A Deep Dive on Praliciguat
Investigational sGC Stimulator for HFpEF and Diabetic Nephropathy
Welcome

Jessi Rennekamp
Investor Relations and Corporate Communications, Cyclerion
Safe Harbor Statement

This presentation contains forward-looking statements. Any statements contained in these slides that are not based on historical facts may be deemed to be forward-looking statements. Words such as “anticipates,” “believes,” “has the potential to,” “expects,” and similar expressions are intended to identify these forward-looking statements. These forward-looking statements are based on Cyclerion’s current expectations and involve risks and uncertainties. Investors are cautioned not to place undue reliance on these forward-looking statements, such as statements about the size and design of clinical trials; the application, and potential benefits of, sGC stimulators; our strategy, including development and commercialization plans; the potential clinical efficacy of our product candidates; the timing of completion, and potential success, of our clinical trials and discovery efforts; the size of potential markets for our product candidates; and potential changes to current development and regulatory approval pathways.

Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statements. Applicable risks and uncertainties include those related to our lack of independent operating history; the risk that the separation from Ironwood may adversely impact our ability to attract or retain key personnel; the effectiveness of our development and commercialization efforts; risks generally associated with preclinical and clinical development and formulation development; the risk that findings from our completed nonclinical and clinical studies may not be replicated in later studies; risks and uncertainties pertaining to the efficacy, safety and tolerability of our product candidates; decisions by regulatory authorities; the risk that we may never get sufficient patent protection for our product candidates or that we might not be able to successfully protect such patents; the risks listed under the heading “Risk Factors” and elsewhere in our Registration Statement on Form S-1 filed with the Securities and Exchange Commission (SEC) on April 18, 2019, and in our subsequent SEC filings. These forward-looking statements speak only as of the date of this overview, and we undertake no obligation to update these forward-looking statements.
Cyclerion: Overview, Strategy, and the Power of sGC Stimulation

Peter Hecht
Chief Executive Officer, Cyclerion

Mark Currie
President and Chief Scientific Officer, Cyclerion

Andy Busch
Chief Innovation Officer, Cyclerion
The *time is now* for HFpEF and diabetic nephropathy

- New insights into pathophysiology highlight potential benefits of sGC stimulation
- Development and regulatory advances — Potential opportunity for more rapid and efficient path to global approval
- Cyclerion capitalizing on the moment: molecule, team, strategy
Event Agenda
8-10 a.m.

• Cyclerion Overview, Strategy, and the Power of sGC Stimulation
  o Peter Hecht, PhD, Chief Executive Officer, Cyclerion
  o Mark Currie, PhD, President, Cyclerion
  o Andy Busch, PhD, Chief Innovation Officer, Cyclerion

• Praliciguat in Heart Failure with Preserved Ejection Fraction (HFpEF)
  o James Udelson, MD, Tufts Medical Center
  o Cheryl Gault, Head of Strategy, Cyclerion

• Praliciguat in Diabetic Nephropathy
  o Barbara Gillespie, MD, MMS, FASN, University of North Carolina / Covance
  o Chris Wright, MD, PhD, Chief Medical Officer, Cyclerion

• Q&A
Nitric oxide (NO) signaling: Clinically validated pathway

- Multiple drugs created by targeting different steps in pathway
  - NO donors for angina (e.g., Nitropress®, Imdur®, Corvasal®, Corvaton®)
  - PDE5 inhibitors for erectile dysfunction and pulmonary arterial hypertension (e.g., Viagra®, Cialis®, Revatio®, Adcirca®)
  - sGC stimulator indicated for multiple forms of pulmonary arterial hypertension: Adempas®

- The sGC stimulator mechanism has the potential to fully leverage the NO-sGC-cGMP pathway
  - Target is broadly expressed in the body (unlike PDEs)
  - Synergizes with endogenous NO (unlike NO donors)
  - Drives cGMP levels at the source (unlike PDE inhibitors)
  - Has a durable response (unlike NO donors)
sGC: A single target with potential to address multiple aspects of disease

- **Therapeutic potential**
  - Cardiovascular
  - Renal
  - Metabolic
  - Vascular
  - CNS
  - Liver
  - Lung

- **Initial Breakthrough**
  - Neuronal function
  - Smooth muscle and vascular function

- **Emerging Insights**
  - Metabolism
  - Inflammation
  - Fibrosis
sGC stimulation amplifies endogenous NO signaling to impact multiple disease-relevant physiological responses

Example targets:
- MLCP/ion channels
- Titin
- TGFβ
- VASP/NFκB
- AMPK
- CREB

Physiological response:
- Blood flow
- Cardiomyocyte relaxation
- Fibrosis
- Inflammation
- Metabolism
- LTP, neuroprotection

Initial target indications:
- HFpEF
- Diabetic nephros.
- Sickle Cell Dis.
- Neurodegen.

MLCP: myosin light chain phosphatase; TGFβ: transforming growth factor β; VASP: vasodilator-stimulated phosphoprotein; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; AMPK: 5’ adenosine monophosphate-activated protein kinase; CREB: cAMP response element binding protein; LTP: long term potentiation; PKG: protein kinase G; PDE: phosphodiesterase
A wholly owned pipeline of differentiated molecules

**Clinical Programs**

- **Praliciguat**
  - Phase 2 proof-of-concept studies in diabetic nephropathy (DN) and heart failure with preserved ejection fraction (HFpEF)
  - Topline data expected Q4 2019

- **Olinciguat**
  - Phase 2 proof-of-concept study in sickle cell disease (SCD)
  - Topline data expected mid-2020

- **IW-6463**
  - Phase 1 study to determine profile for further study in serious neurodegenerative diseases
  - Topline data expected Q4 2019

**Preclinical**

- **Liver-targeted**
  - Liver

- **Lung-targeted**
  - Lung
Early clinical data support promising profile for potential treatment of cardiometabolic diseases

**Early clinical profile**

- Robust pharmacokinetics (oral, once-daily, large volume of distribution, non-renal clearance)
- Clear target engagement (\(\uparrow\) cGMP)
- Vascular pharmacology (\(\downarrow\) blood pressure)
- Metabolic effects in exploratory Ph2 in patients with diabetes and hypertension
  - \(\downarrow\) LDL-C, triglycerides, fasting plasma glucose
  - \(\uparrow\) Insulin sensitivity (reduction in HOMA-IR)
- Safety and tolerability supported advancement
Heart Failure with Preserved Ejection Fraction (HFpEF)

Dr. James Udelson
Chief, Division of Cardiology, Tufts Medical Center
Professor of Medicine and Radiology, Tufts University School of Medicine

Cheryl Gault
Head of Strategy, Cyclerion
Heart failure occurs when the heart is unable to maintain blood flow to meet the body’s needs

- Left ventricle is the main pumping chamber
- Systole = the period of cardiac contraction
- Diastole = the period of cardiac relaxation

**HFpEF**

**HFrEF**

**Systolic Heart Failure**
- Less blood pumped out of ventricles
- Weakened heart muscle can't squeeze as well

**Normal Heart**

**Diastolic Heart Failure**
- Stiff heart muscle can't relax normally
- Less blood fills the ventricles
HFpEF is associated with high morbidity and mortality

- Patients with HFpEF have shortness of breath, are functionally limited, require frequent hospitalizations, and have generally poor quality of life.
- 5-year survival post-hospitalization for HF is only 35-40%.
- HFpEF patients show high rates of comorbidities, including diabetes, obesity, hypertension, and chronic kidney disease.
- There are no approved therapies for HFpEF; standard of care therapy is focused on treatment of comorbidities.

Co-morbidities in HFpEF Patients

Note: Average age of patients is 76.8 and gender split is 53% female, 47% male. BMI=Body-Mass Index; IHD=Ischemic Heart Disease; Afib=Atrial Fibrillation; TIA=Transient Ischemic Attack.

A recent FDA Guidance highlights the opportunity for approval based on a functional endpoint

- Recent FDA guidance emphasizes that an effect on symptoms or physical function, without a favorable effect on survival or hospitalization, could be a basis for approving drugs to treat heart failure

- Potential for a more efficient path to approval
Changing views of HFpEF pathophysiology highlight the role of NO deficiency driven by comorbidities

Shah et al., Circulation. 2016;134:73-90
sGC stimulation has the potential to address at least 4 aspects of HFpEF pathophysiology

- Hemodynamics and coronary blood flow
- Myocardial Compliance
- Microvascular Inflammation
- Fibrosis

Potential benefits outside the heart
- Blood flow to skeletal muscle
- Renal function
- Metabolism
- Endothelial function

The PARAGON trial of ENTRESTO® in N=4822 HFpEF patients with EF≥45%, elevated NT-proBNP and structural heart disease showed a modest, nonsignificant trend on the primary endpoint (p = 0.059)

The result was driven by reductions in total HF hospitalizations (not CV death), and was greatest in patients with low EF and women

Results highlight the heterogeneity of HFpEF and the need for thoughtful patient selection for clinical trials

Results also highlight the difficulty of seeing a mortality benefit in HFpEF patients; trials with functional outcomes are more practical and could support approval

In Phase 2 SOCRATES-Preserved study, vericiguat (sGC stimulator) treatment was associated with improvements in quality of life measures. Majority of patients on 10 mg vericiguat showed moderate or large improvement.

KCCQ-CSS

Note: KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score

Filippatos G et al Eur J Heart Fail. 2017
Scientific Advisory Board

James E. Udelson, MD-Chair
Chief, Division of Cardiology, Tufts Medical Center
Professor, Tufts University School of Medicine

Marvin A. Konstam, MD
Chief Physician Executive, The CardioVascular Center Tufts Medical Center,
Professor, Tufts University School of Medicine, Boston, MA

Sanjiv Shah, MD, FAHA, FACC, FASE
Director of the T1 Center for Cardiovascular Therapeutics, Director of
the Heart Failure with Preserved Ejection Fraction Program,
Professor, Division of Cardiology, Department of Medicine,
Northwestern University Feinberg School of Medicine, Chicago, IL

John Burnett, Jr., MD
Mayo Clinic, Rochester, MN

Margaret Redfield, MD
Director, Mayo Circulatory Failure Program
Co-Director, Mayo Cardiovascular Research Laboratory
Mayo Clinic, Walter and Leonore Annenberg Professor in Cardiology and
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Professor of Medicine, Mayo Clinic College of Medicine, Rochester, MN

Michael Zile, MD
Director of Cardiology, Ralph H. Johnson VA Medical Center
Charles Ezra Daniel Professor of Medicine
Medical University of South Carolina, Charleston, SC

John D. Parker, MD
Head of the Division of Cardiology of the University Health Network
Professor of Medicine and Pharmacology, University of Toronto
Mount Sinai Hospital, Toronto, Ontario
CAPACITY HFpEF incorporates four novel features to maximize probability of success

1. **Entry criteria designed to enrich for patients with HFpEF and NO deficiency**
   - >2 concomitant conditions: diabetes/pre-diabetes, hypertension, obesity, advanced age (>70)

2. **No requirement for elevated NT-proBNP; patients with low NT-proBNP may be more responsive to therapy**
   - In prior HFpEF trials (e.g., I-PRESERVE, TOPCAT), patients with lower baseline NT-proBNP showed benefit while those with higher baseline NT-proBNP did not
   - Patients with elevated NT-proBNP have higher levels of myocardial fibrosis

3. **Quantitative primary endpoint (CPET peak VO₂) associated with clinical improvement**
   - Other CPET parameters will provide insight to function at low, intermediate, and peak exercise capacity

4. **Includes secondary endpoints that are important to patients and potential basis for approval**
   - 6-minute walk distance
   - KCCQ (SOCRATES-preserved showed encouraging effects of sGC stimulation on physical limitation domains)
Phase 2 HFpEF trial will quantitatively measure exercise capacity that we believe will provide clear POC

Objective: to assess safety and tolerability of praliciguat and the effects on peak exercise capacity in patients with HFpEF

PATIENTS
n=196 (≤ 36 w/atrial fribillation)

- Ejection fraction ≥ 40%; male or female; ≥45 years; NYHA class II-IV
- Evidence of heart failure by ≥1 of the following: HF hospitalization, elevated NT-proBNP, elevated filling pressure, echocardiographic evidence
- ≥2 concomitant conditions associated with decreased NO signaling:
  - Diabetes/prediabetes
  - Hypertension
  - Obesity
  - Advanced age (>70)
- Reduced exercise tolerance by peak VO2

Double-Blind Period [12 weeks] 1:1 Randomization

High dose praliciguat [~90 patients]

Placebo [~90 patients]

ASSESSMENTS

- Primary endpoints: change in peak VO2 (CPET) and TEAEs
- 6-minute walk test
- KCCQ and other patient-reported outcomes
- Echocardiography
- Metabolic: fasting glucose, HOMA-IR, HbA1c, lipids
- Exploratory plasma biomarkers
- Pharmacokinetics

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- Exploratory plasma biomarkers
- Pharmacokinetics
HFpEF patients with lower NT-proBNP levels have less myocardial fibrosis and may be more responsive to therapy.

I-PRESERVE (irbesartan)

**Primary endpoint:** Composite of all-cause mortality and CV hospitalization

Elevated NT-proBNP is associated with myocardial fibrosis.

1. Anand et al, Circ Heart Failure, 2011
2. Liu et al., J Am Coll Cardiol 2017; 70:3102

ECV = Extracellular Volume Fraction
The cardiopulmonary exercise test (CPET) is a robust, quantitative measure of exercise capacity¹

- CPET uses exercise by bicycle or treadmill with the simultaneous measurement of vital signs, gas exchange, and ECG
- Oxygen consumption at peak exercise (pVO₂) provides an integrated measure of pulmonary, cardiovascular and skeletal muscle function
  - A 6% increase in pVO₂ is considered clinically meaningful
- Other parameters measured by CPET provide additional information on exercise capacity
- CPET pVO₂ correlates well with other exercise assessments (e.g., 6-minute walk test)²
- CPET is being used as the primary endpoint in ongoing pivotal cardiovascular trials

²Swank et al., Circ Heart Fail. 2012;5:579-585.
Recent advances have the potential to accelerate development of effective HFpEF therapeutics

- Increased understanding of the pathophysiology of HFpEF and relationship to common comorbidities
  - Importance of selecting appropriate patients

- Recognition of the importance of physical function and quality of life to HFpEF patients
  - Shift toward functional endpoints such as CPET, 6MWD, and PRO measures in clinical studies
  - Regulatory guidance supporting potential for approval based on improved symptoms or function
Cheryl Gault
Head of Strategy, Cyclerion
By improving quality of life through exercise tolerance and reduced hospitalizations, once-daily, oral praliciguat has blockbuster potential.

- Large and growing patient population
- Motivated Patient Population
  Shortness of breath, limited function, frequent hospitalizations
- Strong payer value proposition driven by a high cost of care
- No approved treatments despite high unmet need
- $16B global market
Heart failure is a rapidly rising global epidemic and HFpEF represents upwards of 72% of new cases.

- Large and growing prevalence of HFpEF patients due to aging population, and cardiac and noncardiac conditions (e.g., diabetes)
- 90% of patients are NYHA II-IV and fall within addressable population
The costs of managing heart failure patients is expected to reach $53B by 2030 in the US alone\(^1\)

- Heart failure is the most common cause for hospitalizations among individuals above 65 years of age\(^3\)
- Hospitalization rates in HFpEF are rising at a faster rate than that of HFrEF\(^4\)
- Two thirds of patients are readmitted to hospital within one year\(^2\)
- Greatest cost predictors are in patients with comorbid HF, diabetes and kidney disease\(^2\), a target population that we believe will be ideally suited for praliciguat

\(^1\) Konstam, Marvin, JACC: Heart Failure Volume 6, Issue 5, May 2018. DOI: 10.1016/j.jchf.2018.02.005
A better understanding of the importance of functional improvement is leading to a resurgence in effort to develop HFpEF therapies

- Multiple readouts expected in next 18 months
- Increasing appreciation for functional improvement as the best clinical measure
- Opportunity for approval based on functional endpoints reiterated in recent FDA draft guidance
- Praliciguat has the potential to be complementary with other mechanisms
Praliciguat has the potential to transform treatment for patients suffering from HFpEF, a >$16B global market\(^1\)

Key Takeaways

- **Significant unmet need** – No approved pharmacotherapies, poor QoL associated with shortness of breath, functional limitations and frequent hospitalizations drive low quality of life for patients and high cost of care for the system (US $53B by 2030\(^2\))

- Growing appreciation for importance of functional benefit in HFpEF by clinicians and regulators

- Broad recognition of the role impaired NO signaling plays in the HFpEF pathophysiology

- **CAPACITY HFpEF trial uses an innovative design** with novel entry criteria to recruit patients more likely to respond and a rigorous measure of exercise capacity, CPET peak VO\(_2\), as the primary endpoint

- Once-daily, oral praliciguat has the potential to improve quality of life and improve exercise tolerance and reduce hospitalizations for patients with HFpEF

\(^1\) Company estimates  
\(^2\) Konstam, Marvin. Heart Failure Costs, Minority Populations, and Outcomes, JACC: Heart Failure Volume 6, Issue 5, May 2018. DOI: 10.1016/j.jchf.2018.02.005
Diabetic Nephropathy

Dr. Barbara Gillespie
Adjunct Professor, Division of Nephrology and Hypertension,
University of North Carolina School of Medicine
Vice President and Therapeutic Head of Nephrology, Covance*

Dr. Chris Wright
Chief Medical Officer, Cyclerion

*Covance is Cyclerion’s primary contract research organization for the study of praliciguat in DN.
Covance is also a CRO for the CAPACITY-HFpEF study.
Diabetic nephropathy (DN) is a common and serious complication of diabetes leading to progressive loss of kidney function

- Affects up to 40% of diabetes patients
- Leads to end-stage renal disease (ESRD) requiring renal replacement therapy (dialysis or kidney transplant)
  - Survival on dialysis is worse than for many types of cancer
- DN patients are also at higher risk of heart failure, MI, stroke and death
- Medicare expenditures for DN reached $22B in 2016

1 United States Renal Data System 2018 Annual Report

CHF=Chronic Heart Failure; MI=Myocardial Infarction; TIA=Transient ischemic attack; RRT=Renal Replacement Therapy

Diabetic nephropathy shortens life span by 16 years

<table>
<thead>
<tr>
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<th>Life span lost at age 30 vs. reference for patients with early DN</th>
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<tbody>
<tr>
<td>Men</td>
<td>14.8 years</td>
</tr>
<tr>
<td>Women</td>
<td>16.9 years</td>
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DN patients show a progressive increase in albuminuria and decline in glomerular filtration rate (GFR)

Williams et al., 2005, Am J Nephrol 25:77
GFR and urine albumin creatinine ratio (UACR) are prognostic of disease progression in patients with chronic kidney disease (CKD)

Reduced NO signaling is implicated in DN pathophysiology

Healthy Kidney | Diabetic Nephropathy
---|---

Dysregulated renal blood flow

Endothelial dysfunction

Mesangial expansion / fibrosis

Podocyte Loss

Albuminuria

Inflammation

Impaired NO signaling is associated with these effects in preclinical models

Van den Born et al., Diabetes 2016, 65:331-345
Krishnan et al., Int J Mol Sci 2018, 19:1712

Genetic polymorphisms in NO signaling are linked to DN risk

Dellamea et al., BMC Medical Genetics, 2014
The prevalence of diabetes is increasing globally

Total number of adults with diabetes (20-79 years, millions)

Diabetic nephropathy is the leading cause of ESRD, which is increasing in incidence and prevalence

Number of new ESRD patients and total ESRD patients, 1980-2015

Existing standard of care has modest efficacy

**RENAAL (Losartan)**

- Risk reduction, 18%
- $P = 0.02$
- Residual risk

**INDT (Irbesartan)**

- Residual risk

NO. AT RISK

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Losartan</th>
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<tr>
<td>Months of Study</td>
<td>782</td>
<td>751</td>
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<td>12</td>
<td>689</td>
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<tr>
<td>48</td>
<td>36</td>
<td>52</td>
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NO. AT RISK

<table>
<thead>
<tr>
<th>No. of Months</th>
<th>Irbesartan</th>
<th>Amlodipine</th>
<th>Placebo</th>
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<td>6</td>
<td>579</td>
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</tr>
<tr>
<td>54</td>
<td>304</td>
<td>287</td>
<td>280</td>
</tr>
</tbody>
</table>


SGLT2 inhibitors slow progression of DN in clinical trials, but patients remain at risk for end-stage kidney disease and death

**CREDENCE Trial Results**

Hazard ratio, 0.70 (95% CI, 0.59–0.82), \( P = 0.00001 \). Note: All patients in CREDENCE were on standard background therapy for glucose and blood pressure control.

Source: CREDENCE trial results

<table>
<thead>
<tr>
<th>Weeks Since Randomization</th>
<th>SOC + Placebo</th>
<th>SOC + Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2199</td>
<td>2202</td>
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<tr>
<td>26</td>
<td>2178</td>
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<td>156</td>
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<td>646</td>
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<td>182</td>
<td>170</td>
<td>196</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.70 (95% CI, 0.59–0.82), \( P = 0.00001 \). Note: All patients in CREDENCE were on standard background therapy for glucose and blood pressure control.

Source: CREDENCE trial results
Regulators are discussing novel surrogate endpoints that could streamline chronic kidney disease drug development

• 2008 NKF Workshop: focused on albuminuria and proteinuria as endpoints (considered eGFR)

• Dec 2012: NKF/FDA Workshop, shift to an endpoint other than doubling of SCr: “GFR Decline as an End Point in Clinical Trials in CKD” meeting proposed that a 30 or 40% decline in GFR would be an acceptable alternative endpoint in clinical trials in some circumstances.

• However... limited applicability of these endpoints at higher baseline GFRs and for drugs that cause an “acute effect” on GFR (e.g., SGLT-2 Inhibitors)

• March 2018: NKF/FDA/EMA Workshop to address the above:

Candidate Surrogate Endpoints:
1) Decline in UACR
2) Change in mean slope of GFR decline
3) Both in combination

Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies

Evaluating Glomerular Filtration Rate Slope as a Surrogate End Point for ESKD in Clinical Trials: An Individual Participant Meta-Analysis of Observational Data

GFR Slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Meta-Analysis of Treatment Effects of Randomized Controlled Trials

Performance of GFR Slope as a Surrogate Endpoint for Kidney Disease Progression in Clinical Trials: A Statistical Simulation

Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials

Dr. Chris Wright
Chief Medical Officer, Cyclerion
By protecting kidney function, once-daily, oral praliciguat has blockbuster potential in DN

Current treatments are inadequate

$40B global market

Large and growing patient population

Serious unmet need: Leading cause of renal failure; significantly shortens lifespan

High cost of managing end stage renal disease represents a strong payor value proposition

sGC stimulation has the potential to preserve and improve renal function in 4 ways based on preclinical studies.

**Potential benefits beyond the kidney**

- Blood pressure
- Metabolic parameters (e.g., lipids, glucose)
- Endothelial function

Praliciguat preclinical data demonstrate kidney protection in multiple models

Dahl salt-sensitive rat model: Renal protection also observed in ZSF1 rat model, alone and in combination with Renin-angiotensin-aldosterone (RAAS) blocker.
**PDE5 inhibitor PF-00489791, which inhibits cGMP breakdown, reduced albuminuria in DN patients**

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**Phosphodiesterase Type 5 Inhibition Reduces Albuminuria in Subjects with Overt Diabetic Nephropathy**

Wim Scheele,* Susan Diamond,† Jeremy Gale,* Valerie Clerin,* Nihad Tamimi,† Vu Le,* Rosalind Walley,‡ Fernando Grover-Páez,§ Christelle Perros-Huguet,* Timothy Rolph,* and Meguid El Nahas

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**PF-00489791 treatment effect compared to placebo**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>UACR Change from baseline to week 12¹</td>
<td>↓ 15.7%</td>
<td>0.73-0.98</td>
</tr>
<tr>
<td>Geometric mean ratio</td>
<td>0.843</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
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</tr>
</tbody>
</table>

¹Primary outcome (Bayesian analysis)
Phase 2 DN trial uses primary endpoint predictive of clinical benefit

Objective: to assess safety and tolerability of praliciguat and the effect on renal function in patients with DN on RAAS inhibitors

**PATIENTS [n=156]**
- Type 2 diabetes mellitus
  - Diagnosed for ≥6 months
  - ≥1 anti-hyperglycemic medication (≥12 wk with regimen stable ≥4 wk)
- Stable ACEi or ARB for ≥4 wk
- Albuminuria (UACR 200-5000 mg/g)
- eGFR 30-75 mL/min/1.73 m²
- SBP 110-160 mmHg

**Double-Blind Period [12 weeks] 1:1:1 Randomization**
- **High dose praliciguat [~50 patients]**
- **Low dose praliciguat [~50 patients]**
- **Placebo [~50 patients]**

**ASSESSMENTS**
- Primary endpoints: Urine albumin creatinine ratio (ΔUACR) and TEAEs
  - eGFR
  - Hemodynamics (cuff and ambulatory SBP, DBP, MAP, HR)
  - Metabolic: serum glucose, HOMA-IR, HbA1c, lipids
  - Pharmacokinetics
  - Exploratory plasma biomarkers

RAAS-Renin-Angiotensin-Aldosterone System; ACE – Angiotensin-Converting Enzyme; ARB – Angiotensin II Receptor Blockers; UACR – Urine Albumin-to-Creatinine Ratio; eGFR – Estimated Glomerular Filtration Rate; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; MAP – Mean Arterial Pressure; HR – Heart Rate; TEAEs – Treatment Emergent Adverse Events; HOMA-IR - Homeostatic Model Assessment of Insulin Resistance; HbA1C – Hemoglobin A1C
Treatment effects on albuminuria predict effects on clinical outcomes in CKD patients (recent meta-analysis of clinical trial data)

<table>
<thead>
<tr>
<th>Treatment effect on UACR (change over 6 months)</th>
<th>Treatment effect on clinical endpoint (Hazard Ratio)¹</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ 50%</td>
<td>0.52 (0.32-0.77)</td>
<td>1.00</td>
</tr>
<tr>
<td>↓ 40%</td>
<td>0.61 (0.41-0.84)</td>
<td>1.00</td>
</tr>
<tr>
<td>↓ 30%</td>
<td>0.70 (0.49-0.96)</td>
<td>0.98</td>
</tr>
<tr>
<td>↓ 20%</td>
<td>0.79 (0.56-1.10)</td>
<td>0.93</td>
</tr>
<tr>
<td>↓ 10%</td>
<td>0.87 (0.62-1.26)</td>
<td>0.80</td>
</tr>
<tr>
<td>No change</td>
<td>0.95 (0.66-1.45)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

¹Predicted results for a modest-size trial in participants with baseline UACR ≥30 mg/g
²Composite of time to doubling of serum creatinine, ESRD, or eGFR <15 mL/min/1.73 m²

A 20-30% or greater decline from baseline in UACR predicts improvements in clinical outcomes²
Praliciguat has the potential to improve outcomes for patients with diabetic nephropathy, a $40B global market.\(^1\)

### Key Takeaways

- **DN is the most common cause of renal failure** and a major burden for patients and the healthcare system.
- Available therapies provide benefits for patients, **but substantial residual risk remains**.
- **Regulatory agencies are actively encouraging more efficient phase 3 designs**, considering new surrogate markers.
- **Praliciguat has the potential to protect kidney function through multiple NO mechanisms**; this supported by strong preclinical data and suggestive clinical studies.
- **Our Phase 2 trial will assess the effect of praliciguat on albuminuria (UACR)** which provides a strong predictive link to Phase 3 success.
Q&A