

# Urinary CD163 Predicts Complete Renal Response with Zetomipzomib Treatment in the Open-label MISSION Phase 2 Study in Patients with Lupus Nephritis

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## Introduction

- Complete renal response (CRR) defined by ACR/EULAR guidelines is a desirable clinical outcome associated with long-term preservation of kidney function in patients with lupus nephritis (LN) as demonstrated in clinical trials when achieved after 1-2 years<sup>1</sup>
- Urinary CD163 (uCD163), a protein released from macrophages in the kidney, is a promising biomarker that correlates with histologic inflammation and has been observed to predict clinical response to therapy<sup>2</sup>
- Results previously reported on MISSION (NCT03393013), a Phase 2 open-label study evaluating the safety/tolerability of zetomipzomib in active proliferative LN, demonstrated clinically meaningful renal responses along with reductions in uCD163 and strong correlation with UPCR<sup>3</sup>
- Decrease in uCD163 at early timepoints and its prediction in proteinuria response may increase probability of achieving a meaningful treatment effect in LN patients
- Data from the MISSION Phase 2 study of zetomipzomib was used to evaluate uCD163 as a potential predictor of CRR for patients with LN

## Methods

- In the MISSION Phase 2 (Amendment 4) study, patients with active proliferative LN (Class III or IV ± V) received 60 mg of zetomipzomib subcutaneously once weekly (first dose 30 mg) in addition to stable background therapy for 24 weeks
- End-of-treatment (EOT) was at Week (W) 25, and end-of-study (EOS) occurred at W37
- uCD163 was measured as an exploratory endpoint in 13 patients and was normalized to the urine creatinine for analysis
- uCD163 data at W13 and W25 were used to model a predictive association with CRR at W25 & W37, respectively
- CRR was defined as: UPCR ≤0.5, eGFR ≥60 mL/min/1.73m<sup>2</sup> or no worsening of eGFR from baseline of ≥25%, prednisone (or equivalent) ≤10 mg and no use of prohibited medication
- A logistic regression model and the Youden Index were used to generate Receiver Operating Characteristics (ROC) curves to help evaluate accuracy and identify optimal cut-off points to differentiate responders and non-responders

## Results

### Summary of uCD163 and UPCR

For the 13 patients who consented to urine biomarker analysis, baseline 24-hour UPCR was: mean=2.8 mg/mg, SD=3.3, median=1.8 mg/mg, range 0.93-13.4; uCD163: mean=1.7 mg/mmol, SD=2.3, median=0.97 mg/mmol, range 0.28-8.9

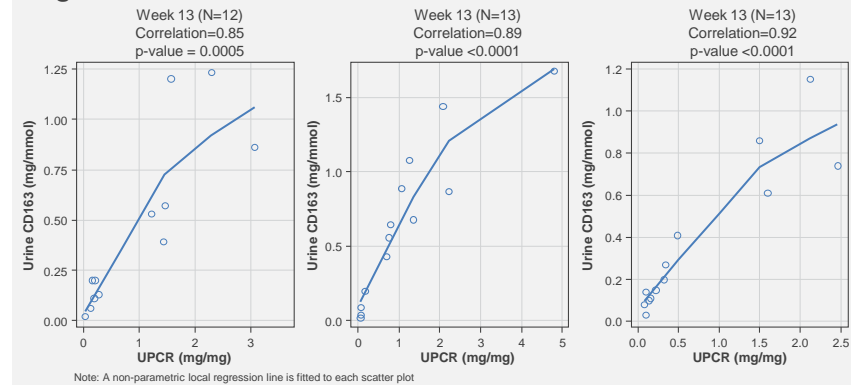
### Clinically relevant CRR was observed in the MISSION Ph 2 study

- Of the 21 patients enrolled in MISSION Phase 2 (Amendment 4), 17 reached EOT and EOS. CRR was achieved in 35% (6/17) and 41% (7/17) of patients at W25 and W37
- 4 additional patients achieved UPCR <0.5 at W37 although did not meet the daily steroid criteria (≤10 mg/day) for CRR

### Correlation of uCD163 with UPCR and CRR

Anti-inflammatory potential of zetomipzomib was demonstrated by reduction of uCD163, which was strongly correlated with UPCR improvement at W13, W25 and W37 (Figure 1)

Figure 1. uCD163 and UPCR Correlation Plots



### ROC (Receiver operating characteristic) analysis

ROC analysis results from the MISSION study suggests that LN patients with uCD163 values of ≤0.13 at W13 and ≤0.09 at W25 are more likely to achieve a CRR at W25 and W37 following treatment with zetomipzomib (Table 1)

### Using ROC AUC to show prediction of uCD163 on CRR

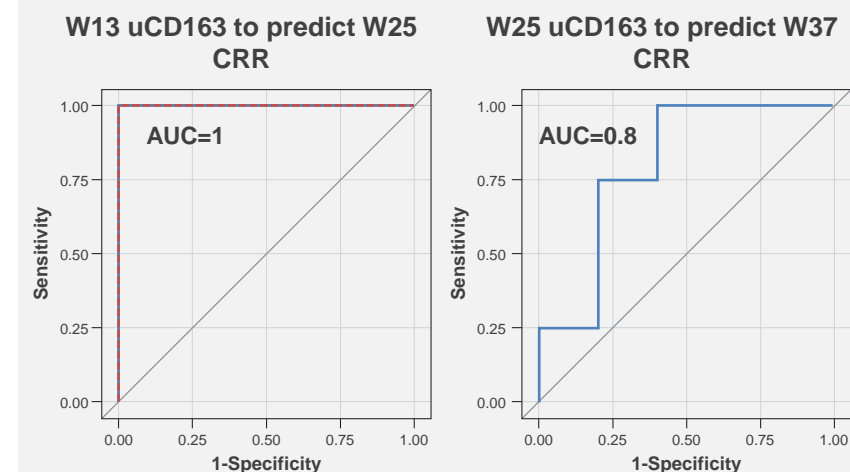
AUC=1, a perfect prediction, was produced when using uCD163 at W13 to predict CRR at W25  
 AUC=0.8 was generated when using uCD163 at W25 (end of treatment) to predict CRR at W37 (Figure 2)

## Results (cont'd)

Table 1. Summary of ROC analysis based on Logistic Regression Model

Predictor	uCD163 at W13	uCD163 at W25
Outcome	CRR at W25 (4 CRR)	CRR at W37 (5 CRR)
N used in ROC analysis	12 (1 missing)	13
Youden cut point	uCD163 = 0.13	uCD163 = 0.09
ROC AUC (max=1)	1.0	0.8
P-value	p=0.3615	p=0.1218
Sensitivity (0-1)	1.0	0.6
Specificity (0-1)	1.0	1.0
Predictive probability in CRR	100%	100%

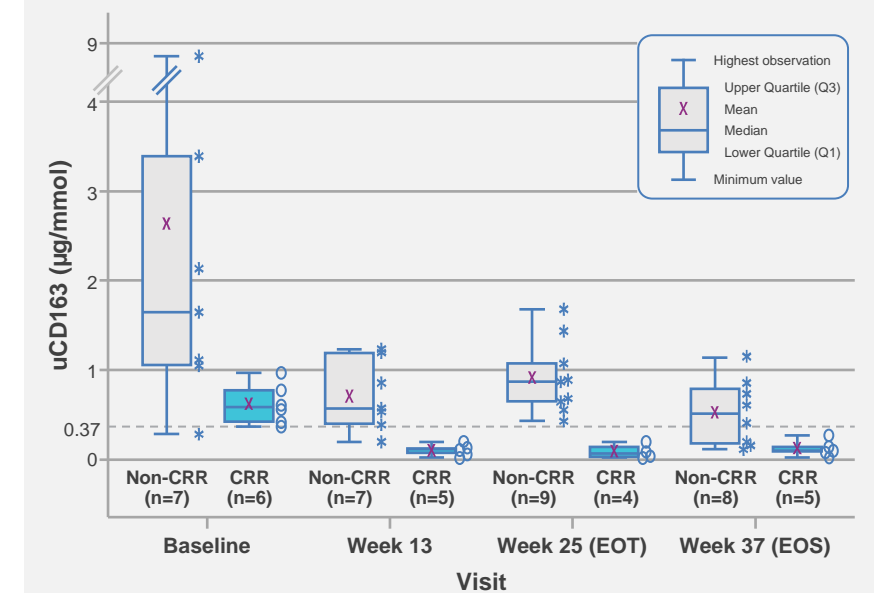
Figure 2. ROC AUC Plots\*



\*Area under the curve with 1 indicating perfect prediction and 0.5 or diagonal line indicating random prediction

## Results (cont'd)

Figure 3. A clear separation between CRR and non-CRR was observed in uCD163 values



## Conclusions

- Post-hoc analysis of data from the MISSION Phase 2 study showed that uCD163 levels may be able to predict CRR endpoints up to 3 months later
- There was an apparent separation in uCD163 values between CRR and non-CRR. uCD163 data maintains its low value in CRR responders even after EOT at W25 for the following 12 weeks at W37 (EOS). Decrease in uCD163 was also observed among non-CRR or non-responders throughout the study visits
- Further evidence is needed from larger randomized LN trials with zetomipzomib to confirm the utility and limits of uCD163 as a predictive biomarker

## References

1. Fanouriakis A, et al. *Ann Rheum Dis*. 2020;79(6):713-723. 2. Mejia-Vilet JM, et al. *JASN*. 2020;31(6):1335-1347. 3. Parikh SV, et al. Poster presented at: ASN Kidney Week 2022; Orlando, Florida; November 3, 2022.

## Author Disclosures and Acknowledgements

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