Clinical Development Strategies and Trial Designs for New TB Treatment Regimens

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November 25, 2016

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

EMA Draft Guidance 2016

- Not prescriptive; flexibility in approach encouraged
- Regimen development (multiple drugs developed simultaneously in a regimen) supported
  - In vitro, animal, and early human data can be used to document individual contributions of drugs in regimen
- Indication based on sensitivity to drugs in test regimen
  - "DS-" and "MDR-TB" categories not relevant to novel treatments
  - Not necessary to study "DS-" and "MDR" patients in separate trials
- Showing superiority of single drug addition to SOC for MDR-TB likely no longer viable
  - Optimized background therapy based on DST now has 80% success rate in MDR-TB clinical trials
  - Cf. 85% success rate of HRZE in modern DS-TB clinical trials

Additional Background Considerations

- No one approach or trial design fits all
  - Depends on question, rationale, and development strategy
  - Superior efficacy not the only possible advantage of new drug or regimen
    - Risk : benefit
    - Multiple other highly important advantages possible
    - Proving the exact degree of efficacy may not be of highest importance
- Difficult phase 2 to phase 3 transition in TB
  - Different efficacy endpoints
  - Wide confidence intervals in phase 2
- Phase 3 endpoint really clinical, supported by bacteriology
  - Will need small adjustments for liquid medium

Regimen Development

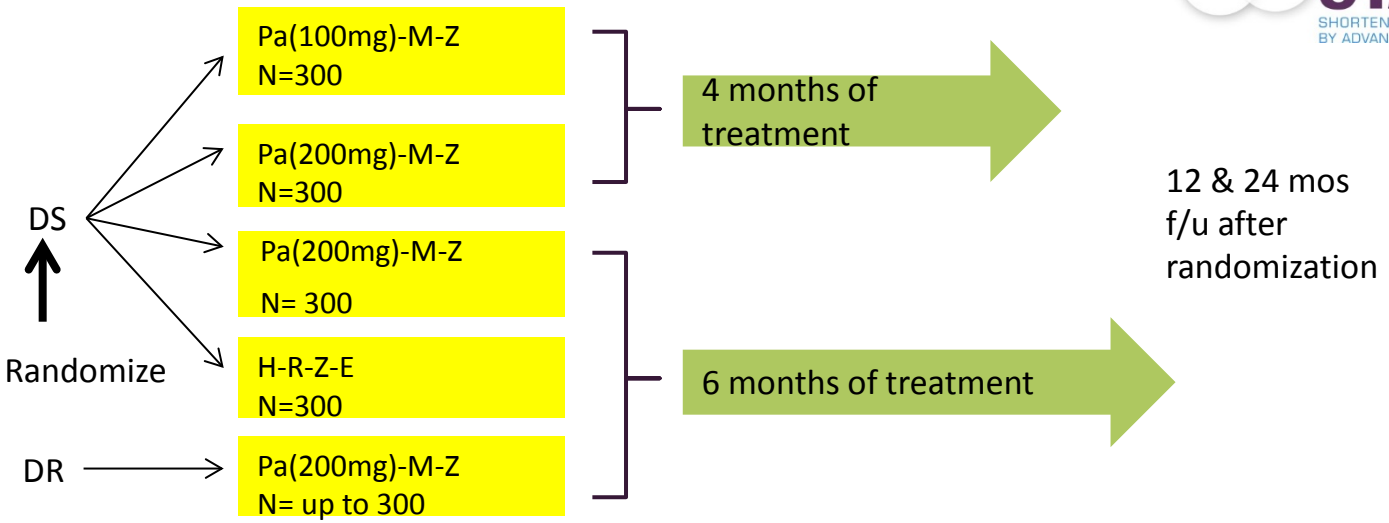
- Efficacy, safety, risk : benefit
  - Contribution of each individual drug to efficacy assessed in animal studies and in EBA clinical studies
  - Safety issues may require deconvolution
- Impact: optimal method of use of regimen described at launch
  - Also efficiency of development pathway
- Cf. single drug addition to (MDR) or substitution in (DS) background regimen
  - Difficult to prove superiority in MDR if “SOC” individualized based on DST
  - Difficult to prove efficacy in DS: effect on non-inferiority margin
  - Optimal method of use of drug not always described at launch

Unified Development Pathway

- DS- and MDR-TB studied together
  - Primary endpoint is in DS patients
    - Vs HRZE control in randomized comparison
  - MDR patients not randomized; assessed for similarity of response to same regimen in DS-TB
- No MDR-TB control group
  - Length, difficulty, expense
- Optimization of impact

STAND - Phase 3 Trial of PaMZ

Participants with newly diagnosed smear positive DS- and MDR-TB



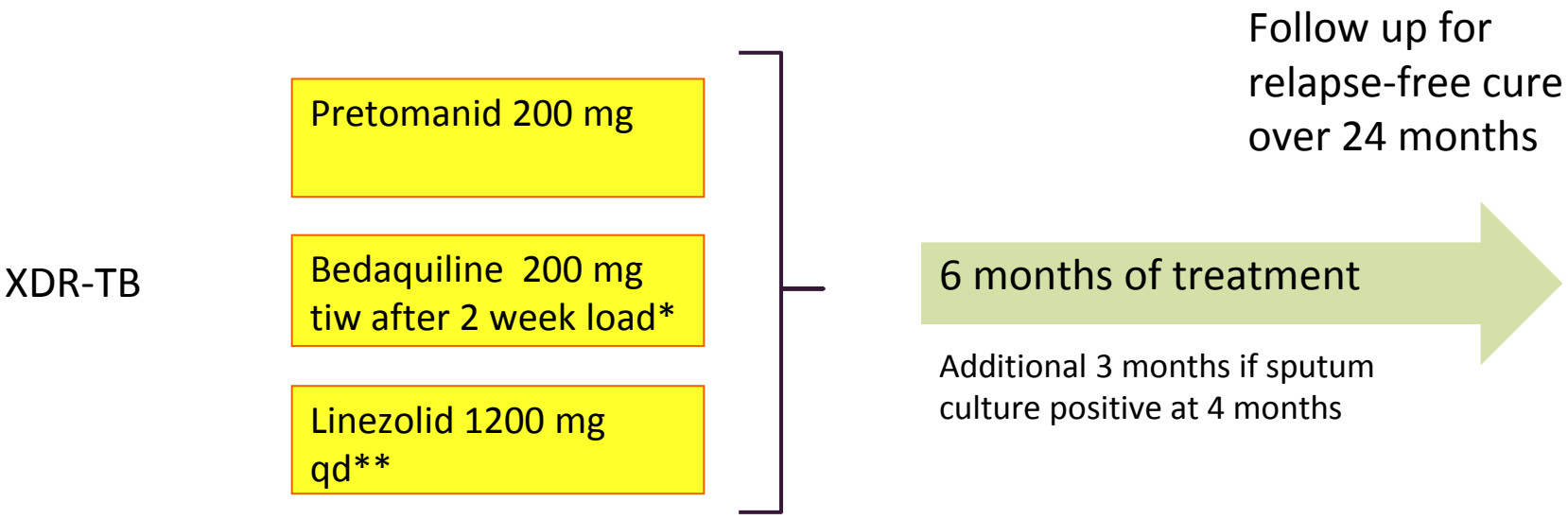
Pa = pretomanid **M = moxifloxacin 400 mg** **Z = pyrazinamide at 1500mg**

Nix-TB Approach

- Skipping phase 2 in highly select population (XDR-TB)
  - Toxicity of one of the drugs in the regimen restricted the population studied
  - Unmet medical need of this population allowed skipping of phase 2
- Historical control, small numbers
  - Advantage not only efficacy
  - Exact degree of efficacy not the most important aspect of the Nix-TB regimen

Nix-TB Pilot Phase 3 Trial in XDR-TB

Patients with XDR-TB or Who Have Failed MDR-TB Treatment



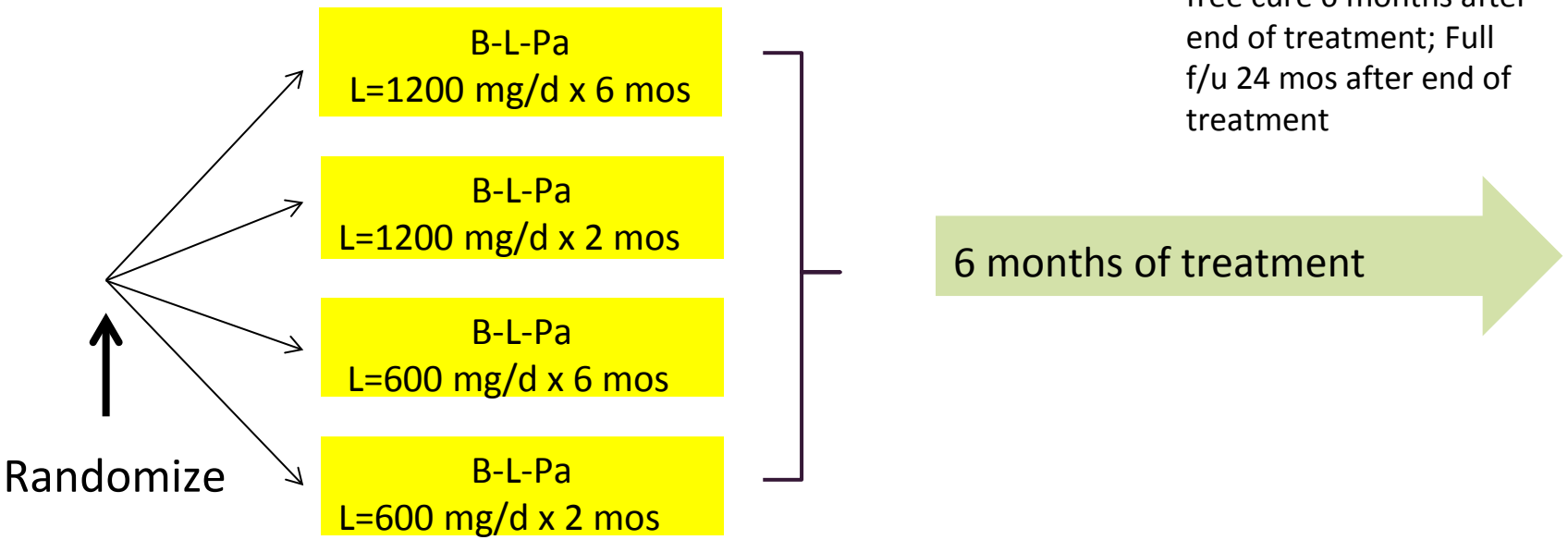
*May adjust dosing based on NC-005

**Just amended from 600 mg bid strategy

Sites: Sizwe and Brooklyn Chest, South Africa

B-Pa-L Linezolid Optimization Trial: TB Alliance Study NC-007

Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB Treatment



Pa dose = 200 mg daily; B Dose = 200 mg daily

Conclusions

- No one approach or trial design fits all
  - Depends on question, rationale, and development strategy
  - Superior efficacy (or shorter treatment) not the only possible advantage of new drug or regimen
    - Risk : benefit
    - Multiple other highly important advantages possible
    - Proving the exact degree of efficacy may not be of highest importance
- Regimen development and unified development pathway make sense in many situations
- Nix-TB approach to regimen development made sense when dealing with a fairly toxic compound (linezolid for long-term use)
- Novel approaches will continue to emerge as landscape changes