Praliciguat Phase 2 Proof of Concept Studies in HFpEF and DN

Topline Results

October 30th, 2019

Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Our forward-looking statements are based on current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions, and uncertainties, including statements about the progression of our discovery programs into clinical development; our business and operations; our sufficiency of cash; our interpretation of the data from the clinical trials, including regarding the clinical site whose results are inconsistent with the overall study population; the potential of further evaluation of praliciguat; the potential commercial opportunities of praliciguat, including the potential for a future out-license of praliciguat by us; and the anticipated timing of release of data from our ongoing clinical trials.

We may, in some cases use terms such as "predicts," "believes," "potential," "continue," "anticipates," "estimates," "expects," "plans," "intends," "may," "could," "might," "likely," "will," "should" or other words that convey uncertainty of the future events or outcomes to identify these forward-looking statements. 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 statement. Our statements about the results and conduct of our Phase 2 proof-of-concept clinical trial of praliciguat could be affected by the possibility that there are changes in the data or interpretation of the data; our statements about the potential out-licensing commercial opportunity could be affected by the possibility that we are unable to identify a commercial partner to in-license praliciguat; and our statements about our estimates regarding our use of cash may prove inaccurate. In addition, applicable risks and uncertainties regarding our business include those listed under the "Risk Factors" section and elsewhere in our Registration Statement on Form S-1 filed on April 18, 2019, with the Securities and Exchange Commission (SEC), and in subsequent reports that we file with the SEC, including our Quarterly Report on Form 10-Q filed with the SEC on August 12, 2019. Investors are cautioned not to place undue reliance on these forward-looking statements. These forward-looking statements (except as otherwise noted) speak only as of the date of this presentation, and we undertake no obligation to update these forward-looking statements, except as required by law.

Praliciguat DN and HFpEF phase 2 study results

- HFpEF: terminated development
  - Missed primary endpoint with no observed improvement on HFpEF symptoms
  - Evidence of pharmacological activity
  - Generally well tolerated
- Diabetic nephropathy: merits further investigation and discussion with potential partners
  - Missed primary endpoint
  - Positive efficacy trends (UACR and cardiometabolic) suggest potential for a large and underserved patient population
  - Generally well-tolerated

Diabetic Nephropathy (DN) Proof of Concept Study: Topline Results

Praliciguat DN proof of concept study overview

Study Design

- RCT designed to assess safety and tolerability of praliciguat and the effect on renal function in patients with DN on RAAS inhibitors
- Primary endpoints: Urine albumin creatinine ratio (ΔUACR) and TEAEs
- Secondary endpoints: BP, HR, and metabolic measures such at HBA1c and lipid levels.
- Key inclusion criteria: DM2 on stable medical regimen, ACE/ARB required, albuminuria (200-5000 mg/g), eGFR 30-75 mL/min/1.73 m2, SBP 110-160 mmHg

Study Population

- n=156 randomized 1:1:1 praliciguat 20mg vs. 40mg vs. placebo
- Demographics were balanced across the treatment arms largely consistent with the known epidemiology of the disease.
- Baseline characteristics also generally well-balanced: UACR in the 1000 mg/g range and, even though on concomitant standard of care treatments, HBA1c and blood pressure were elevated at baseline.

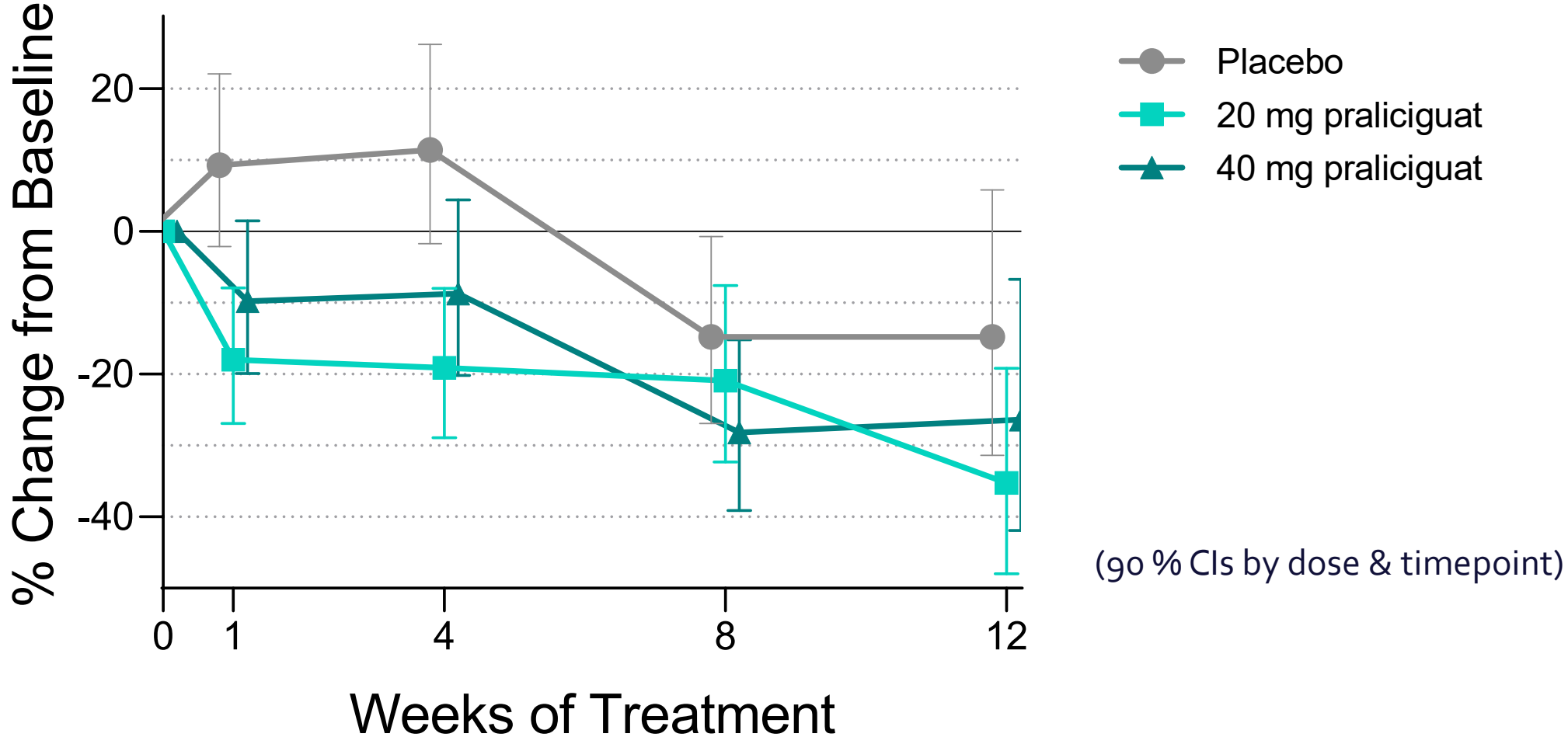
DN study results overview

Outcome Variable: UACR	PBO (n=54)	PRL 20 mg (n=50)	PRL 40 mg (n=52)	PRL Combined (n=102)
Average of Weeks 8 and 12 (primary analysis)				
Geometric Mean % Change (90% CI)	**-14.8%** (-27, +0.4)	**-28.4%** (-39, -15)	**-27.3%** (-39, -13)	**-27.8%** (-36, -18)
Pbo Adj. Geo. Mean % Change (90% CI) P-Value		**-16.0%** (-33, +6)	**-14.6%** (-33, +8)	**-15.3%** (-31, +4) 0. 1736
Week 12				
Geometric Mean % Change (90% CI)	**-14.8%** (-31.4, 5.8)	**-35.2%** (-48.0, -19.2)	**-26.4%** (-41.9, -6.7)	**-30.9%** (-41.4, -18.6)
Pbo Adj. Geo. Mean % Change (90% CI) P-Value		**-23.9%** (-44.0, 3.3)	**-13.6%** (-37.1, 18.6)	**-18.9%** (-38.0, 5.9) 0.1956*

- Treatment was associated with improvements in several vascular and metabolic parameters including blood pressure, HbA1c and LDL cholesterol levels.
- Praliciguat was generally well tolerated. Most common AEs were dizziness, diarrhea and constipation. Discontinuations due to AEs were 2% in the placebo group, 4% in the 20mg praliciguat group, and 12% in the 40mg praliciguat group. Serious AEs (SAEs) were observed in 2% of patients in the placebo group, 2% of patients in the 20mg praliciguat arm, 8% of patients in the 40mg arm and; all SAEs were judged unrelated to study drug.

* Nominal p-value; not adjusted for multiplicity

DN study: change in UACR over 12 weeks

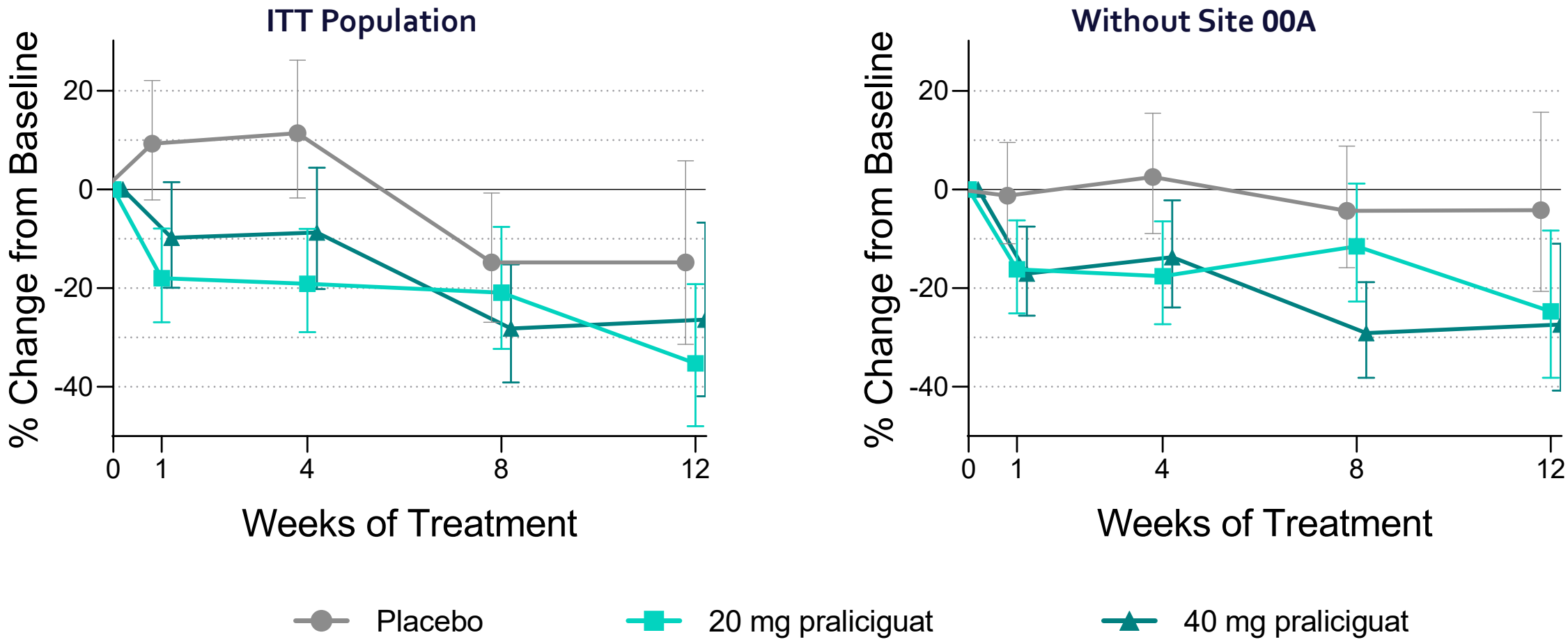


(90 % CIs by dose & timepoint)

DN study: data from one site inconsistent with overall study population

- During statistical validation, data from one clinical trial site (00A) were found to be inconsistent with those of the overall study population
- At site 00A, a significantly greater percentage of patients assigned to the praliciguat treatment arms had undetectable or very low praliciguat plasma concentrations than was seen across the broader study population
- In a post-hoc sensitivity analysis in which data from this site are excluded, an increased treatment effect and reduced variability are observed

DN study: comparison of UACR change over time with and without site 00A



DN study: primary analysis and week 12 data with and without site 00A

Outcome Variable: UACR	ITT (n=156)		Without Site 00A (n=133)	
	PBO	**PRL Combined**	**PBO**	**PRL Combined**
Average of Weeks 8 and 12				
Geometric Mean % Change (90% CI)	**-14.8%** (-27, +0.4)	**-27.8%** (-36, -18)	**-4.2%** (-16.7, 10.1)	**-23.5%** (-31.2, -14.8)
Pbo Adj. Geo. Mean % Change (90% CI) P-Value		**-15.3%** (-31, +4) 0.1736		**-20.1%** (-32.6, -5.3) 0.0303*
Week 12				
Geometric Mean % Change (90% CI)	**-14.8%** (-31.4, 5.8)	**-30.9%** (-41.4, -18.6)	**-4.1%** (-20.6, 15.7)	**-26.1%** (-36.0, -14.6)
Pbo Adj. Geo. Mean % Change (90% CI) P-Value		**-18.9%** (-38.0, 5.9) 0.1956*		**-22.9%** (-38.9, -2.6) 0.0672*

cyclerion

* Nominal p-value; not adjusted for multiplicity

Praliciguat in diabetic nephropathy: next steps

- Based on these results, we believe praliciguat warrants further investigation as a potential treatment to improve kidney function and cardiometabolic parameters in diabetic nephropathy
- We intend to pursue an out-license of praliciguat for late-stage global development and commercialization to capture its full therapeutic potential

DN is a common and serious complication of diabetes leading to progressive loss of kidney function

Diabetic Nephropathy:

- 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
- Patients are at higher risk of heart failure, MI, stroke and death[3]
- Shortens life span by 16 years[1]
- Lead to $22B in Medicare expenditures in 2016[2]

1. Wen CP, et al. Kidney Int. 2017;92:388-396 2.United States Renal Data System 2018 Annual Report 3. Foley RN, J Am Soc Nephrol 2005; 16: 489-95

Strategic focus

- Praliciguat diabetic nephropathy out licensing
- IW-6463 CNS (phase 1) topline results expected Q4 2019
- Olinciguat sickle cell disease (phase 2) topline results expected mid-2020
- Preclinical programs
- Reduce our monthly cash expenses by 25%; expect cash on hand to cover operations through Q1 2021

Conclusion: Praliciguat DN and HFpEF phase 2 study results

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Appendix

Capacity-HFpEF Proof of Concept Study

Topline Results

CAPACITY HFpEF (C1973-204) Study Design and Topline Results

Study Design

- Designed to assess safety and tolerability of praliciguat and the effects on peak exercise capacity in patients with HFpEF (EF ≥ 40%)
- Primary endpoints: change in peak VO2 (CPET) and TEAEs at 12 weeks
- n=196 randomized 1:1 praliciguat 40mg vs. placebo

Topline Study Results

- No statistically significant effects on primary efficacy measure
- Clear evidence of drug exposure and pharmacologic activity (modest effects on blood pressure)
- Positive trends in reduction in HbA1c levels in patients with diabetes
- Most common AEs reported in praliciguat-treated patients: headache, dizziness, urinary tract infection, and hypotension. The frequency of AEs and SAEs were similar between treatment and placebo groups

Change from Baseline to Week 12 Peak VO2 (mL O2/kg/min)	Placebo (N=78)	Praliciguat 40 mg (N=65)
n'*	72	64
LS mean (95% Confidence Interval)	0.036 (-0.492, 0.565)	-0.261 (-0.830, 0.308)
LS mean difference (95% CI of LS mean difference) [2]		-0.297 (-0.949, 0.354)
P Value		0.3681

CPET-cardiopulmonary exercise test, TEAEs-treatment emergent adverse events , NCT03254485. *n' is the number of patients with measurements at both Baseline and the specific visit.
[2] ANCOVA model with treatment group and atrial fibrillation stratification factor as categorical variable terms and baseline peak VO2 value as a covariate. Week 8 and Week 12 are analyzed in separate models. Patients with missing change from baseline values are excluded. No imputation is performed for missing observations.