Development and efficacy of novel nebulized antibiotic formulations for the treatment of *Mycobacterium abscessus* pulmonary infections

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NTM (MABSC and MAC) are destroying lung function, and increasing in prevalence

- NTM infection in CF approx. 13%, and increasing in prevalence within CF\(^1,2\) and within non CF lung disease\(^3,4\)
- MABSC in particular is an aggressive pathogen and leads to rapid loss (>2x) of lung function\(^5\)

Incidence rates of NTM infections in CF, from 2003 (1.4%) to 2011 (8.7%) at the Graub CF Center in Israel\(^6\). Incidence rates in US CF Patients 2017 = ~13%.

Effect on lung function of chronic infection from onset to end stage lung disease in Danish CF patients

References:
Current NTM therapy options

• **NTM are treated with long term oral combination therapy:** current therapeutic options are oral antibiotics with high chronic toxicity\(^1\). Clofazimine (oral) has skin, GI, neuro, and cardiac side effects.

• **Treatment outcomes are unsatisfactory:** discontinuation is frequent (10-30%) and overall treatment success low (40-60%)\(^2, 3\).

• **Inhaled liposomal Amikacin in development:** Phase 2 results indicate seroconversion of NTM, and focus on MAC\(^4\)

### MIC Values of QRM Program by Comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th><em>M. avium</em></th>
<th><em>M. abscessus</em></th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofazimine</td>
<td>0.12-0.25 µg/ml</td>
<td>0.5 - 1.3 µg/ml</td>
<td>Shen 2010, van Ingen 2012, Obregón-Henao 2015</td>
</tr>
<tr>
<td>QRM-003</td>
<td>1 µg/ml</td>
<td>1 µg/ml</td>
<td>Qrumpharma Data</td>
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Inhalation PK/PD
CMC progress, QRM-003 Formulation

• Current Formulation Development Steps

  • Developed a preservative-free, tolerable formulation suitable for delivery by nebulizer
    • Optimized for lung delivery (pH, osmolarity, particle size, airway compatibility)
  • Suspension particle sizes < 2 mm to facilitate use with vibrating mesh and nozzle type nebulizers
  • Goal: 2 years room temperature stable
QRM-003 Macrophage Uptake Assay

- Macrophage uptake relevant for activity vs. NTM – intracellular bacteria

THP-1 derived macrophages incubated with QRM-003 formulation

24-hr incubation

Observations via light microscopy

QRM-003
QRM-003 is well phagocytosed

Conclusions

- Clofazimine uptake by macrophages maintained in novel formulation
- Will allow for interaction between clofazimine crystals and intracellular NTM bacteria
QRM Aerosol Safety and Tolerability

Balb/C Mouse

3 Treatments;
1x/2 days

Day 1 QRM-003 (Sus.)
1. 10.0 mg/kg
2. 5.01 mg/kg
3. 2.51 mg/kg

Day 3 QRM-003 (Sus.)
1. 10.0 mg/kg
2. 5.01 mg/kg
3. 2.51 mg/kg

Day 5 QRM-003 (Sus.)
1. 10.0 mg/kg
2. 5.01 mg/kg
3. 2.51 mg/kg

*all drug concentrations are calculated on the assumption of a 25g mouse*
MTD, Safety Results – QRM-003

**Observations**
BAR = bright, responsive, alert (Normal mouse)

*all drug concentrations are calculated on the assumption of a 25g mouse

**Figure 4.** Weight (g) of female Balb/C mice following instillation of QRM-003 (Sus.). (n = 3)
QRM Program Efficacy vs. *M. abscessus* – SCID mouse model

**Day 1**
3 Mice Culled (MABSC Uptake)

**Day 2 – Tx Initiation**
Treatment groups:

a) Control (Saline)
b) Amikacin (150 mg/kg SQ)
c) Clofazimine (20 mg/kg, Oral)
d) QRM-003 (Sus.) (10.0 mg/kg, IT)

**Euthanasia**

**Bacterial Recovery**
(Tissue Homogenate):
- Lung
- Spleen
- Liver

*all drug concentrations are calculated on the assumption of a 25g mouse\footnote{Qrumpharma Inc.}
Aerosol QRM-003 suspension resulted in a 3 log reduction in lung CFU

Figure 6. Bacterial counts in the lungs of SCID mice after pulmonary infection with 1x10^6 CFUs of *M. abscessus*. (n = 6)
- Received 8 total treatments, administered every other day
- Treatment Groups:
  - Saline (IT) (White bar);
  - Amikacin 150 mg/kg (SQ) (White striped);
  - Clofazimine 20 mg/kg (gavage) (Red striped);
  - QRM-003 (Sus.) 10 mg/kg (IT) (Red);
- Results represent the average bacterial recovery, expressed as average Log_{10} CFU (± SEM) cells. Statistical analysis performed by one-way ANOVA.

*p<0.05 vs. Saline control
γ*p<0.05 QRM-003 vs. Amikacin

*all drug concentrations are calculated on the assumption of a 25g mouse
Aerosol QRM-003 suspension resulted in bacterial reduction in Spleen, Liver

Figure 7. Bacterial recovery from a) spleen, and b) liver of SCID mice with following pulmonary infection with 1x10⁶ CFUs of *M. abscessus* 103.

*p<0.05 vs. Saline control*
QRM Program Efficacy vs. M. avium – Beige Mouse Model

Day 1
3 Mice Culled (MAC Uptake)

10 Treatment Days; 1x/2 days

Euthanasia

Bacterial Recovery (Tissue Homogenate):
- Lung
- Spleen
- Liver

Day 7 – Tx Initiation
Treatment groups:

a) Control (Saline)
b) Clofazimine (20 mg/kg, Oral)
c) QRM-003 (Sus.) (10.0 mg/kg, IT)

*A all drug concentrations are calculated on the assumption of a 25g mouse
Aerosol delivery of QRM-003 resulted in 1.7 log reduction in lung CFU

Figure 8. Bacterial counts in the lungs of Beige mice after high-dose aerosol infection with $1 \times 10^8$ CFUs of *M. avium* 2285. (n = 6)

- Received 10 total treatments, administered every other day
- Treatment Groups:
  - Saline (IT) (White bar);
  - Clofazimine 20 mg/kg (gavage) (Red striped);
  - QRM-003 (Sus.) 10.0 mg/kg (IT) (Red);
- Results represent the average bacterial recovery, expressed as average Log$_{10}$ CFU (± SEM) cells. Statistical analysis performed by one-way ANOVA.

* $p < 0.05$ vs. Saline control
+ $p < 0.05$ QRM-003 vs. clofazimine (gavage)

*all drug concentrations are calculated on the assumption of a 25g mouse
Timeline for Inhaled Clofazimine Development

**Status:**
- Formulation, CMC and animal studies (pre-clinical efficacy)

**Next steps:**
- CMC upscaling and inhalation tox to prepare IND
Conclusions

• QRM-003 (aerosolized) demonstrates optimal anti-NTM activity
  • Safe at highest possible dose \textit{in vivo} (\textit{multiple of clinical dose})
  • Greatest reduction of bacteria in the lung in all experimental models (MAC and MABSC; various formulations)
  • Significantly reduces NTM bacteria from lung/spleen/liver
  • QRM-003 Clofazimine is taken up by macrophages in vitro

QRM-003 (Clofazimine) has been chosen as lead therapeutic candidate, and will be taken into toxicology and IND