NTCP RNA in NHPs in vivo n=6, Early generation EONs, IV, LNP formulation, 72 hours, dPCR 0 5 10 15 20 25 30 0 2 4 6 8 10 Editing of NTCP RNA (%) Plasma Bile Acids (fold increase from baseline) R2 = 0.51 â€¢ NTCP target engagement with Axiomer EONs leads to the desired changes in biomarkers â€¢ Correlation between plasma bile acids and early-generation EONs editing level in NHPs in vivo (linear regression R2 = 0.51)Plasma TBA in Humanized Mice (N=4, 20mg/kg, 6 doses, GalNac conjugation, SC, D25) Plasma TBA in NHP (N=1, 1-4mg/kg, 4 doses, LNP formulation IV, up to D39) PLASMA TOTAL BILE ACIDS Control EON A 0 2 4 6 Change from Baseline (Fold Change) ProQR Therapeutics â€“ Investor and Analyst Event 2024 52 EON mediated editing demonstrates consistent editing of NTCP and impact on biomarker in vivo â€¢ EON A results in consistent editing data in humanized mouse model and NHP in vivo with approx. 15% editing reaching expected NTCP modulation â€¢ Reaching >2-fold changes in biomarkers -

expected impact on plasma bile acids levels following NTCP EON treatment MICE in vivo NHP in vivo EON A 0 5 10 15 20 25 Editing (%) NTCP RNA Editing in NHP (N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D46, ddPCR) NTCP RNA Editing in Humanized Mice (N=4, 20mg/kg, 6 doses, GalNAc conjugation, SC, D25, ddPCR) EDITING EFFICIENCY Control EON A 0 2 4 6 Change from Baseline (Fold Change) EON A 0 10 20 Editing (%)NTCP editing demonstrates favorable composition of bile acids profile in NHP Increase in conjugated bile acids confirms NTCP engagement in vivo ProQR Therapeutics â€“ Investor and Analyst Event 2024 53 â€¢ Conjugated bile acids are transported by NTCP back to the liver â€¢ The observed change in plasma BA profile confirms NTCP specific modulation â€¢ In view of the preclinical data, high confidence on NTCP EON treatment to positively impact BA toxic load in the liver Conditions in humanized mice: N=4, 20mg/kg, 6 doses, GalNAc conjugation, SC, D25, ddPCR; Conditions in the NHP experiment N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D42, ddPCR. Mao F, et al. J Biol Chem. 2019 Aug 2;294(31):11853-11862; Haag M, et al. Anal BioanalChem. 2015 Sep;407(22):6815-25.; Wedemeyer H, et al. N Engl J Med. 2023 Jul 6;389(1):22-32. Change in Plasma BA Profile NHP Baseline EON A NHP Unconjugated Bile Acids Conjugated Bile Acids Human Normal values Human NTCP variant Bulevirtide post treatment 0 50 100 Bile acids % Unconjugated Bile Acids Conjugated Bile AcidsProQR Therapeutics â€“ Investor and Analyst Event 2024 54 EON mediated NTCP editing demonstrates reduced clearance in bile acids challenge assay in NHP â€¢ TUDCA is a Tauro-conjugated bile acids specifically transported by NTCP from the plasma to the liver â€¢ In an NHP experiment using administration of TUDCA following NTCP EON treatment, TUDCA plasma clearance into the liver was assessed â€¢ Decrease in plasma clearance kinetics further confirm NTCP target engagement for EON treated NHP TUDCA elimination rate from plasma in NHP (Exploratory study, early generation EON, n=5-7, 10mg/kg, 4 doses, SC, D51) Control EON treated 0.04 0.06 0.08 0.10 kel (min-1) P=0.047 âœ±AX-0810 clinical candidate has an enhanced potency profile over EON A in PHH Transfection, n=3, 72 hours, dPCR, meanÂ±SEM AX-0810 clinical candidate selected with enhanced potency and stability profile ProQR Therapeutics â€“ Investor and Analyst Event 2024 55 â€¢ AX-0810 clinical candidate is a GalNAc conjugated EON â€¢ 5.5-fold increase in potency over early generation NTCP editing oligonucleotide â€¢ Improved stability profile in vitro â€¢ Confirmed class safety, with no hepatotoxicity or immunostimulatory score 0 20 40 60 80 100 0 20 40 60 Concentration (nM) Editing (%) AX-0810 EON A 5.5-fold increaseGLP tox studies ProQR Therapeutics â€“ Investor and Analyst Event 2024 56 CTA enabling activities ongoing for AX-0810 In vitro safety screening Delivery method Manufacturing Regulatory â€¢ AX-0810 clinical candidate passed in vitro screening for class toxicities â€¢ Chemical modifications and Z-base derisked in genotoxicity tests Preferential distribution of GalNAc conjugated EONs confirmed â€¢ Dose ranges and margins established for GLP toxicity studies, ongoing studies in two species â€¢ Bioanalytical methods to measure clinical candidates in plasma and tissue established Scale-up of EON manufacturing process successfully completed, stability of formulated EON confirmed, and favorable shelf life achieved Interactions with regulatory authorities ongoingFirst in human trial of AX-0810 to establish target engagement ProQR Therapeutics â€“ Investor and Analyst Event 2024 57 Integrated single/multiple ascending dose study design Cohort 1 Cohort 2 Cohort 3 Cohort 4 Treatment AX-0810 GalNAc conjugated editing oligo-nucleotide Objectives â€¢ Confirm target engagement as measured by biomarkers â€¢ Assess safety, tolerability, and PK of AX-0810 Trial design â€¢ Combined single and multiple ascending dose â€¢ â‰¥60 heathy volunteers, 4 weeks dosing phase followed by 12 safety weeks follow-up â€¢ 5 weekly subcutaneous injections â€¢ Baseline and placebo-controlled design â€¢ Standardized conditions for assessment of bile acids at multiple timepoints â€¢ DMC safety reviews before proceeding to next dose and dose escalation Key endpoints â€¢ Change in bile acids levels and profile in plasma and urine, liver biomarkers â€¢ Circulating RNA as exploratory endpoint Top-line data in Q4 2025 Follow-up Weekly dose A Weekly dose B Weekly dose C Weekly dose D Follow-up Follow-up Follow-upSummary & next steps AX-0810 for cholestatic diseases ProQR Therapeutics â€“ Investor and Analyst Event 2024 58 Modulating NTCP activity to reduce hepatic bile acids load is a promising target for hepatoprotection in cholestatic diseases Promising and consistent results reported to date in humanized mice and NHPs Meaningful impact on bile acid plasma level and bile acids profile build confidence for data readout in FIH clinical trial Axiomer NTCP EON impact on biomarkers in line with preclinical disease model and clinical data reported with NTCP inhibition Favorable safety profile observed AX-0810 GalNAc candidate with optimized potency and stability to enter clinic CTA submission in Q2 2025 Top-line data from FIH expected in Q4 2025 NTCP and bile acids are involved in a variety of therapeutic areas Providing opportunity across multiple indications ProQR Therapeutics â€“ Investor and Analyst Event 2024 59 Cholestatic diseases â€¢ Primary Sclerosing Cholangitis (PSC) â€¢ Biliary Atresia â€¢ Primary Biliary Cholangitis (PBC) â€¢ Alagille syndrome â€¢ Dubin-Johnson Syndrome â€¢ Progressive Familial Intrahepatic Cholestasis (PFIC) â€¢ Drug-Induced Cholestasis â€¢ Alcoholic Liver Disease â€¢ Secondary Biliary Cirrhosis â€¢ Rotor syndrome â€¢ Neonatal cholestasis Neurological diseases â€¢ Multiple Sclerosis â€¢ Amyotrophic Lateral Sclerosis â€¢ Neurological diseases â€¢ Epilepsy â€¢ Parkinsonâ€™s Disease Infectious disease â€¢ Parasitic Infections â€¢ Sepsis-Associated Cholestasis â€¢ Viral Hepatitis: Hepatitis A, B, C, D, E Metabolic diseases â€¢ Hyperlipidemia â€¢ Hypertension â€¢ MASH â€¢ Obesity â€¢ Diabetes â€¢ Lysosomal storage diseases â€¢ Hyper-cholesterolemia â€¢ ASCVDTargeting MECP2 to restore protein functionality in Rett Syndrome, a severe neurodevelopmental disorder AX-2402 Program ProQR Therapeutics â€“ Investor and Analyst Event 2024 60 Presenters: Monica Coenraads, MBA and Gerard PlatenburgCNS is a prime target organ for Axiomer RNA editing technology â€¢ Numerous neurological disorders lack effective therapies, urge for new therapeutic approaches â€¢ ADAR enzymes are highly expressed in the brain with very active editing capacity â€¢ EONs have shown broad distribution, durability and were observed to have a favorable safety profile making them a well-suited approach for CNS indications ProQR Therapeutics â€“ Investor and Analyst Event 2024 61 ADAR mediated A-to-I editing in human tissues1 Editing level 1Figure adapted from Tan et al. Nature. 2017 Oct 11;550(7675):249-254Robust ADAR expression across cell type and regions in mouse brain Cell type specific expression of Adarb1 and Adarb2 genes ProQR Therapeutics â€“ Investor and Analyst Event 2024 Cell type clusters ADAR1 Glut neurons Thalamus Glut neurons Cerebellum GABA neurons olfactory bulb GABA neurons cortex ADARB1 ADARB2 High expression of Adar genes in different cell type and regions in the mouse brain Whole Mouse Brain Transcriptomic Cell Type Atlas â€“ Allen brain atlas 62ProQR Therapeutics â€“ Investor and Analyst Event 2024 63 Predictive CNS models to inform development of RNA editing Development of reproducible, region-specific neural stem cell (NSC)-derived spheroids addresses limitations of 3D iPSC-derived organoids, offering a robust and predictive tool for accelerating drug discovery in neurodegenerative diseases, substance abuse, and pain management. â€¢ Spheroids are 3D cultures that model specific brain regions depending on the mix of hIPSC-derived neuronal subpopulations used â€¢ They can give rise to pre-frontal cortex-like (PFC`) or ventral tegmental area (VTA)- like 3D structures â€¢ Uniformly-shaped PFC, form within 24-48 hours with size yield of ~400 Î¼m iPSC-derived mature neuronal subtypes and astrocytes Thaw and mix of select neuronal subtypes/astrocytes at desired ratios in 384w, round bottom plates Culture 3 weeks for matured region-specific neuronal spheroidsHighly efficient RNA editing in brain organoid recapitulating human cortex Reaching 90% editing in neurospheroids ProQR Therapeutics â€“ Investor and Analyst Event 2024 PFC-like spheroids are composed by 90% neurons and 10% astrocytes and exhibit a 70:30 ratio of excitatory (Glutamatergic) and inhibitory (GABAergic) neurons recapitulating the cellular composition of the human cortex RNA editing of APP in human PFC-like spheroids Transfection, 5 ÂµM, single dose, n=3, 7 days, mean, SD, ddPCR Control EON 0 20 40 60 80 100 Editing (%) Merge vGlut Merge BIII Tub vGAT Hoechst GFAP Hoechst 64ProQR Therapeutics â€“ Investor and Analyst Event 2024 65 Consistent CNS editing demonstrated across species â€¢ Up to 40% editing in vivo leading to 26-fold change in protein function recovery in brain tissues of interest at 4 weeks with a single dose in mice model â€¢ In rat, Axiomer EONs demonstrated up to 50% editing in vivo with sustained editing between W2 and W4 after single dose â€¢ Up to 30% RNA editing reported in brain and approx. 50% in spinal cord in NHP in vivo ICV, 250Î¼g, undisclosed target, single dose, n=6, 4 weeks, ddPCR, mean, SD ICV, 500Î¼g, APP, single dose, n=5, 2 weeks, ddPCR, mean, SD Control Spinal cord Lombar W2

Cerebellum W2 Medulla W2 Spinal cord Thoracic W2 Spinal cord Cervical W2 Cortex W2 Pons W2 Midbrain W2 Hippocampus W2 0 10 20 30 40 50 Editing % Cerebellum Parietal cortex Frontal cortex Pons Medulla Spinal cord Cervical Temporal cortex Spinal cord Thoracic Spinal cord Lumbar 0 10 20 30 40 50 Editing (%) IT administration, undisclosed target 12mg, single dose, n=3*, 7 days, ddPCR MICE in vivo NHP in vivo Cortex Hippocampus Cerebellum Midbrain 0 10 20 30 40 50 Editing (%) Control EON RAT in vivo * Data of 2 NHPs not analyzable due to human error during injection procedure. Axiomer holds strong potential to make a meaningful impact to CNS diseases ProQR Therapeutics â€“ Investor and Analyst Event 2024 66 Strong RNA Editing Performance â€¢ Robust RNA editing in critical CNS regions validating the efficiency of Axiomer platform in CNS indications Broad Applicability Across CNS Regions â€¢ RNA editing was successfully achieved in multiple regions of the nervous system, indicating the platformâ€™s broad applicability across different CNS regions Consistent and Durable Results with Well Understood Safety Profile â€¢ Consistent RNA editing across species, with durable effects observed â€¢ EONs have been observed to have a favorable safety profile in CNSProQR Therapeutics â€“ Investor and Analyst Event 2024 AX-2402 RNA editing therapy targeting MECP2 for Rett Syndrome 67 Rett Syndrome is a devastating and progressive neurodevelopmental disorder caused by variants in the transcription factor Methyl CpG binding protein 2 (MECP2). There is a high unmet need for a disease modifying therapy. Nonsense variants lead to severe phenotypes. They represent more than one third of Rett Syndrome cases and are projected to affect 20,000 individuals in US and EU.1,2 Rett Syndrome is not a neurodegenerative disorder and restoring levels of the MECP2 protein has shown to reverse symptoms in mice.3 Axiomer has the potential to restore the precise level of MECP2 protein regulatory function, which is lacking in Rett Syndrome, and become a disease modifying therapy. Rett Syndrome Research Trust partnership includes $9.1 M in funding; collaboration established in January 2024, expanded in December 2024 1Krishnaraj R, et al. Hum Mutat. 2017 Aug;38(8):922-93; 2RSRT 2023 conference; 3Guy J, et al. Science. 2007 Feb 23;315(5815):1143-7.â€¢ Monica Coenraadsâ€™ involvement with Rett syndrome began the day her then-two-year-old daughter was diagnosed with the disorder. A year later, in 1999, she co-founded the Rett Syndrome Research Foundation (RSRF) and held the position of scientific director during the eight years of the Foundationâ€™s drive to stimulate scientific interest and research in Rett syndrome, culminating with the groundbreaking work in 2007 which demonstrated the first global reversal of symptoms in preclinical models of the disorder. Monica launched the Rett Syndrome Research Trust in late 2008 to pursue the next steps from that milestone. â€¢ As chief executive officer she oversees all aspects of the organization, including day-to-day operations, strategic direction, fundraising, and communications. Together with her colleagues and with input from advisors and the scientific community at large, Monica sets and executes RSRT's research agenda. â€¢ Under Monicaâ€™s leadership at RSRF and RSRT, $117 million has been raised for Rett syndrome. ProQR Therapeutics â€“ Investor and Analyst Event 2024 68 Monica Coenraads, MBA Founder, Chief Executive Officer at Rett Syndrome Research TrustProQR Therapeutics â€“ Investor and Analyst Event 2024 AX-2402 RNA editing therapy targeting MECP2 for Rett Syndrome 69 Rett Syndrome is a devastating and progressive neurodevelopmental disorder caused by variants in the transcription factor Methyl CpG binding protein 2 (MECP2). There is a high unmet need for a disease modifying therapy. Nonsense variants lead to severe phenotypes. They represent more than one third of Rett Syndrome cases and are projected to affect 20,000 individuals in US and EU.1,2 Rett Syndrome is not a neurodegenerative disorder and restoring levels of the MECP2 protein has shown to reverse symptoms in mice.3 Axiomer has the potential to restore the precise level of MECP2 protein regulatory function, which is lacking in Rett Syndrome, and become a disease modifying therapy. Rett Syndrome Research Trust partnership includes $9.1 M in funding; collaboration established in January 2024, expanded in December 2024 1Krishnaraj R, et al. Hum Mutat. 2017 Aug;38(8):922-93; 2RSRT 2023 conference; 3Guy J, et al. Science. 2007 Feb 23;315(5815):1143-7.â€¢ MECP2 gene, encoding methyl-CpG binding protein 2 (MeCP2): â€¢ Master epigenetic modulator of gene expression and plays a vital role in neuronal maturation and function â€¢ Mutations lead to misfolded, truncated or absent protein and loss of function â€¢ This loss of MECP2 regulating function leads to Rett syndrome and 35% of point mutations cause a premature termination codon (PTC) â€¢ In 2007, Adrian Bird's lab demonstrated that Rett syndrome symptoms are reversible in mice1 ProQR Therapeutics â€“ Investor and Analyst Event 2024 70 MECP2 gene is frequently mutated in Rett syndrome (RTT) WT mice Mecp2 mutant mice Mecp2 mutant treated mice Direction of improvement 1Guy J, et al. Science. 2007 Feb 23;315(5815):1143-7. Figure adapted from Guy J, et al. Science. 2007 Feb 23;315(5815):1143-7.MECP2 expression level tightly regulated in neurons Axiomer is a well-suited approach to restore physiological levels of MECP2 ProQR Therapeutics â€“ Investor and Analyst Event 2024 71 â€¢ Axiomer approach makes use of ADAR endogenous system to restore physiological levels of functional MECP2 â€¢ Axiomer avoid the risk of expressing unsafe levels of MECP2, potentially leading to MECP2 duplication syndrome Overexpression leads to toxicity (1.5-fold increase) Deficit due to lack of MECP2 MECP2 expression level Physiological MECP2 level MECP2 duplication syndrome RETT syndromeAxiomer has the potential to restore physiological levels of functional MECP2 AX-2402 correcting MECP2 R270X into WT-like R270W ProQR Therapeutics â€“ Investor and Analyst Event 2024 72 â€¢ MeCP2 protein restoration/recovery â€¢ MeCP2 R270W (Arg > Trp) mouse model indistinguishable from wild type mice Postnatal microcephaly, stereotypic hand movements, ataxia, abnormal breathing, and growth retardation, social withdrawal, loss of speech, seizures GGGGCUGA>GAAGCCG EXON 3 EXON 4 EXON 3 EXON 4 EXON 5 GGGGCC>UGAAAGCCG RETT syndrome WT like phenotypeProQR Therapeutics â€“ Investor and Analyst Event 2024 73 R270W variant demonstrates wild-type like profile AX-2402 can restore physiological levels of functional MECP2 potentially reverting Rett syndrome into a WT like phenotype1 Severity score (0-12) Probability of survival Body weight (g) Brain weight (mg) v 1Colvin, S. (2023) thesis. Massachusetts Institute of Technology. Figures adapted from: Colvin, S. (2023) thesis. Massachusetts Institute of TechnologyEON mediated editing in patient's cells increases mRNA levels and restores protein expression PTC recoding leading to absent NMD mediated RNA degradation ProQR Therapeutics â€“ Investor and Analyst Event 2024 74 Up to 80 % editing of R270X MECP2 in patient fibroblasts Increased MECP2 RNA levels due to PTC recoding and NMD inhibition Increased R270W MECP2 protein levels Control EON A EON B 0 20 40 60 80 100 Editing (%) Control EON A EON B 0 2 4 6 Fold change (vs. control) MeCP2-R270X EON A 0 2 4 6 8 10 Fold increase from MeCP2-R270X Non treated EON, Editing oligonucleotide; NT, Non-treated; TF, transfection, Conditions panel on the left and middle: 100 nM EON, transfection, 48h, N=2, meanÂ±SEM. Conditions panel on the right: MeCP2-R270X-NanoLuc activity; 100 nM EON, transfection, 48h, N=8, meanÂ±SEM. ProQR Therapeutics â€“ Investor and Analyst Event 2024 75 Preliminary clinical trial design Single dose Repeated dose â€¢ Preliminary Phase 1/2 SAD & MAD design â€¢ Up to 18 subjects with the R270X mutation â€¢ Primary objective: safety, tolerability and pharmacokinetics â€¢ Secondary objectives: target engagement and biomarkers â€¢ Financially supported by $8.1M funding provided by Rett syndrome Research Trust â€¢ Clinical candidate selection in 2025 â€¢ Top-line data expected in 2026 Dose 1, N=3, IT Dose 2, N=3, IT Dose 3, N=3, IT Dose 1, N=3, IT, Q3-6M Dose 2, N=3, IT, Q3-6M Dose 3, N=3, IT, Q3-6MTargeting B4GALT1 to reduce the risk of cardiovascular diseases AX-1412 Program ProQR Therapeutics â€“ Investor and Analyst Event 2024 76 Presenter: Gerard PlatenburgProQR Therapeutics â€“ Investor and Analyst Event 2024 77 AX-1412 RNA editing therapy targeting B4GALT1 for cardiovascular diseases Leading causes of death in the world ~18 million people die from CVDs every year (32% of all global deaths) Despite therapies, the unmet medical need remains. AX-1412 is designed to provide people with a protective genetic variant of B4GALT1 that is associated with 36%1 reduction in the risk of cardiovascular disease. AX-1412 may become a stand-alone cardiovascular therapy that may also work synergistically with standard of care to further reduce risk of CVDs. 1Montasser ME, et al. Science. 2021 Dec 3;374(6572):1221-1227ProQR Therapeutics â€“ Investor and Analyst Event 2024 78 B4GALT1 p.Asn352Ser variant reduces CVD risk â€¢ It is described that people who carry missense variants like the p.Ans352Ser in B4GALT1, have 36% lower chance of the development of coronary artery disease.1 This variant is known as the â€œold Amish order variantâ€ â€¢ This variant reduces CVD risk through 2 independent risk factors, fibrinogen and LDL-C, through independent pathways from PCSK9 â€¢ This protective variant is a A-to-

G variant, on that can be introduced by Axiomer mediated ADAR editing â€¢ B4GALT1 is not suitable for knockdown technologies, as leads to semi-lethality and severe development abnormalities in mouse studies 1Montasser ME, et al. Science. 2021 Dec 3;374(6572):1221-1227ProQR Therapeutics â€“ Investor and Analyst Event 2024 79 Glycosylation is a key process in lipid metabolism â€¢ Glycosylation stabilizes the folding and conformation of apolipoproteins (e.g., ApoB, ApoE), ensuring proper assembly and secretion of lipoproteins such as LDL and HDL. â€¢ Glycosylation of receptors like LDLR is critical for their membrane localization and ligand binding, enabling efficient lipoprotein clearance from the bloodstream. â€¢ Aberrant glycosylation can lead to dysfunctional lipoproteins, a key driver of atherosclerosis. 1Pirillo A, et al. Cardiovasc Res. 2021 Mar 21;117(4):1033-1045. Physiological lipoprotein glycosylation1B4GALT1 p.Asn352Ser variant to reduce galactosylation of CVD risk factors ProQR Therapeutics â€“ Investor and Analyst Event 2024 80 Fibrinogen ApoB EON ADAR Fibrinogen ApoB B4GALT1 mRNA B4GALT1 mRNA B4GALT1 protein B4GALT1-p.Ans352Ser protein Reduction in galactosylation INTRODUCTION OF PROTECTIVE VARIANT WT SITUATIONSEON-mediated editing of B4GALT1 leads to reduced glycosylation activity In line with natural population ProQR Therapeutics â€“ Investor and Analyst Event 2024 81 1Montasser ME, et al. Science. 2021 Dec 3;374(6572):1221-1227. Percentage of 352Asn B4GALT1 galactosylation activity of 352Asn B4GALT1 and 352Ser B4GALT1 immunoprecipitated proteins B4GALT1 activity reported in Montasser et al.1 COS-7 cells, cell lysate, transfection, n=4, mean, SEM EON mediated editing of B4GALT1 in PHH 5ÂµM transfection, dPCR, mean, SD, n=3 B4GALT1 activity following editing PMH, cell lysate, transfection 5ÂµM, 4 days, mean, SD, ANOVA Control EON A EON B 0 10 20 30 40 Editing (%) Control EON A EON B 0 50 100 B4GALT1 activity per total protein (mU/Âµg) 0.0224 352Asn 352Ser 0 50 100 B4GALT1 activity (%) P=0.027ProQR Therapeutics â€“ Investor and Analyst Event 2024 82 E3L.CETP mice disease model is industry standard for assessing CVD therapeutics â€¢ CETP facilitates the transfer of cholesteryl esters from HDL to VLDL and LDL, a key process in human lipid metabolism that is absent in most rodent models. â€¢ These mice, fed a high-fat high-cholesterol diet (HFCD), exhibit a biphasic dyslipidemic response, closely mimicking plasma lipid changes in humans â€¢ The presence of CETP in this model makes it uniquely suited to study dyslipidemia and cholesterol metabolism, especially in relation to B4GALT1, which is involved in glycosylation processes affecting lipid metabolism. â€¢ In humans, most circulating lipids are confined to VLDL/LDL particles . Human E3L.CETP mice disease model Wildtype healthy miceB4GALT1 editing impacts activity of key proteins involved in lipid metabolism Minimal changes in transcript and protein levels associated with decrease in CETP activity in vivo ProQR Therapeutics â€“ Investor and Analyst Event 2024 83 Control EON 1 0 5 10 15 20 Log2 (read_counts) CETP RNA Control EON 1 0 5 10 15 20 Log2 (Intensity) CETP PROTEIN Control EON 1 0 20 40 60 80 nmol/hr/mL âœ± âœ± -34% CETP activity CETP RNA, protein and activity following EON B treatment E3L.CETP mice, LNP formulation, 2mg/kg, Q1W, D31, RNAseq, Roar, mean, max-min n=3, T-test Reduced CETP activity in the absence of changes at the transcriptomic or proteomic levels highlights the impact of EON on glycosylation rather than on expression levelsD1 D19 D33 D46 3 4 5 6 7 8 Plasma LDL-c (mM) - 30% ProQR Therapeutics â€“ Investor and Analyst Event 2024 84 EON-mediated editing of B4GALT1 leads to meaningful effect on key biomakers in E3L.CETP Mice Following treatment with EON B, a marked reduction in total cholesterol, ApoB, and LDL-c by observed already at Day 19 confirms our approach to address cardiovascular diseases D1 D19 D33 D46 0 10 20 30 CETP activity (nmol/mL/h) Control EON B - 39% CETP activity D1 D19 D33 D46 0.0 0.5 1.0 1.5 ApoB (mg/mL) - 72% ApoB D1 D19 D33 D46 0 1 2 3 4 5 Fibrinogen (mg/mL) - 55% Fibrinogen Plasma LDL-c B4GALT1 editing and biomarkers in E3L.CETP mice (N=10, 2mg/kg, LNP formulation, IV Q1W, D46, ddPCR) D1 D19 D33 D46 0 5 10 15 20 25 Total cholesterol (mmol/L) - 61% Total Cholesterol Control EON B 0 5 10 Editing (%) (G/G+A) Control EON Bâ€¢ Treatment with EON B significantly decreases VLDL and LDL cholesterol compared to control â€¢ These lipoproteins are associated with increased cardiovascular risk due to their role in atherosclerotic plaque formation â€¢ HDL cholesterol which supports reverse cholesterol transport and is associated with reduced cardiovascular risk, remains unchanged B4GALT1 EON leads to a positive shift in lipoprotein profiles Specifically targeting atherogenic lipoproteins ProQR Therapeutics â€“ Investor and Analyst Event 2024 85 Impact on lipoprotein profile following editing of B4GALT1 in E3L.CETP mice (N=10, 2mg/kg, LNP formulation, IV Q1W, D46) 0 10 20 0 2 4 Fraction Cholesterol (mmol/L) Control EON B VLDL LDL HDL Direction of improvement Control EON BSummary & next steps AX-1412 for CVD ProQR Therapeutics â€“ Investor and Analyst Event 2024 86 EON-mediated RNA editing of B4GALT1 leads to the required reduction in galactosylation reflecting the human genetics observed effect LNP-delivered EON editing B4GALT1 leads to editing and meaningful changes in biomarker effect on LDLC, CEPT, cholesterol and fibrinogen in an industry-standard in vivo disease model Further optimization of a GalNAc delivered EON ongoing to achieve a TPP desirable for CVD Expected to provide an update on the optimization efforts in mid 2025Targeting PNPLA3 to address unmet medical needs in MASH AX-2911 Program ProQR Therapeutics â€“ Investor and Analyst Event 2024 87 Presenter: Gerard PlatenburgMASH and subsequent stages of liver disease are very prevalent and still on the rise worldwide. MASH individuals have a high unmet medical needs due to the progressive nature of the disease (cirrhosis and hepatocellular carcinoma) and limited therapeutic options available1 PNPLA3 (patatin-like phospholipase domain-containing 3) I148M is a variant commonly reported in the MASH population worldwide (20-60% of the patients) and is known as associated risk factor. 2,3 Approximately 8 million individuals in US and EU are homozygous for the 148M variant. Axiomer EONs have the potential to change the Methionine into a Valine bringing the PNPLA3 protein back to a WT-like functional conformation. AX-2911 RNA-editing therapy to address Metabolic dysfunction associated steatohepatitis (MASH) ProQR Therapeutics â€“ Investor and Analyst Event 2024 88 1Sandireddy R, et al. Front Cell Dev Biol. 2024 Jul 16;12:1433857; 2Romeo S, et al. Nat Genet. 2008 Dec;40(12):1461-5; 3Salari N, et al. BMC Endocr Disord. 2021 Jun 19;21(1):125. PNPLA3 148I (WT) Isoleucine (ATC) PNPLA3 148M (Mutant) Methionine (ATG) PNPLA3 148V (Axiomer de-novo variant) Valine (GTG) ProQR Therapeutics â€“ Investor and Analyst Event 2024 89 Axiomer creates a PNPLA3 protein with WT-like functionality Electrostatic potential Hydrophobicity In silico analysis of variants â€¢ 148M shows a non-conservative substitution with predicted functional consequences, with change in binding cavity volume limiting access of substrate to the active site â€¢ Equivalent potential between Isoleucine (WT) or Valine (Axiomer correction) at location 148 in 3D models â€¢ 148I and 148V predict no functional consequences for PNPLA3, with valine expected to behave like isoleucine F226 not included herePNPLA3 148V variant has WT-like lipid metabolizing properties 148I and 148V reports equivalence in lipid droplet sizes ProQR Therapeutics â€“ Investor and Analyst Event 2024 90 148I (WT) 148M (mut) 148V (de-novo) Treatment conditions: HeLa cells, plasmid, transfection, 250uM linoleic acids, 24h, cell lipase activity by IF One-way ANOVA, ****, P<0.0001; Mean, SEM. 148I Mean area of Bodipy per cell (Âµm2) 148M 148V Hoechst (nuclei), Bodipy (Lipids) and M2 anti-flag (PNPLA3) â€¢ The wild-type 148I shows smaller lipid droplets, reflecting normal lipid metabolism â€¢ The 148M variant induces significantly larger lipid droplets, consistent with its pathogenic role in lipid metabolism disorders â€¢ The corrected variant 148V results in wild-type like droplet sizes, suggesting a corrective effect on lipid accumulation, similar to 148IProQR Therapeutics â€“ Investor and Analyst Event 2024 91 EON mediated PNPLA3 editing leads to over 50% RNA editing and change in lipid droplet Editing of PNPLA3 in PHH 100nM EON, transfection, 72h, dPCR, mean, SEM, n=3 Change in intracellular lipid droplets post PNPLA3 148V EON treatment in HepG2 Bodipy/DAPI stainings, 5ÂµM EON, transfection, exposure to linoleic acid, mean, SEM, n=2 Control EON A EON B EON C 0 20 40 60 Editing (%) 24 hours 48 hours 120 hours -40 -30 -20 -10 0 % Change compared to MockSummary & next steps AX-2911 for MASH ProQR Therapeutics â€“ Investor and Analyst Event 2024 92 Final optimization of AX-2911 EONs ongoing for clinical candidate selection in 2025 Development activities to start in 2025 Expected 3-6 monthly dosing interval subcutaneous GalNAc-delivered Start clinical trial in 2026Daniel A. de Boer Closing summary ProQR Therapeutics â€“ Investor and Analyst Event 2024 93DEVELOPMENT PIPELINE AX-0810 for Cholestatic diseases NTCP CTA filing in Q2 2025 ~100K patients AX-2402 for Rett syndrome MECP2 R270X Candidate selection in 2025 ~5K patients AX-1412 for Cardiovascular disease B4GALT1 Scientific update in mid 2025 ~200M patients AX-2911 for MASH PNPLA3 Candidate selection in 2025 ~8M patients DISCOVERY PIPELINE AX-1005 for CVD Undisclosed ~200M patients AX-0601 for obesity and T2D Undisclosed ~650M patients AX-9115 for rare metabolic condition Undisclosed AX-2403 for Rett syndrome MECP2 R168X ~6K patients AX-2404 for Rett syndrome MECP2 R255X ~5K patients AX-2405 for Rett syndrome MECP2 R294X ~6K patients AX-2406 for Rett syndrome MECP2 R133H AX-3875 for rare metabolic & CNS disorder Undisclosed AX-4070 for rare CNS disorder Undisclosed PARTNERED PIPELINE 10 targets (option to expand to 15) Undisclosed ProQR Therapeutics â€“ Investor and Analyst Event 2024 ProQR development pipeline 1Approximately 100K people affected with Primary Sclerosing Cholangitis and Biliary Atresia in US and EU5. 2Approximately 200 million people suffer from too high a level of cholesterol in US and EU5. SLC10A1 is the gene that encodes for NTCP protein. CVD: Cardiovascular Diseases, NASH: Nonalcoholic steatohepatitis, T2D: Type 2 Diabetes. | References: Trivedi PJ, et al. Clin Gastroenterol Hepatol. 2022 Aug;20(8):1687-1700.e4; Schreiber RA, et al. J Clin Med. 2022 Feb 14;11(4):999; Tsao CW, et al. Circulation. 2022;145(8):e153â€“e639. World Health Organization, World Gastroenterology Organization 94 Progress undisclosed TARGET DISCOVERY NON-CLINICAL CLINICAL NEXT MILESTONE ESTIMATED POPULATIONAX-0810 for Cholestatic disease â€¢ CTA submission Q2 2025 â€¢ Top-line data Q4 2025 AX-2402 for Rett Syndrome â€¢ Clinical candidate selection in 2025 â€¢ Anticipated trial start and top-line data in 2026 AX-1412 for Cardiovascular disease â€¢ Non-clinical data update in mid 2025 AX-2911 for MASH â€¢ Clinical candidate selection in 2025 â€¢ Anticipated trial start and top-line data in 2026 Partnerships â€¢ Opportunity to earn up to $3.75B in milestones in the Lilly partnership â€¢ Opportunity to receive a $50 M opt-in fee from Lilly for expansion to 15 targets â€¢ Opportunity for other strategic partnerships ProQR Therapeutics â€“ Investor and Analyst Event 2024 95 Catalyst overview 4 trial readouts expected in 2025-2026, cash runway into mid-2027Well positioned to advance Axiomer ProQR Therapeutics â€“ Investor and Analyst Event 2024 96 â,¬ Clinical trial results across 4 trials in 2025 and 2026 expected â€¢ Clinical PoC data of NTCP trial in 2025 â€¢ Up to 4 clinical trials with data readouts in 2025/2026 Rich discovery pipeline with potential for broad pipeline expansion â€¢ Large number of potential therapeutic applications in discovery pipeline â€¢ Broad applicability beyond current discovery pipeline Leading IP position â€¢ Axiomer is protected by >20 published patent families â€¢ Continuously investing in expanding IP estate Validating Strategic Partnerships â€¢ Eli Lilly collaboration valued up to $3.9B, with opportunity for near-term milestones â€¢ Rett Syndrome Research Trust cofinancing of AX-2402 program â€¢ Selectively form additional partnerships Strong balance sheet â€¢ â,¬89.4 million cash and cash equivalents as of end of Q3, plus $82.1 million gross proceeds from October financing â€¢ Cash runway to mid-2027, excluding potential for additional BD-related upsideQ&ADaniel de Boer Founder and Chief Executive Officer Gerard Platenburg Chief Scientific Officer RenÃ© Beukema Chief Corporate Development Officer Q&AITâ€™S IN OUR RNA GRAPHIC 3 tm2430675d1_ex99-1img001.jpg GRAPHIC

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