# Efficacy of Bremelanotide (BMT) to Stabilize Podocyte Function and Reduce Proteinuria in Adults with Type II Diabetic Nephropathy: Results from a Phase IIb, Open-Label Study

NephroNet Clinical Trials Group

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### Introduction

National Kidney Foundation

**Spring Clinical Meeting** 

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- Diabetic nephropathy is the most common cause of end-stage renal disease in many populations<sup>1</sup>
- There is evidence that injury to the glomerular podocyte is central to the pathogenesis of diabetic nephropathy<sup>2-4</sup>
- Hyperglycemia can lead to podocytes undergoing morphological changes, including detachment and apoptosis<sup>2,3</sup>
- Melanocortin receptors (MCRs) comprise a complex system of 5 different receptors with broad and varying physiologic functions, and they are expressed in several kidney cell types, including podocytes, glomerular endothelial cells, mesangial cells, and tubular epithelial cells<sup>5,6</sup>
- MCR activation has been shown to reduce proteinuria through stabilization of synaptopodin and reduction in podocyte apoptosis<sup>7</sup>
- Bremelanotide (BMT) is a novel peptide analogue of α-melanocytestimulating hormone<sup>8</sup> and is a potent MC1R agonist with no activity at the MC2R, and BMT may have efficacy in reducing proteinuria through MC1R activation in Type II diabetic nephropathy

### Methods

- This phase Ilb, prospective, single-arm, open-label study assessed the efficacy of the MCR agonist BMT after 6 months of treatment in patients with Type II diabetic nephropathy
- Patients were also receiving renin-angiotensin-aldosterone system (RAAS) inhibition therapy (ie, angiotensin-converting enzyme [ACE] or angiotensin receptor blocker [ARB])
- Key inclusion criteria
- Male or female aged 18 to 80 years
- Diagnosis of Type II diabetes mellitus in controlled state (hemoglobin A1c  $\leq$  10%)
- Body mass index ≤45 kg/m²
- Diagnosis of diabetic nephropathy, confirmed by renal biopsy within 5 years of screening
- Stable dose of diabetes medications prior to enrollment
- Stable maximum tolerated dose of an ACE or ARB as primary antihypertensive therapy (blood pressure of <140/90 mmHg at screening)
- Stable dose for ≥3 months prior to enrollment of mineralocorticoid receptor antagonists, sodium-glucose cotransporter (SGLT) inhibitors, or nondihydropyridine channel blockers
- If taking a medication that the investigator believes could alter urinary protein or estimated glomerular filtration rate (eGFR), patient must agree to maintain a stable dose throughout the study period, including SGLT2 inhibitors
- eGFR by the Chronic Kidney Disease Epidemiology Collaboration formula ≥20 mL/min/1.73 m<sup>2</sup>, at screening
- Average urine protein-to-creatinine (UP/Cr) ratio >1000 mg/g

- Key exclusion criteria
- Allergy or intolerance to ACE inhibitor, ARB, or melanocortin peptides
- Significant medical illnesses that cannot be adequately controlled with appropriate therapy and may obscure toxicity, dangerously alter drug metabolism, or compromise the patient's ability to participate in the trial
- Current or prior receipt of BMT therapy within the past year
- Used cyclosporine A, adrenocorticotropic hormones, long-term corticosteroids (>20 mg once daily or its equivalent for >3 months), or cytotoxic agents within the past 3 months
- Positive antinuclear antibodies, or anti-double-stranded DNA serology and considered by the site principal investigator to have active lupus
- Solitary kidney or on dialysis
- History of hyperosmolar states (requiring hospitalization within 2 months of screening), nondiabetic glomerular disease (with the exclusion of hypertensive glomerulopathy), acute kidney injury (requiring renal replacement therapy within 2 months of screening), kidney transplant, or cancer (within 2 years of screening with the exception of nonmelanoma skin cancer)

#### Study Medication

- BMT was provided as an aqueous solution for injection in a prefilled syringe containing 0.5 mg; each prefilled syringe was a single dose and was intended for one-time use
- Study medication was first administered on Day 0 while the patient was under observation at the investigative site
- Subsequent doses were self-administered at home or at the investigative site on selected trial visit days

#### Study Design

- An estimated 45 patients were planned to be enrolled in the 12-month study consisting of a 6-month treatment period and a 6-month posttreatment period with an optional 1-year follow-up period
- After signing an informed consent form, patients' historical medical and laboratory data were collected at approximately 24, 18, 12, and 6 months prior to Day 0, to be used as baseline values
- During the 6-month treatment period, BMT was administered twice daily in addition to RAAS inhibition therapy
- Patients continued in the 6-month posttreatment period for further assessment and diagnostic renal biopsy to assess the effect of melanocortin therapy on diabetic histopathology at 12 months
- A 2-year follow-up and biopsy were optional

#### Primary and Key Secondary Outcomes

- The primary efficacy outcome was achievement of a partial remission, defined as a reduction in the UP/Cr ratio of ≥50% from baseline at 6 months
- Secondary efficacy outcomes included the following:
- Proportion of patients with a clinical response, defined as a reduction in UP/Cr ratio of ≥30% from baseline at 6 months
- Proportion of patients with eGFR decrease <5.0 mL/min/1.73 m² from baseline at</li> 6 months

#### **Key Post Hoc Analyses**

- Change in vascular endothelial growth factor (VEGF) level from baseline at 6 months
- Change in urinary synaptopodin levels from baseline at 6 months

#### Safety

Adverse events (AEs) were recorded and assessed over 1 year

#### Results

#### **Patients**

- Of 43 patients screened for the study, 16 patients were enrolled and treated Mean (SD) age was 60.5 (8.1) years (range, 43-76 y), with 81% (13/16) aged 50 to 70 years; 62.5% of the patients were male (Table 1)
- Eight patients (50%) completed the 6-month treatment period and were considered evaluable for efficacy
- Eight patients discontinued treatment early due to withdrawal of consent (n=4), AEs (n=2), patient decision (n=1), and noncompliance (n=1), making them not evaluable for efficacy; however, 6 of the 8 continued to be followed for safety

**Table 1. Baseline Characteristics** 

	Efficacy-Evaluable Cohort (n=8)	Not Efficacy- Evaluable Cohort (n=8)	All Patients (safety population) (N=16)
Age, y			
Mean (SD)	63.3 (7.9)	57.8 (7.9)	60.5 (8.1)
Median (range)	59.5 (56-76)	61.0 (43-67)	61.0 (43-76)
Age group, n (%), y			
40 to <50	0 (0.0)	1 (12.5)	1 (6.3)
50 to <60	4 (50.0)	2 (25.0)	6 (37.5)
60 to <70	2 (25.0)	5 (62.5)	7 (43.8)
70 to <80	2 (25.0)	0 (0.0)	2 (12.5)
Sex, n (%)			
Male	5 (62.5)	5 (62.5)	10 (62.5)
Female	3 (37.5)	3 (37.5)	6 (37.5)
Race, n (%)			
White/Caucasian	5 (62.5)	5 (62.5)	10 (62.5)
Black/African American	2 (25.0)	3 (37.5)	5 (31.3)
Asian Indian	1 (12.5)	0 (0.0)	1 (6.3)
Ethnicity, n (%)			
Hispanic or Latino	2 (25.0)	5 (62.5)	7 (43.8)
Not Hispanic or Latino	6 (75.0)	3 (37.5)	9 (56.3)

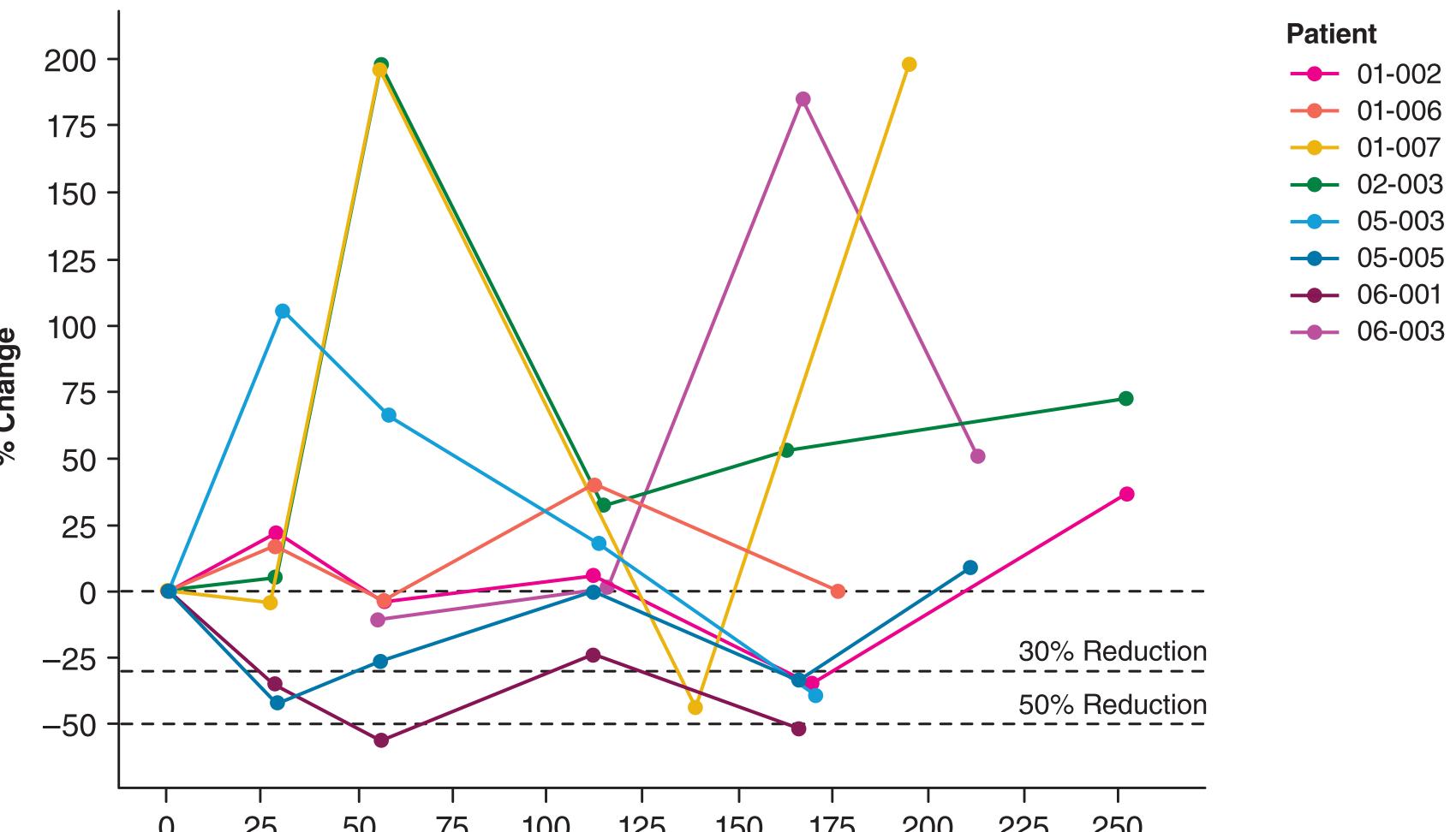
#### Efficacy Outcomes

- Partial remission (UP/Cr ratio reduction from baseline ≥50%) was shown for 1 of the 7 patients (14.3%) with available data at 5 months in the efficacyevaluable cohort with available data (Table 2, Figure 1)
- A clinical response (UP/Cr ratio reduction ≥30%) was shown for 4 of 7 patient (57.1%) with available data at 5 months in the efficacy-evaluable cohort

Table 2. Change in UP/Cr Ratio Levels From Baseline to 6 Months

UP/Cr Ratio	Efficacy-Evaluable Patients (n=8)
Pretreatment, n	8
Mean (SD)	2196.2 (1847.0)
Median (range)	1402.7 (782-6334)
Visit 5 (6 months), n	7
Mean (SD)	2251.0 (1913.2)
Median (range)	2056.0 (616-6358)
Mean (SD) of change	11.5 (84.3)
Median (range) of change	-33.1 (-52 to 185)
UP/Cr ratio 30% reduction	4/7 (0.184-0.901)
UP/Cr ratio 50% reduction	1/7 (0.004-0.579)

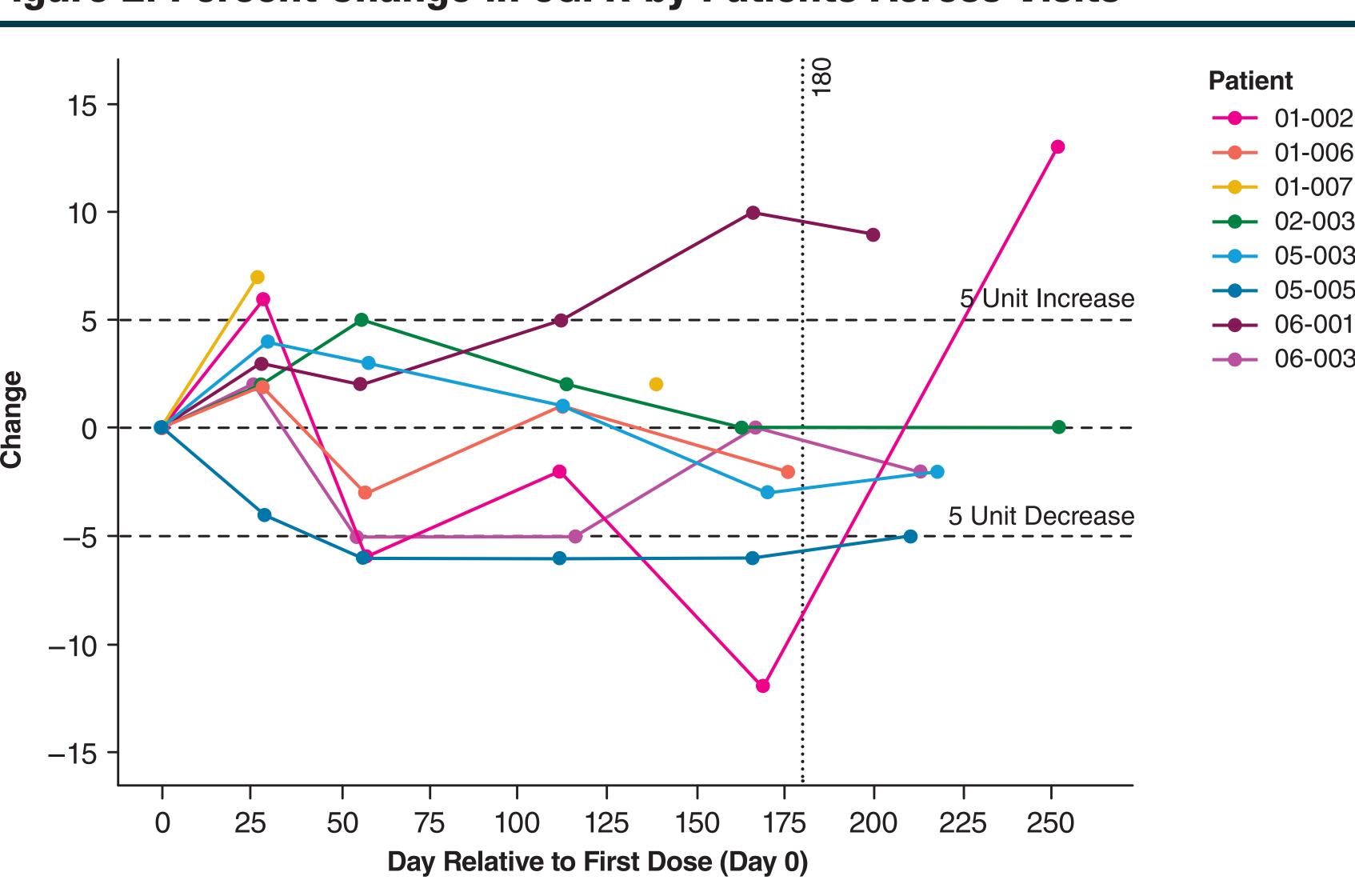
Figure 1. Percent Change in UP/Cr Ratio by Patients Across Visits



 eGFR fell by >5 mL/min/1.73 m² in 2 of 7 patients (28.6%) but remained steady or increased by >5 mL/min/1.73 m<sup>2</sup> in 5 of 7 patients (71.4%) (**Figure 2**)

Figure 2. Percent Change in eGFR by Patients Across Visits

Day Relative to First Dose (Day 0)



eGFR, estimated glomerular filtration rate.

UP/Cr ratio, urine protein-to-creatinine rat

#### Post Hoc Results

 BMT increased urinary VEGF levels >50% from baseline at 6 months in 3 of 8 patients (37.5%) in the efficacy-evaluable cohort (Table 3), and this rise correlated with a 30% reduction in UP/Cr ratio in 2 of the 3 patients

Table 3. Change in VEGF Levels From Baseline to 6 Months

VEGF (pg/mL)	Efficacy-Evaluable Patients (n=8)
Pretreatment, n	8
Mean (SD)	457.4 (550.5)
Median (range)	305.5 (94-1780)
Visit 5 (6 months), n	8
Mean (SD)	344.6 (261.6)
Median (range)	272.0 (80-884)
Mean (SD) of change	-112.8 (546.7)
Median (range) of change	-22.5 (-1405 to 413)

- Additionally, 8 of the 16 enrolled patients (50%) had urinary VEGF increased by ≥30% from baseline at 6 months
- In the analysis of the change in urinary synaptopodin levels at 6 months, BMT reduced urinary synaptopodin levels by ≥30% in 3 of 6 evaluable patients (50%), with measurable synaptopodin levels at baseline and at 6 months

- All 16 patients in the safety population had 1 or more AEs, for a total of 75 AEs
- The primary AE in this study was hyperpigmentation, which was observed in 75.0% of patients (n=12)

Table 4. Adverse Events in ≥1 Patient for All Enrolled Patients (N=16)

	n (%)	Events
≥1 adverse event	16 (100)	75
Skin hyperpigmentation	12 (75.0)	12
Pigmentation disorder	3 (18.8)	3
Anemia	2 (12.5)	2
Hypertension <sup>a</sup>	2 (12.5)	2
Nausea	2 (12.5)	10
Pain in extremity	2 (12.5)	2
Peripheral edema	2 (12.5)	2
Vomiting	2 (12.5)	10

- Serious AEs (SAEs) were reported in 23.5% of patients (n=4 of 17, which included 1 additional patient who experienced an SAE of hypertension during the screening visit and was not enrolled)
- None of the SAEs were considered treatment-related
- Treatment-related AEs were reported in 94.1% of patients (n=16 of 17), with a total of 39 AEs reported
- Treatment-related AEs reported in >1 patient each were skin hyperpigmentation (n=12), pigmentation disorder (n=3), and nausea (n=2)
- Of the 15 patients with treatment-related skin hyperpigmentation or pigmentation disorder, 9 had resolution of the AE during the study
- Of the remaining 6 patients, 3 reported resolution in 2-7 months after study completion, and 3 reported ongoing AE with improvement

#### Conclusions

- BMT therapy for 6 months in patients with established Type II diabetic nephropathy reduced UP/Cr ratio by ≥50% in 14.3% of patients and improved or stabilized eGFR in 71.4% of patients
- Post hoc analyses demonstrated that BMT therapy increased urinary VEGF levels in 37.5% of patients and reduced urinary synaptopodin levels by ≥30% in 50% of evaluable patients
- These findings were consistent with previous reports that activation of MCRs can block synaptopodin degradation and stabilize podocyte function and viability
- Further studies will need to be conducted using various combinations of MCR agonists and antagonists to fully optimize this promising treatment pathway

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