# Tissue Distribution of Inhaled Clofazimine in Both Naïve and Infected Mouse Models

Brandon Banaschewski[1],Deepshikha Verma[2], Matthew Zimmerman[3], Veronique Dartois[3], Diane Ordway[2], Stefan Ufer[1], Kevin Stapleton[1], and Thomas Hofmann[1]

[1]Qrumpharma Inc, Doylestown, PA; [2]Colorado State University, Fort Collins, CO; [3]Public Health Research Institute, New Jersey Medical School, Rutgers, The State University of New Jersey, Newark, NJ

## Introduction

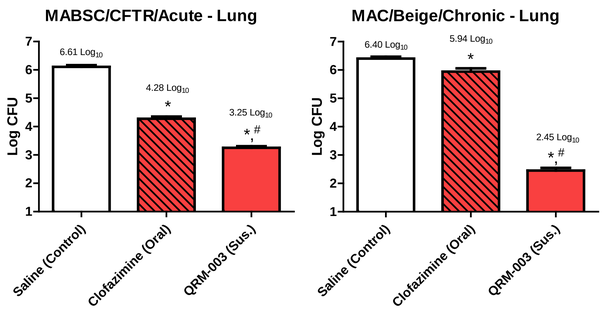
**Nontuberculous mycobacteria (NTM)** infection is continuing to be recognized as an emerging health threat to both non-CF and CF patients[1,2].

- These infections have been shown to reduce lung function and survival.

Despite this, there remains few therapeutic options for treating NTM-PD that are both safe and effective.

- Treatment strategies involve long, intensive, systemic antibiotic regimens, often involving toxicity/adverse drug reactions[3,4].

Qrumpharma has recently demonstrated that the use of QRM-003 (Clofazimine inhalation suspension) can effectively reduce bacterial burden in NTM-infected mouse models of both *Mycobacterium avium* and *Mycobacterium abscessus*[5].




Oral clofazimine administration has often been associated with a number of adverse events, such as skin discoloration, ichythosis and gastrointestinal intolerance, which may be due to it's extrapulmonary tissue accumulation[6,7].

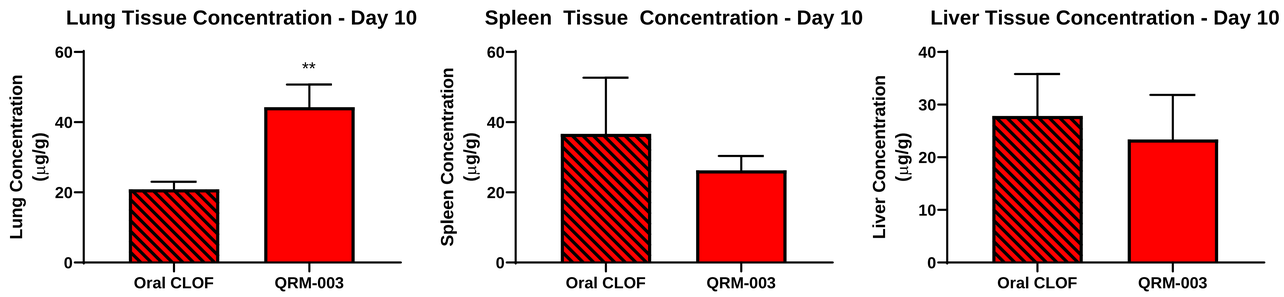
*Purpose*: To compare the tissue accumulation of clofazimine following oral and inhaled drug delivery.

## Hypothesis

1) **QRM-003 will lead to greater pulmonary accumulation than oral clofazimine.**
2) **QRM-003 delivery will reduce clofazimine accumulation in extrapulmonary tissues.**

## Study 1: Clofazimine Distribution in Naïve Mouse Models

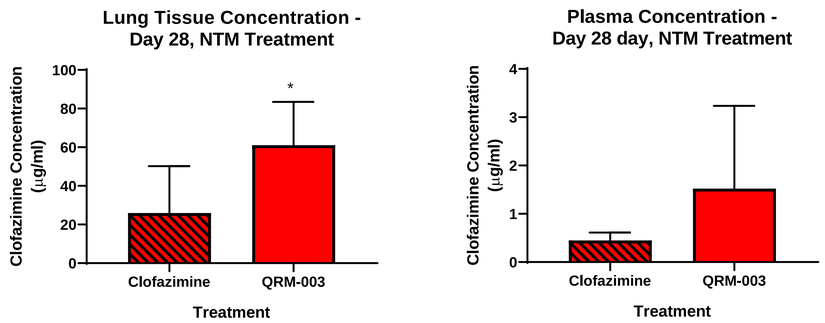
- Naïve C57Bl/6 mice were administered either oral clofazimine (20 mg/kg) or QRM-003 (28 mg/kg) daily for 10 days.
- On Day 10, lung, spleen, and liver tissues were collected to quantify clofazimine accumulation.




- A 40% increase in clofazimine dose by inhalation (i.e. QRM-003) led to a 120% increase in lung tissue accumulation.
- The increased clofazimine dose did not significantly change extrapulmonary tissue levels following inhaled delivery.

## Study 2: Clofazimine Distribution in Chronic NTM Infection Models

- In two chronic models of NTM infection (*M. avium* infection in Beige mice; *M. abscessus* infection in CFTR$^{-/-}$ mice), lung and plasma samples were collected after 28 days of treatment.
- Mice received either oral clofazimine (20 mg/kg) or QRM-003 (10 mg/kg) every other day over 28 days.
- Lung tissue and plasma samples were collected at the end of treatment to quantify clofazimine concentrations.




- Consistent with studies in naïve mice, QRM-003 treatment led to a significant increase in lung tissue concentrations compared to oral dosing, despite receiving 50% of the oral dose.
- There was no statistically significant difference in plasma concentrations between oral delivery and QRM-003.

## Conclusions

- QRM-003 administration led to significant increases in pulmonary tissue concentrations compared to oral clofazimine administration, even after accounting for differences in dose.
- QRM-003 did not lead to significant differences in extrapulmonary tissue concentrations, despite administration of higher doses, after 10 days treatment.
- In the chronic infection model, there was no significant difference in clofazimine plasma concentrations.

## Discussion

- Data to date suggests QRM-003 treatment can lead to increased lung tissue concentration, and a reduction in extrapulmonary tissue concentration.
- This should lead to a reduction in off-tissue side effects, while improving antimicrobial clearance from pulmonary tissue.
- Ongoing studies are evaluating QRM-003 pharmacokinetics in both pulmonary and extrapulmonary space.

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*1. CFF Patient Registry 2017; 2. Adjemian et al., AJCCRM 2012; 3. Griffith et al., AJCCRM 2007; 4. Floto et al., Thorax 2016; 5. Banaschewski et al. J Cyst Fibros 2019; 6. Martiniano et al., Chest 2017; 7. Aznar et al., CJRCCSM 2018*