WGND Meeting
October 26, 2011, Lille
What We’re Trying to Accomplish

Efficiently bring to market affordable and easy-to-use regimen(s) that shorten and simplify treatment for DS- and DR-TB in HIV positive and negative subjects

– Ideally, no pre-existing resistance

– Alternatively, delivery paired with appropriate resistance testing
TB Drug/Regimen Discovery and Development Process

Discovery

Compound 1
Compound 2
Compound 3
Compound 4
Compound 5

Drug Candidate Pool

Regimen Identification

Single Compound Preclinical Development → Phase I → EBA

Phase II → Phase III

Regimen A
Regimen B
Regimen C

Identification of New Drug Candidates
Selection of Potential New Regimens
NC-001
NC-001: Use of EBA to Test Principles Learned From Animal Models and to Begin Clinical Development of Novel Regimens

NC-001 (first novel combination EBA study)
- J-Z synergy
- Pa-Z additivity
- Pa-J antagonism
- Pa-M-Z an enhanced novel regimen

EBA = early bactericidal activity
Pa = PA-824; M = moxifloxacin; Z = pyrazinamide; J = TMC207
First Novel Combo EBA: NC-001

Pa-M-Z
Pa-Z-(M pbo)
J-Z
J-(Z pbo)
J-Pa
Rifafour

2 weeks of treatment

Visits

Day -9 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 29 105

Pre Treatment | TREATMENT | Follow-Up

Pa = PA-824; M = moxifloxacin; Z = pyrazinamide; J = TMC207
NC-001 Conclusions

- Validation of mouse data: J-Z synergy, Pa-Z additivity, Pa-J antagonism, Pa-M-Z contributions
- Pa-M-Z an enhanced novel regimen in 2-wk study
  - All three compounds contribute to observed effect
- EBA can distinguish between treatments
  - Just as it has previously distinguished between doses
- CFU and TTP give similar results

Pa = PA-824; M = moxifloxacin; Z = pyrazinamide; J = TMC207
Post NC-001 Study: Next Steps

- Develop Pa-M-Z for both DS- and DR-TB (in setting of appropriate resistance testing)
  - 2-month “SSCC” study (NC-002)
- Build on J-Z and Pa-Z backbones
- Explore J-Pa building block
- Continue to examine potential regimens in mouse models and bring promising new regimens into clinical development

Pa = PA-824; M = moxifloxacin; Z = pyrazinamide; J = TMC207
NC-002: First Study to Examine DS- and MDR-TB Together Using the Same Treatment for Both
Question: How To Develop a Novel Regimen Most Efficiently in All Susceptible Populations?

Our Answer: Unified DS and DR Development Path
REMox Phase 3 Trial
### Phase 3 REMoxTB Trial Design

#### Randomized, Double-blind; Non-inferiority

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- **630 participants**
  - Standard Regimen
  - Moxifloxacin for Ethambutol
  - Moxifloxacin for Isoniazid

- **All participants followed for 12 months post-treatment**

H = isoniazid; M = moxifloxacin; R = rifampin; Z = pyrazinamide; E = ethambutol
REMox TB Timeline

First Patient In: 1Q 2008
Last Patient In: Dec 2011
Last Patient Out: Jul 2013
Database Lock: Dec 2013
Study Report: April 2014
Thank You!

And Thank You To Our:

- Funders
- Partners
- Staff
- Stakeholders
- Patients