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**VX-147 PHASE 2 RESULTS
SUPPORT ADVANCEMENT TO
PIVOTAL DEVELOPMENT IN A
BROAD POPULATION OF
PEOPLE WITH APOL1-
MEDIATED KIDNEY DISEASE**

DECEMBER 1, 2021

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AGENDA

POSITIVE VX-147 PHASE 2 RESULTS SUPPORT ADVANCEMENT TO PIVOTAL DEVELOPMENT



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President and Chief Executive Officer



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SAFE HARBOR STATEMENT

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, (i) our plans to advance VX-147 into pivotal development in Q1 2022, (ii) our expectation that VX-147 is a potential first-in-class therapy for more than 100,000 patients living with APOL-1 mediated kidney disease, (iii) statements regarding our plans to investigate additional small molecule APOL1 inhibitors in the clinic, and (iv) expectations regarding clinical design and regulatory approval, including our discussions with regulatory authorities. While Vertex believes the forward-looking statements contained in this presentation are accurate, these forward-looking statements represent the company's beliefs only as of the date of this presentation and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, risks related to the company's APOL1 research and development programs, including the potential future clinical trial design and regulatory review of VX-147, that data from the company's research and development programs may not support registration or further development of its compounds due to safety, efficacy, or other reasons, and other risks listed under the heading Risk Factors in Vertex's annual report filed with the Securities and Exchange Commission and available through the company's website at www.vrtx.com and on the SEC's website at www.sec.gov. You should not place undue reliance on these statements or the scientific data presented. Vertex disclaims any obligation to update the information contained in this presentation as new information becomes available.

VX-147 CLINICAL RESULTS VALIDATE APOL1 INHIBITION AS A THERAPEUTIC MECHANISM AND SIGNIFICANT OPPORTUNITY IN APOL1-MEDIATED KIDNEY DISEASE



Phase 2 results for VX-147 showed statistically significant and clinically meaningful reduction in proteinuria, providing strong validation for APOL1 inhibition as a mechanism for treating the underlying cause of APOL1-mediated kidney disease (AMKD)



We now have an opportunity to transform the treatment of AMKD for the more than 100,000 people suffering from the disease



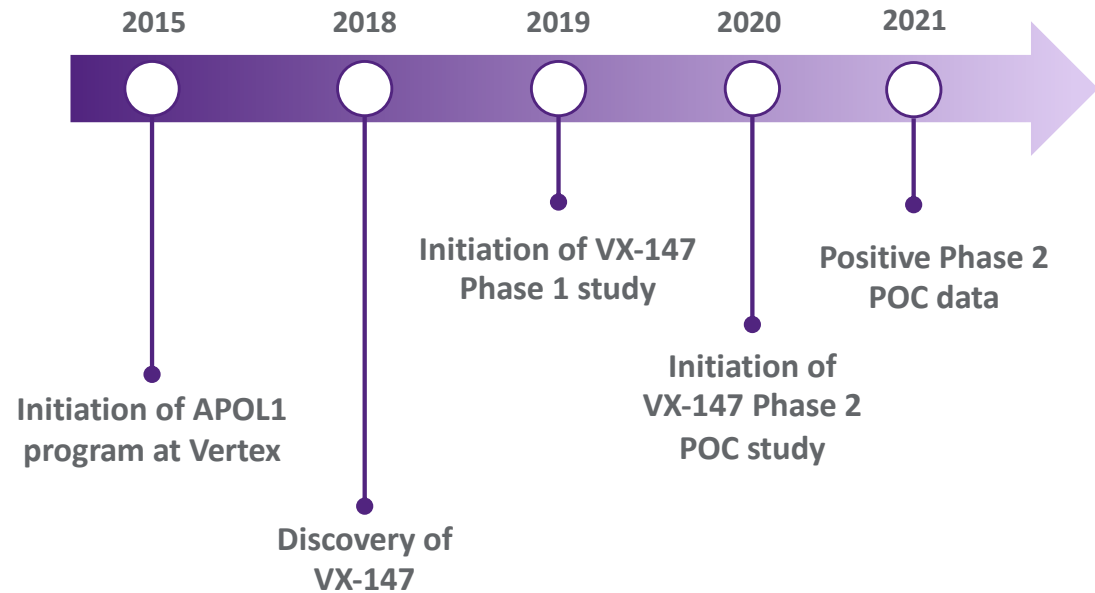
We plan to initiate a pivotal program in Q1 2022

APOL1 AT VERTEX

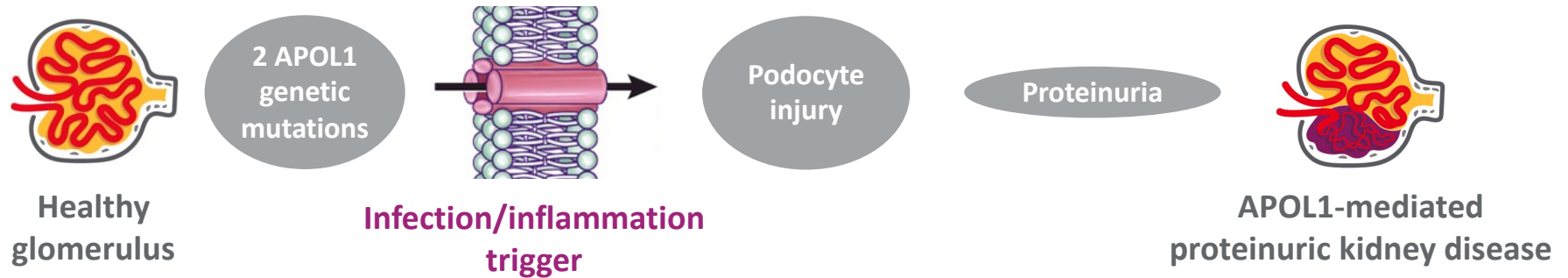
Our vision:

Discover and develop small molecule inhibitors of APOL1 and transform the lives of patients with proteinuric kidney disease

FROM PROGRAM INITIATION TO POSITIVE PHASE 2 PROOF OF CONCEPT DATA IN SIX YEARS



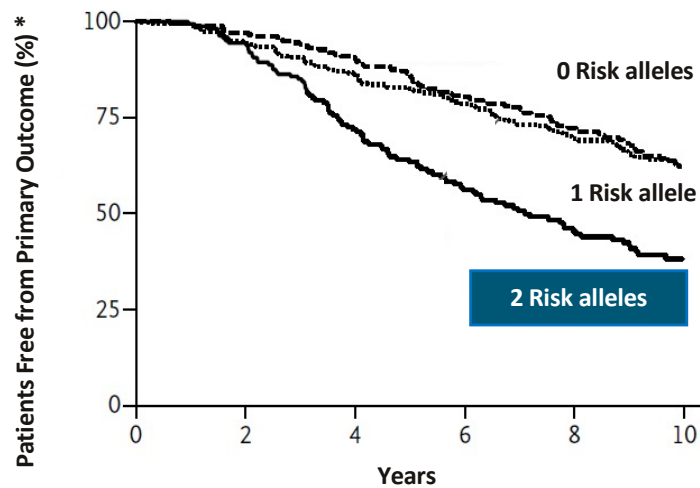
INHERITED APOL1 MUTATIONS ENCODE A TOXIC GAIN-OF-FUNCTION PROTEIN, DAMAGING PODOCYTES, LEADING TO PROTEINURIA AND PROGRESSION TO END-STAGE RENAL DISEASE (ESRD)



Cellular injury driven by APOL1 genetic mutations is the common mechanism leading to progressive glomerular dysfunction and proteinuria across multiple clinically and histologically defined kidney diseases

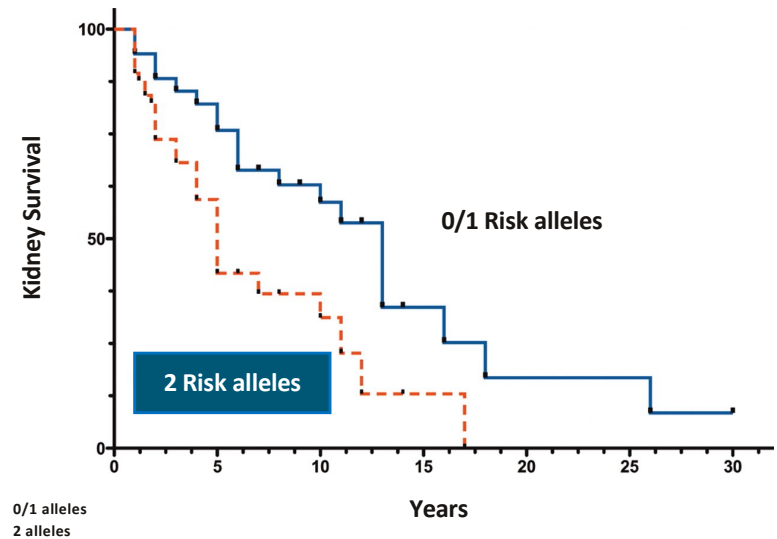
PATIENTS WITH PROTEINURIA AND TWO APOL1 GENETIC MUTATIONS RAPIDLY PROGRESS TO ESRD, REGARDLESS OF CLINICAL OR HISTOLOGICAL PRESENTATION

Interventional study: African American Study of Hypertension and Kidney Disease (AASK)*
N = 693



Parsa et al. NEJM 2013

Observational study: African Americans with Primary FSGS
N = 92



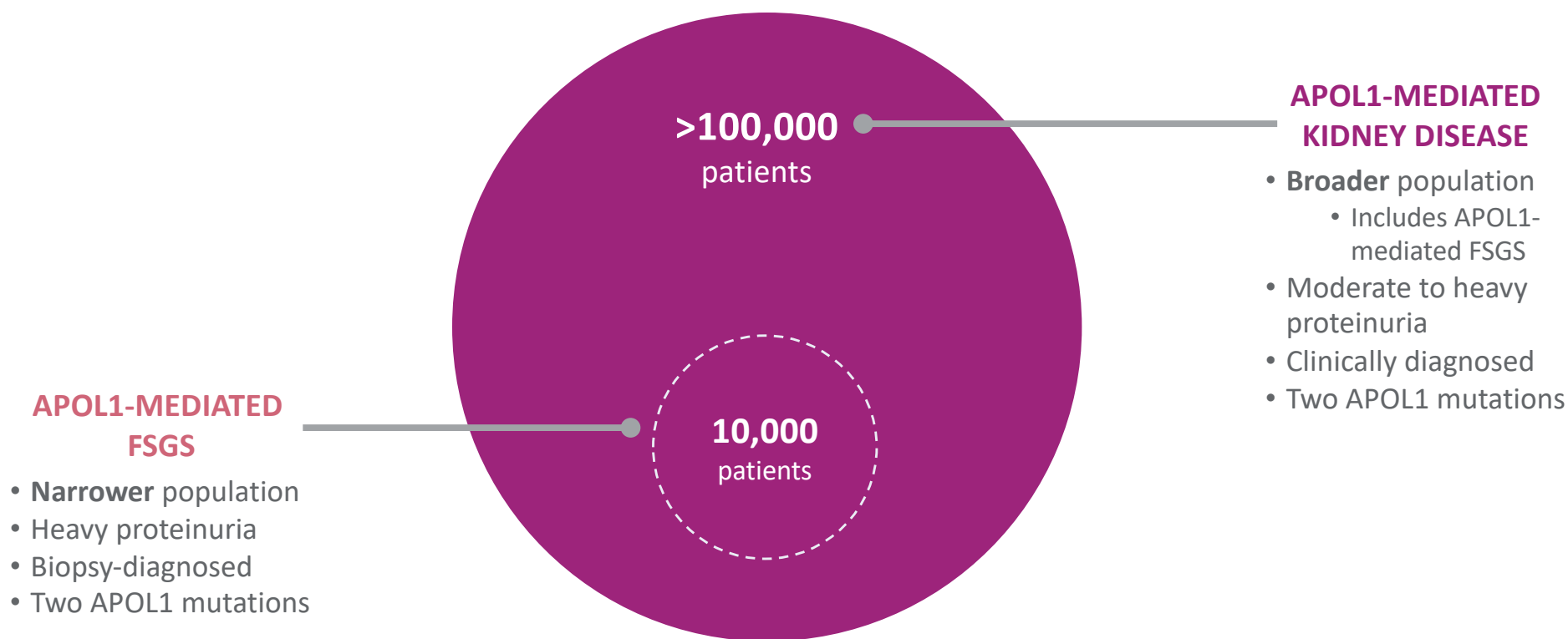
0/1 alleles
2 alleles

Kopp et al. JASN 2011

* In the AASK study, primary outcome (composite) was defined as a doubling of serum creatinine level or incident end-stage renal disease

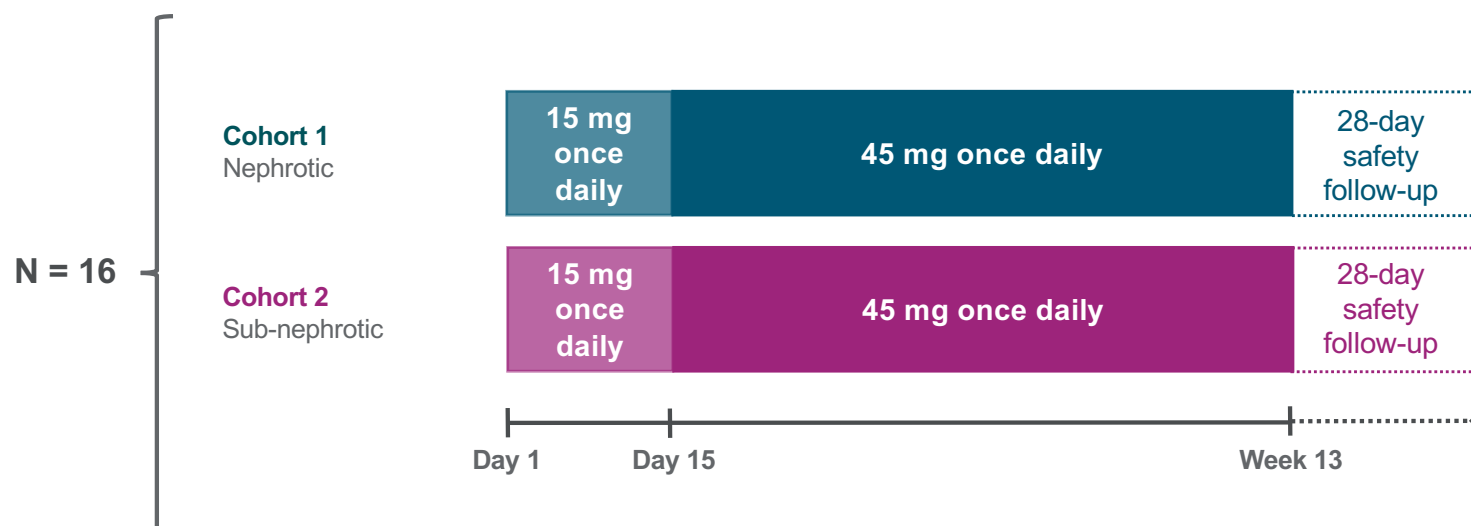
APOL1-MEDIATED KIDNEY DISEASE IS A GENETICALLY DEFINED CONDITION

APOL1-mediated kidney disease includes different clinical/histological presentations with the same genetic cause



VX-147 PHASE 2 RESULTS

VX-147 PHASE 2 PROOF OF CONCEPT STUDY OVERVIEW

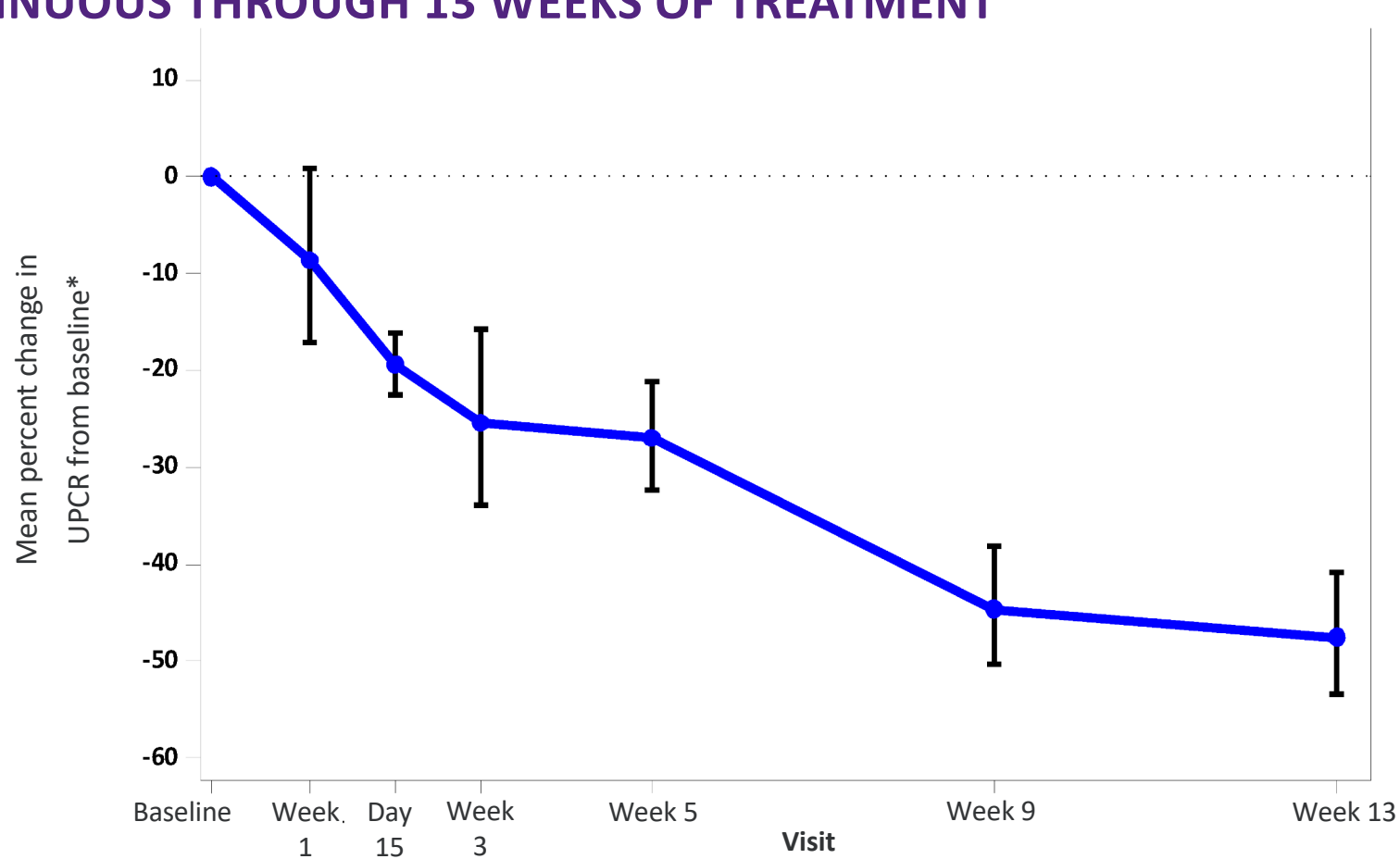


- **Primary Objective:** Evaluate ability of VX-147 to reduce proteinuria in patients with APOL1-mediated FSGS
- **Primary endpoint:** % change from baseline in UPCR (proteinuria) at week 13
- **Secondary endpoint:** Safety and tolerability; plasma pharmacokinetics

Inclusion criteria

- Adults ≥ 18 years to ≤ 65 years with 2 APOL1 genetic variants and biopsy-confirmed FSGS
- $eGFR \geq 27$ ml/min/1.73 m²
- Nephrotic range proteinuria: baseline UPCR ≥ 2.7 to < 10 g/g
- Sub-nephrotic range proteinuria: baseline UPCR ≥ 0.7 to < 2.7 g/g
- Allowed to be on a stable regimen of standard of care medication

REDUCTIONS IN PROTEINURIA WERE OBSERVED EARLY AND WERE CONTINUOUS THROUGH 13 WEEKS OF TREATMENT

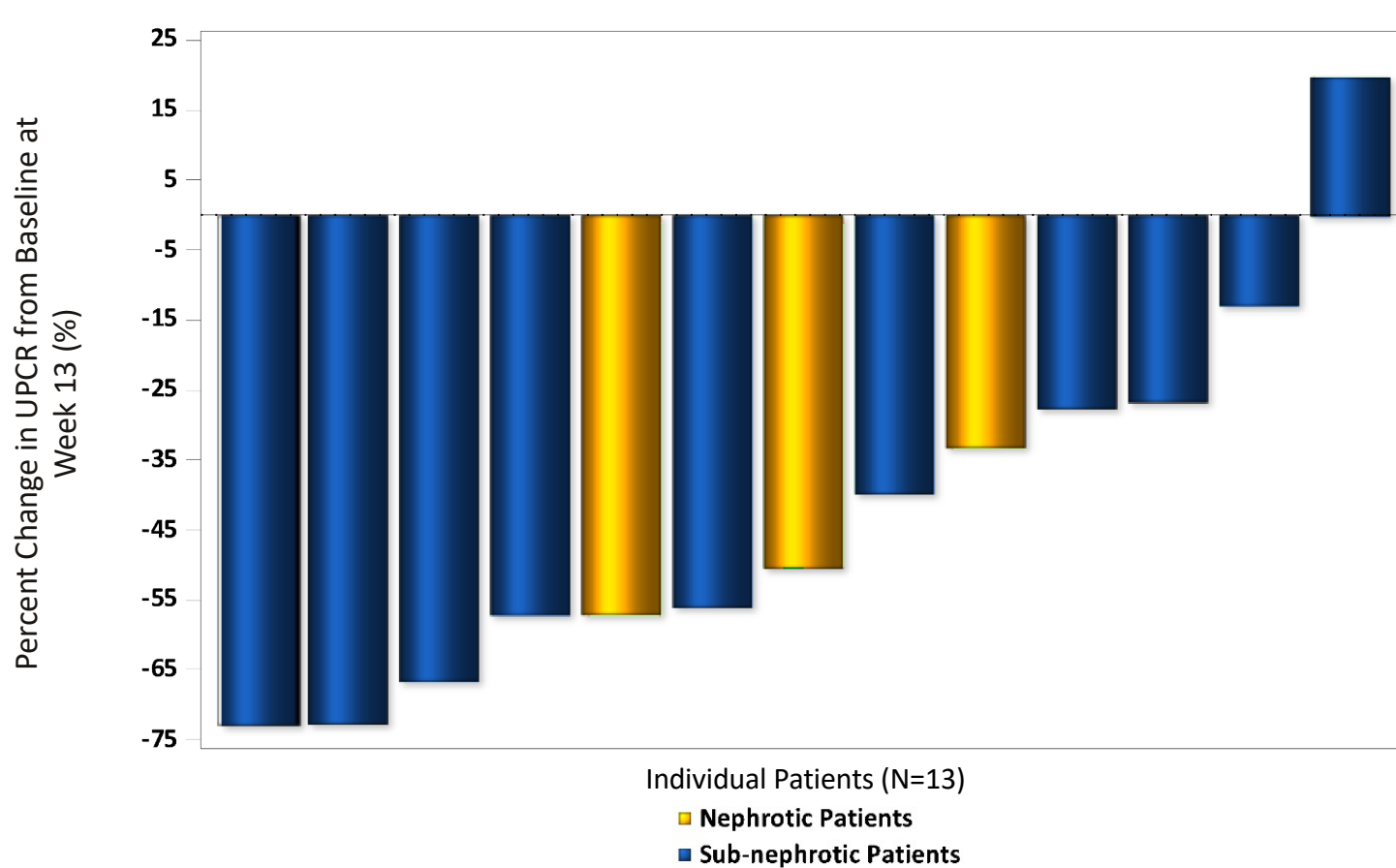


VX-147 SIGNIFICANTLY REDUCED PROTEINURIA IN AN APOL1-MEDIATED FSGS POPULATION

	Total N = 13	Nephrotic N = 3	Sub-nephrotic N = 10
Mean UPCR at Baseline (Standard Deviation)	2.21 (0.95)	3.47 (1.07)	1.84 (0.52)
Mean UPCR at Week 13 (Standard Deviation)	1.27 (0.73)	1.83 (0.58)	1.10 (0.71)
Mean percent change from baseline at Week 13* (95% confidence interval)	-47.6 (-60.0, -31.3)	-47.7 (-70.1, -8.5)	-47.5 (-63.4, -24.6)

* Geometric mean percent change from baseline

INDIVIDUAL PATIENT RESPONSES IN VX-147 PHASE 2 PROOF OF CONCEPT STUDY



VX-147 WAS GENERALLY SAFE AND WELL TOLERATED



No subjects
discontinued VX-147
due to AEs



No SAEs considered
related
to VX-147



All AEs were mild
to moderate

NEXT STEPS

Pivotal Program

- Expect to initiate VX-147 pivotal development in AMKD in Q1 2022
- End of Phase 2 meeting with regulators expected in near term
- Plan to pursue accelerated approval

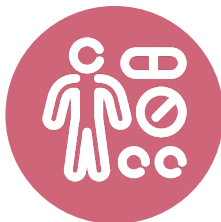
CONCLUSIONS



Phase 2 results for VX-147 showed statistically significant and clinically meaningful reduction in proteinuria, providing strong validation for APOL1 inhibition as a mechanism for treating the underlying cause of APOL1-mediated kidney disease (AMKD)



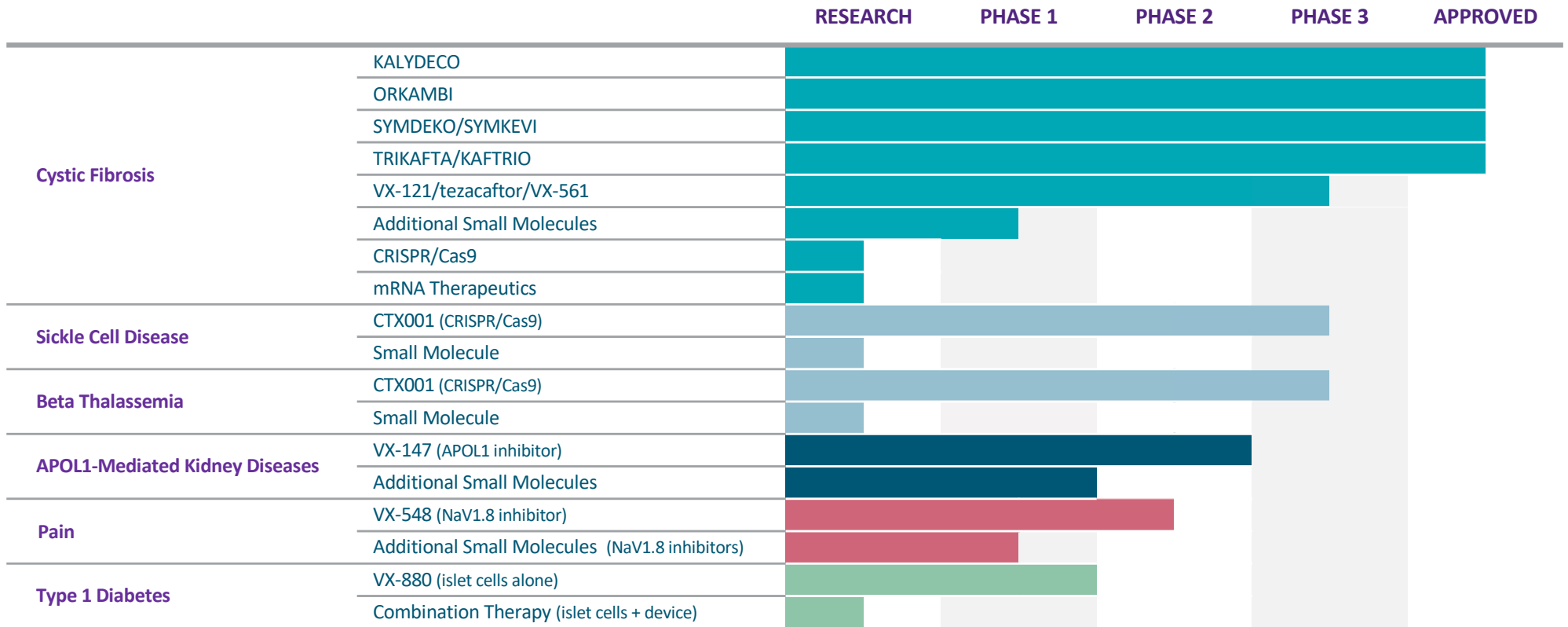
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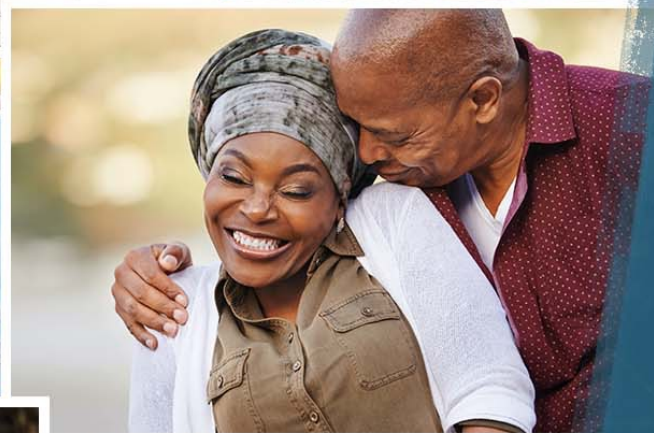


We plan to initiate a pivotal program in Q1 2022

THANK YOU
to all of the patients living with FSGS
who participated in the trial and to
the clinical study investigators

VERTEX R&D STRATEGY IS DELIVERING





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