

# **Clinical Study Results of a Real-Time Point-of-Care Glomerular Filtration Rate Measurement**

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## ABSTRACT

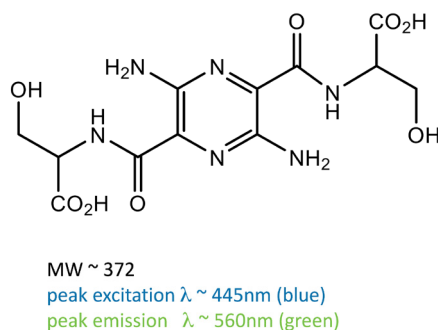
The fluorescent tracer agent MB-102, with chemical name 3,6-diamino-2,5-bis[N-[(1R)-1-carboxy-2-hydroxyethyl] carbamoyl]pyrazine has been engineered to have photophysical properties and clearance properties for use as a direct measure of glomerular filtration rate (GFR). Post intravenous administration, the clearance of this agent may be monitored noninvasively by transdermal fluorescence. Thus its use for real-time point-of-care GFR determination should have great impact in the ICU, as well as in many other settings. In this poster we present results of our recent clinical study conducted on subjects recruited to have a range of renal function, from normal to Stage 4 CKD. We report herein the comparison of plasma pharmacokinetics between MB-102 and the known standard exogenous GFR agent iohexol. A prototype noninvasive fluorescence detection device was employed to simultaneously measure the transdermal fluorescence from MB-102 in these same subjects. Blood samples over a period of 12 hours were collected from each subject to assess pharmacokinetic parameters including clearance. Urine samples were collected over this same period to assess percent injected dose recovered in the urine. Transdermal fluorescence was measured over the same period of 12 hours post administration of the agent to assess correlation with the MB-102 plasma pharmacokinetics.

## BACKGROUND

Measurement of glomerular filtration rate (GFR) is widely accepted as the most reliable measure of renal function (National Kidney Foundation, 2002). As a result there is a growing medical need for determining accurate real-time GFR to hasten identification and intervention for AKI and more closely monitor progression in CKD. The optimum measure of GFR is by the use of exogenous tracer agents. However this methodology requires several blood draws as a function of time and subsequent sophisticated laboratory analysis to measure tracer agent concentration in each blood draw needed for GFR determination. Hence use of these exogenous tracer agents is not amenable to the bedside for point-of-care application, and are mainly employed for research purposes (Endre et al., 2011).

To overcome the deficiencies of the research GFR tracer agents with respect to bedside point-of-care application, we have developed a transdermally-detectable exogenous fluorescent agent which thus combines the optimum measurement of an exogenous tracer agent with point-of-care bedside utility. MB-102, a fluorescent tracer agent that has exhibited characteristics essential for GFR measurement (Rajagopalan et al., 2011), with toxicology studies to date yielding negligible pathological concerns (Bugaj and Dorshow, 2015), has been clinically demonstrated to be a GFR agent in subjects with normal renal function (Dorshow et al., 2015).

- Biocompatible
- Hydrophilic
- Negligible protein binding
- Negligible metabolism
- Negligible photobleaching
- Excellent solubility in PBS
- Physiologic pH formulation
- Small dose
- Chemical stability in solution
- Photo-stability in solution
- Large Stokes shift



**Figure 1: Chemical structure of MB-102 and its properties.**



**Figure 2: Noninvasive transdermal fluorescence detection instrument.**

## OBJECTIVES

1. Simultaneously measure the plasma pharmacokinetics of MB-102 and iohexol in adult subjects with normal to Stage 4 CKD renal function, and compare the GFR determined from the MB-102 data with that determined from the iohexol data.
2. Noninvasively measure the transdermal fluorescence of MB-102, compare this fluorescence pharmacokinetics with the MB-102 plasma pharmacokinetics, and construct the first version of the algorithm to measure transdermal GFR directly.
3. Measure percent administered dose appearing in the urine for each agent.
4. Monitor the safety and tolerability of MB-102 in these adult volunteers.

## METHODS

### Plasma Pharmacokinetics:

Following sequential administration of MB-102 and Omnipaque™ 300 in 60 subjects with renal function ranging from normal to Stage 4 CKD (as determined by serum creatinine measurement and CKD- EPI equation), blood samples were collected for 12 hours. Plasma concentrations of MB-102 and iohexol were measured, and standard pharmacokinetic software (Phoenix WinNonlin (Certara, Princeton, NJ)) was employed to determine clearance (and hence GFR) from the concentration versus time data for each agent.

### Fluorescence Pharmacokinetics:

The noninvasive fluorescence detection instrument sensor head has two LED sources, with center wavelengths of 450 and 570 nm, and two silicon photomultiplier detectors (Figure 3a). The 450 nm LED provides the excitation for MB-102, with fluorescence collected around the 560 nm peak emission. Diffuse reflectance measurements are collected and used to correct the fluorescence signal for variations in tissue optical properties. The sensor is affixed to the body with biocompatible adhesive on the underside and Tegaderm™ film over the top (Figure 3b). The primary attachment site is the sternum. Other attachment sites include the pectoralis major and occipital triangle. A schematic of the system is shown in Figure 3c.

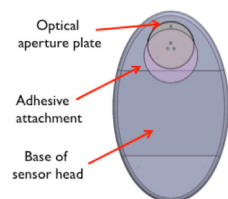


Figure 3a



Figure 3b

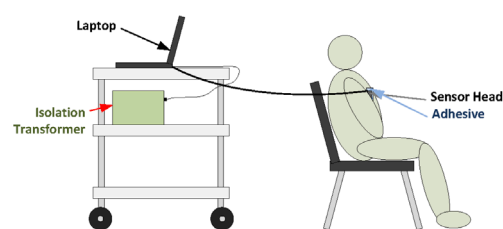


Figure 3c

### Percent Administered Dose in Urine:

Total urine was collected via jug for 12 hours following administration of MB-102 and Omnipaque 300 in all 60 subjects. Concentrations of MB-102 and iohexol were measured in each subject sample, and total concentration with respect to administered dose was calculated for each subject.

# RESULTS AND DISCUSSION

## PLASMA PHARMACOKINETICS

### DEFINITIONS:

eGFR: Estimated GFR using CKD-EPI equation.

mGFR: Measured GFR using plasma  
pharmacokinetic data (MB-102)

nGFR: mGFR normalized to body surface area

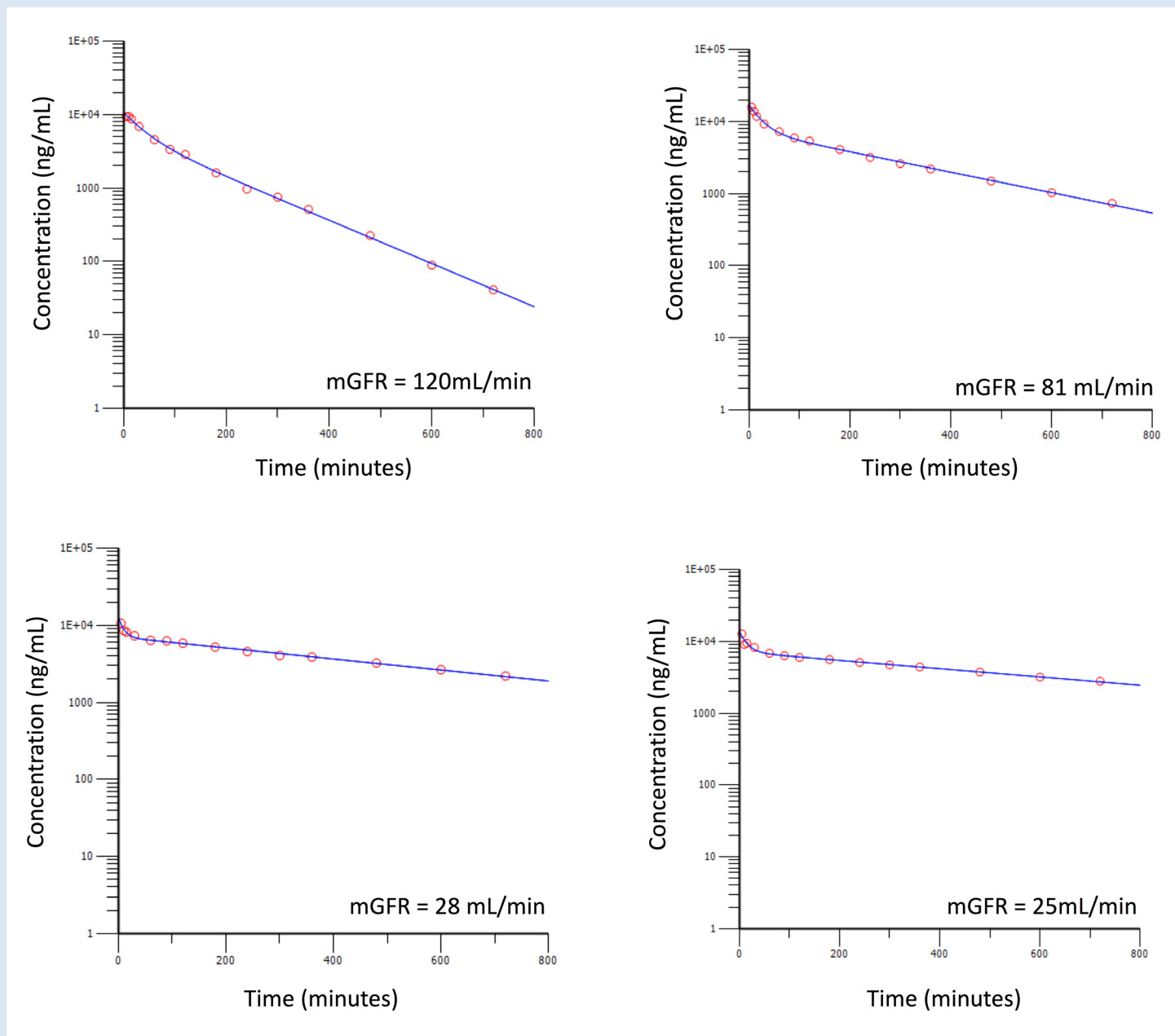
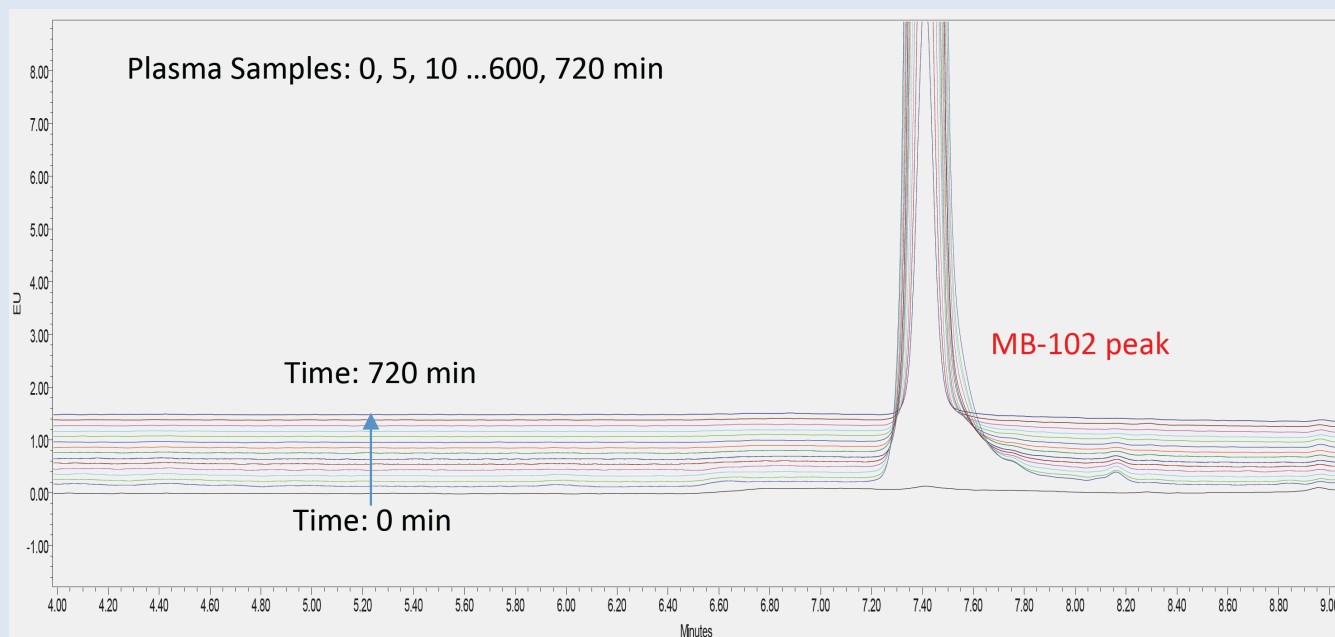
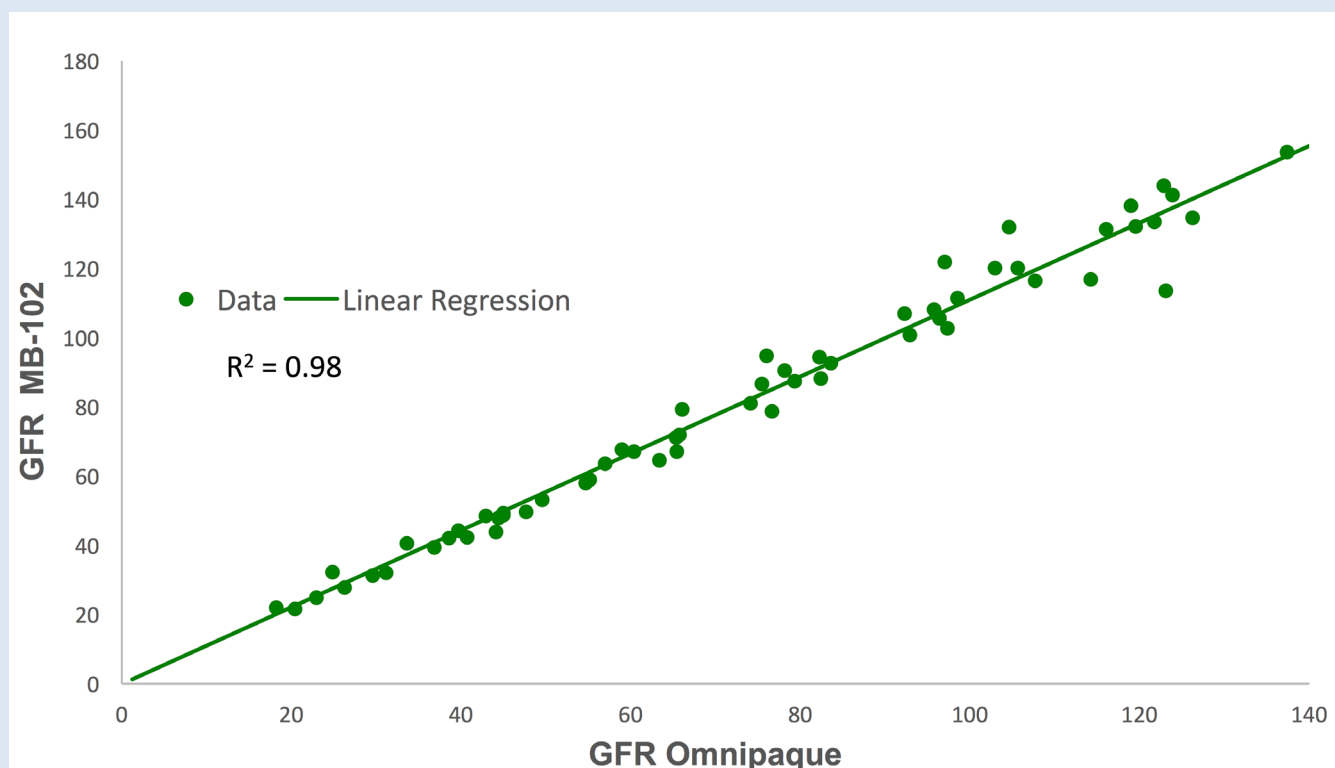


Figure 4: Concentration of MB-102 in plasma over time for subjects with normal to Stage 4 CKD renal function. Red circles are measured concentrations, blue line is two-compartment pharmacokinetic fit.



**Figure 5: HPLC MB-102 plasma chromatograms by fluorescence detection from a single subject.**  
An overlay of all 15 plasma chromatograms from this subject yields no metabolite peaks in the post-dose samples.



**Figure 6: Correlation of MB-102 plasma-derived GFR with Omnipaque plasma-derived GFR.**  
The regression line yields a high correlation over the entire range of GFR values, thus we conclude that MB-102 is a GFR tracer agent for subjects with normal and impaired kidney function.

## FLUORESCENCE PHARMACOKINETICS

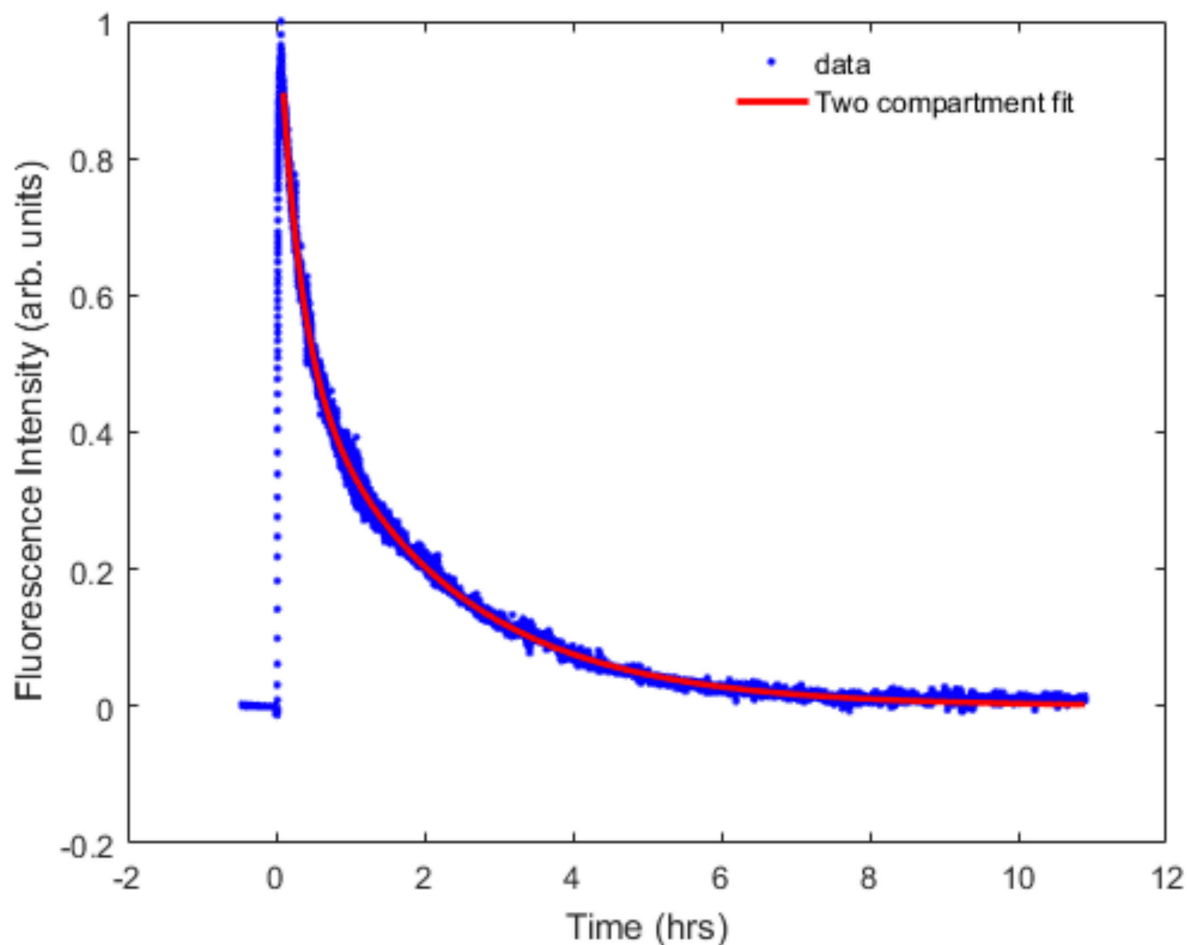
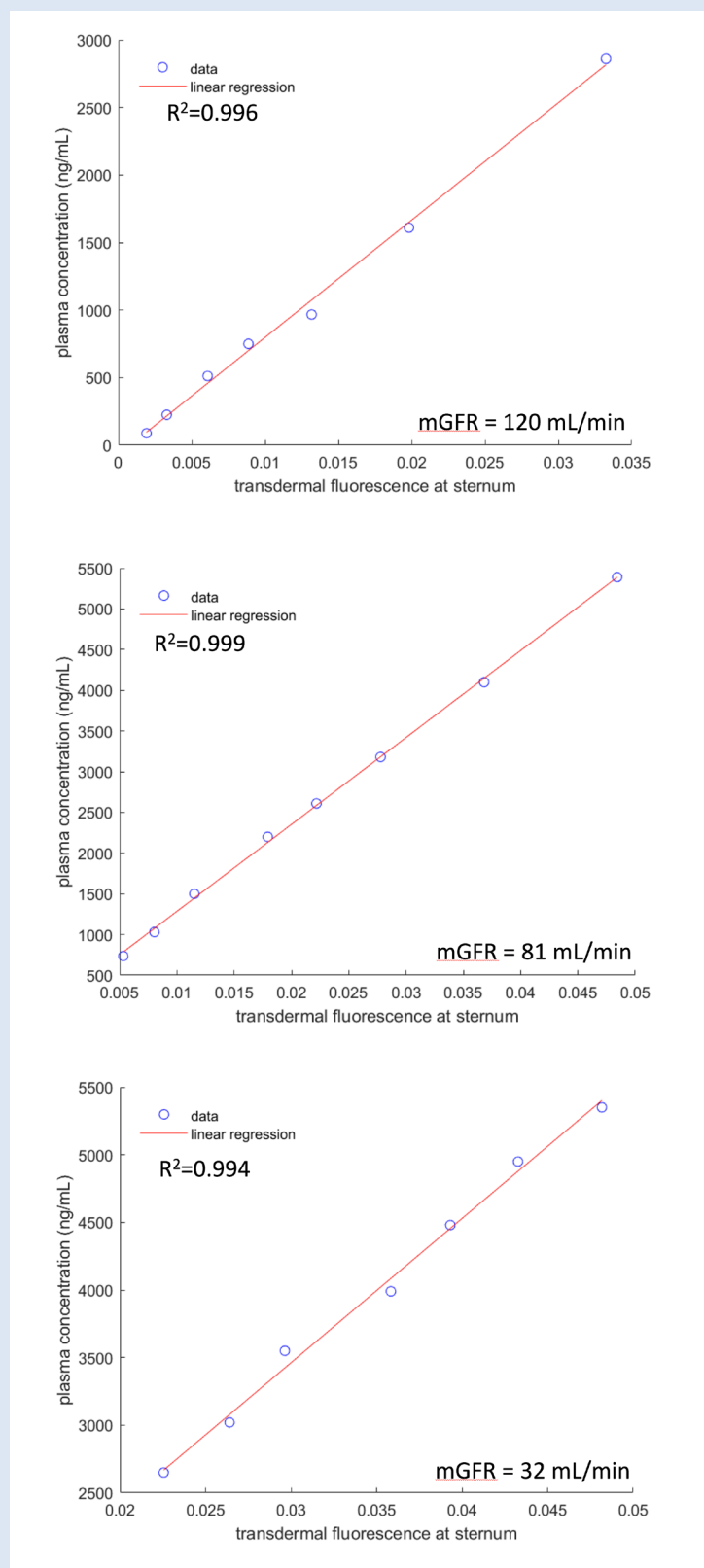


Figure 7: Transdermal fluorescence from MB-102 measured at sternum in Subject 11.

Blue circles are measured values, the red line is a fit to the pharmacokinetic model. The terminal (second compartment) half-life is approximately 84 minutes.



**Figure 8: Transdermal Fluorescence Pharmacokinetics Correlates with Plasma Pharmacokinetics Over Range of GFR.** Plasma concentration versus fluorescence intensity at the same time points in the renal excretion phase yields an almost perfect correlation over the entire range of GFR values.

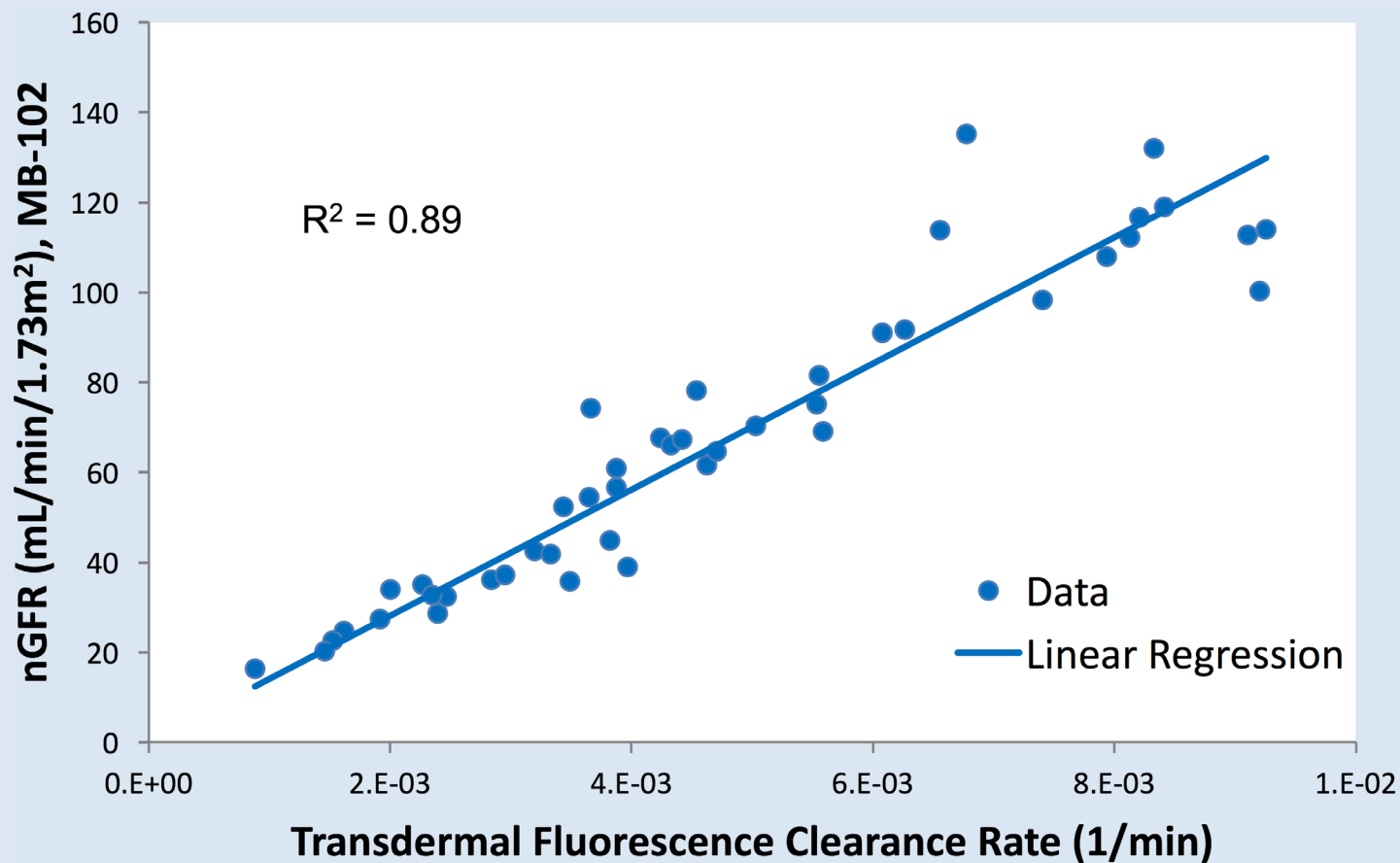


Figure 9: nGFR vs. fluorescence clearance rate (inverse of measured transdermal time constant) for 45 subjects of study (Dorshow-Debreczeny plot).  
The data in Figure 8 was used to construct version 1 of our correlation algorithm between fluorescence time constant and plasma GFR, similar to the work of Rabito et al. (2010).



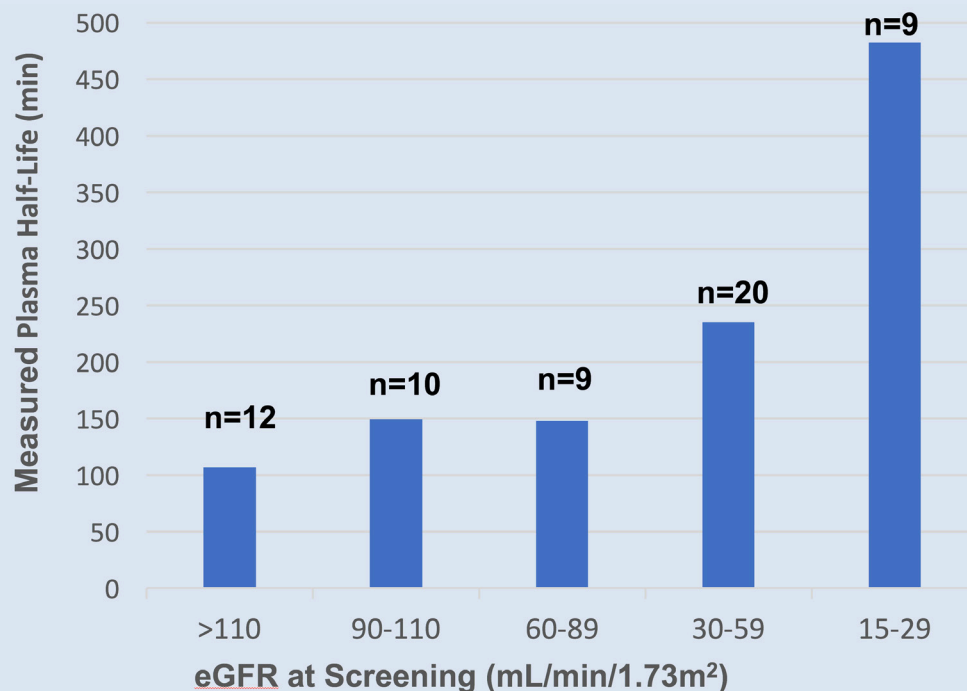


Figure 10: Plasma Concentration Half-Life. Half-life (obtained from pharmacokinetic fit) increases with decreasing renal function as expected. The n values are the number of subjects in each grouping.

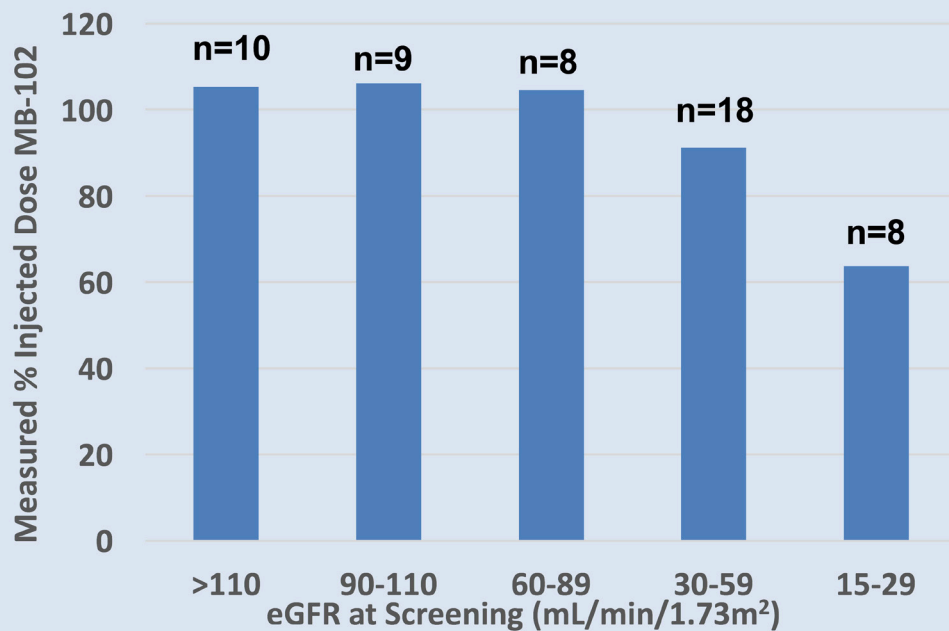


Figure 11: Percentage of Injected Dose MB-102 Recovered in the Urine in 12 hours. Groups with decreasing renal function from normal to Stage 4 CKD are shown. The n values indicate the number of subjects in each group.

# CONCLUSIONS

Point-of-care, clinically amenable, measured GFR for a range of kidney function from normal to Stage 4 CKD is demonstrated using transdermal fluorescence detection of novel fluorescence tracer agent MB-102.

- The measured GFR from MB-102 plasma pharmacokinetics is highly correlated with the measured GFR from iohexol plasma pharmacokinetics (Figure 6).
- The plasma pharmacokinetics of MB-102 is highly correlated with the transdermal fluorescence pharmacokinetics (Figure 8).
- An algorithm has been developed to convert the measured transdermal fluorescence clearance rate into nGFR (Figure 9).
- MB-102 is excreted by the renal system (Figure 11).
- No serious nor significant adverse events reported.

## REFERENCES

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