Inhaled Antibacterial Drug Development

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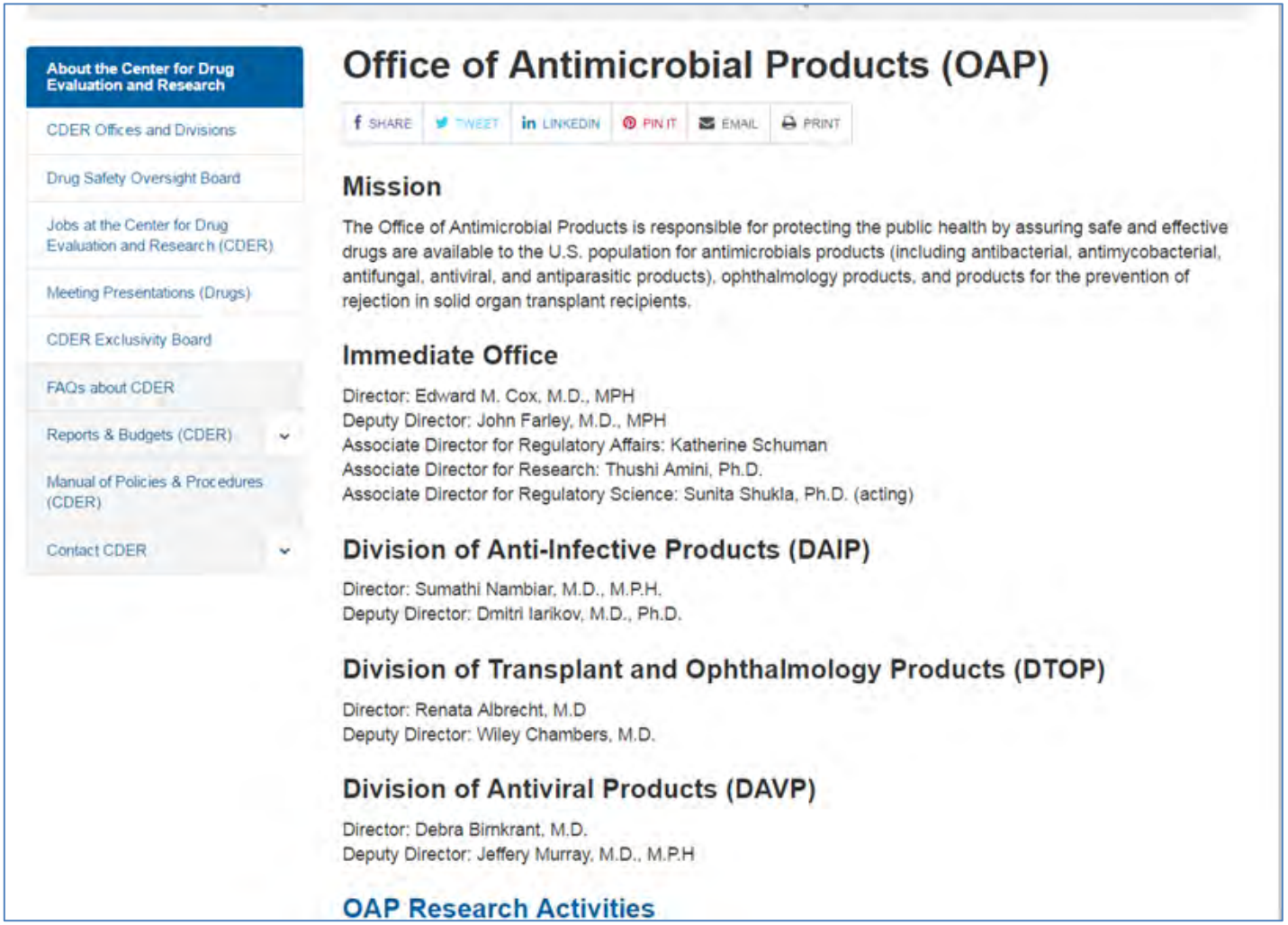
Outline

- Background on effectiveness standards, adequate and well-controlled trials, trial designs
- Discuss inhaled antibacterial drug development for some indications
- Expedited programs for serious conditions, Qualified Infectious Diseases Products (QIDP) designation



The Division of Anti-Infective Products oversees the regulation of antibacterial, antifungal and antiparasitic products, including inhaled anti-infective products

https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm275183.htm

Background

- Approved inhaled antibacterial drugs for cystic fibrosis:
  - Tobramycin inhalation solution (TOBI, Bethkis)
  - Tobramycin inhalation powder (TOBI PODHALER)
  - Aztreonam for inhalation solution (CAYSTON)
- Areas we have seen some interest in developing inhaled antibacterial therapies
  - Non Tuberculous Mycobacterial (NTM) infections
  - Non-CF bronchiectasis (NCFB)
  - Ventilator-associated bacterial pneumonia
  - Cystic Fibrosis (CF)

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Statutory Standards

- Substantial evidence as “evidence consisting of adequate and well-controlled investigations, including clinical investigations,…” (FD&C Act)
- Section 115(a) of the Modernization Act clarified that the Agency may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence

Adequate and Well-Controlled Trials

- Characteristics are outlined in 21 CFR 314.126(b)
- These characteristics are considered in determining whether an investigation is adequate and well-controlled
- Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs

Types of Controls

- Placebo concurrent control
  - Randomized trial in which test drug is compared to inactive drug that is similar in appearance
- No treatment concurrent control
  - Randomized trial in which test drug is compared to no treatment
- Dose comparison concurrent control
  - Randomized trial in which two or more doses of the test drug are compared

Types of Controls

- Active treatment concurrent control
  - Randomized trial in which test drug is compared to known effective therapy (active control)
- Historical control
  - Test drug is compared to historical experience – reserved for special circumstances (e.g., disease with high mortality, course of illness predictable, or where drug effect is self-evident such as in general anesthetics)

Types of Trials

- Superiority trials, where the test drug is better than comparator
  - Placebo, no treatment, dose-comparison, active control
- Noninferiority trials, where the test drug is no worse than an active comparator by a certain pre-specified amount (noninferiority margin)
  - Treatment effect of the active comparator compared to placebo needs to be estimated in the population being studied and for the outcome of interest

Clinical Endpoint

- A clinically meaningful endpoint that is a direct measure of how a patient feels, functions or survives
  - Improved survival
  - Improvement of symptoms or functional capacity

Federal Register/Vol. 57, No.73/April 15, 1992

Regulatory Pathways

- Standard approval
  - Based on an endpoint measuring how a patient feels, functions, or survives
- Accelerated approval
  - Based on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality; [21 CFR 314.500, (Subpart H)]
  - Postmarketing confirmatory trials to verify the predicted clinical benefit

FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Common Indications

- Non-Tuberculous Mycobacterial (NTM) infections
- Non-CF bronchiectasis (NCFB)
- Ventilator-associated bacterial pneumonia (VABP)
- Cystic Fibrosis (CF)

Inhaled Antibacterial Drug Trials: Challenges

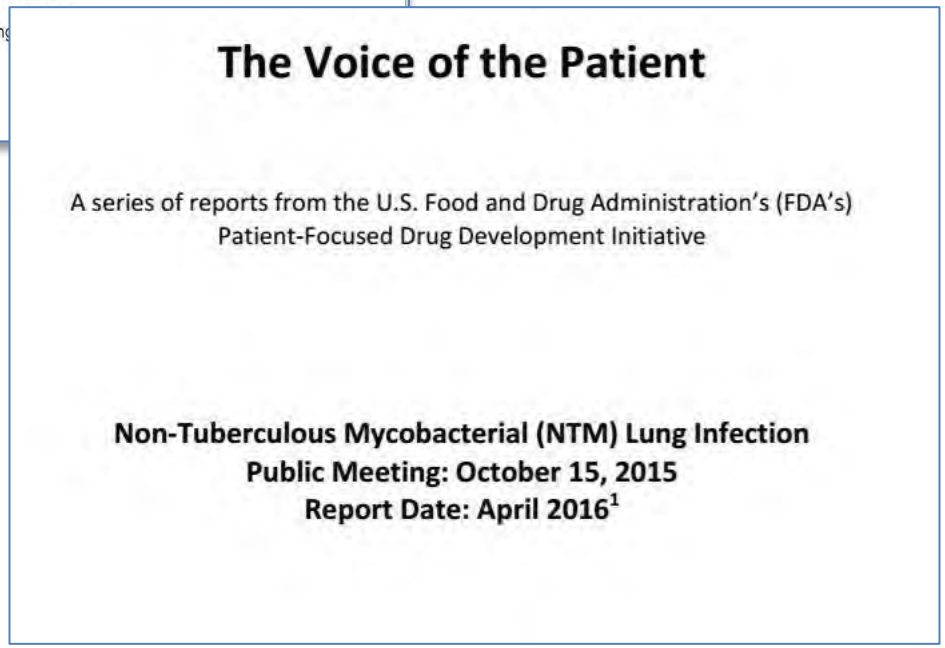
- Patient Population: Often very heterogeneous with regard to severity of illness, underlying patient characteristics and microbiologic etiology
- Endpoints: Defining a clinically meaningful endpoint has been difficult; unlike acute infections persistent symptoms related to underlying clinical condition. Microbiologic endpoints do not necessarily correlate with clinical outcomes

Inhaled Antibacterial Drug Trials: Challenges

- Treatment Regimens: Cyclical on/off therapy has generally been used in NCFB similar to the approach for CF; unclear if other approaches might be better
- Duration of Study: Optimal duration of therapy and length of follow up to determine treatment benefit is not clear
- Impact on microbiologic flora due to long-term exposure to antibacterial drugs; development of resistance and replacement with other microorganisms remain a concern

NTM Lung Infections

- Prevalence of NTM lung infections is increasing in the US
- Treatment involves multi-drug regimens given for > 1 year and is associated with significant toxicity
- No inhaled antibacterial drugs are FDA-approved for NTM lung infections
- Ongoing efforts to facilitate the development of drugs for treatment of NTM infections
  - FDA Public Workshop on patient-focused drug development for NTM lung infections held on October 15, 2015



https://www.fda.gov/Drugs/NewsEvents/ucm453877.htm

Challenges in NTM Lung Infection Trials

- Clinical outcomes are difficult to assess due to symptoms related to underlying comorbidities (bronchiectasis, COPD, cystic fibrosis)
- Response to study drugs may vary by NTM species and underlying lung disease
- Trials are lengthy and can pose challenges with compliance and loss to follow-up

NTM Trial Designs

- Superiority trials:
  - Test drug is added to background regimen (BR) compared to placebo or no treatment added to BR; approach has been used in TB trials
  - New combination regimen that includes test drug compared to a different combination regimen
    - If not feasible to demonstrate the contribution of each component of the combination clinically, this will need to be demonstrated in nonclinical studies (in vitro, animal models)

NTM Trial Designs

- Noninferiority (NI) Trials
  - The test drug replaces a drug in the BR; approach has been used in TB trials to allow treatment shortening
  - NI trials are likely to be extremely challenging; treatment effect of a single drug substitution in NTM is not known and hence difficult to estimate NI margin

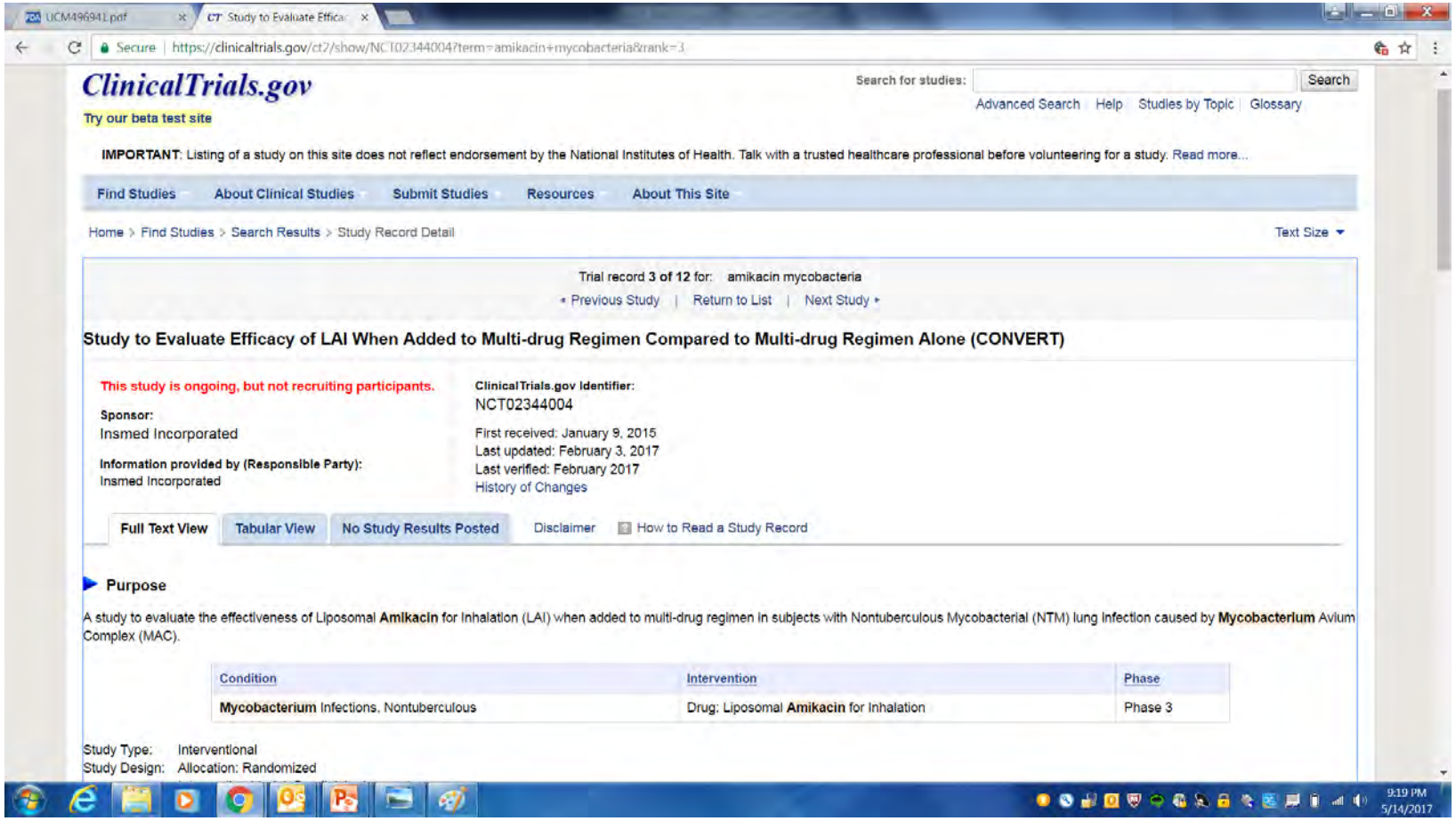
NTM Trials: Potential Endpoints

- Clinician Reported Outcome:
  - Clinical assessment can be confounded by the progression or exacerbation of underlying diseases
  - Performance outcome measures such as the 6-minute walk test (6WT) has been considered as a part of clinical assessment. A clinically important difference in 6WT in NTM patients needs to be defined.
- Patient Reported Outcome: Will need a validated tool that can discern a treatment effect

NTM Trials: Potential Endpoints

- Microbiologic endpoint of culture conversion:
  - May be defined as 3 consecutive negative respiratory cultures measured at defined post-randomization time points
  - Correlation with clinical outcome needs to be established
  - May expedite clinical program if used as a surrogate endpoint; longer follow-up (e.g., a 12-month) will still be needed

NTM Phase 3 trial



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Trial record **3 of 12** for: amikacin mycobacteria

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Study to Evaluate Efficacy of LAI When Added to Multi-drug Regimen Compared to Multi-drug Regimen Alone (CONVERT)

This study is ongoing, but not recruiting participants.

Sponsor:
Insmed Incorporated

Information provided by (Responsible Party):
Insmed Incorporated

ClinicalTrials.gov Identifier:
NCT02344004

First received: January 9, 2015
Last updated: February 3, 2017
Last verified: February 2017
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

A study to evaluate the effectiveness of Liposomal **Amikacin** for Inhalation (LAI) when added to multi-drug regimen in subjects with Nontuberculous Mycobacterial (NTM) lung infection caused by **Mycobacterium** Avium Complex (MAC).

Condition	Intervention	Phase
Mycobacterium Infections, Nontuberculous	Drug: Liposomal **Amikacin** for Inhalation	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized

Endpoints

- Primary Outcome Measure:
  - Proportion of patients achieving culture conversion in the LAI plus a multi-drug regimen arm compared to a multi-drug regimen alone with no relapse or recurrence [Time Frame: by 6 months]
- Secondary Outcome Measure:
  - Change from baseline in 6 Minute Walk Test (MWT) distance in the LAI plus a multi-drug regimen compared to a multi-drug regimen alone [Time Frame: 6 months and up to 16 months]

https://clinicaltrials.gov/ct2/show/NCT02344004?term=liposomal+amikacin&rank=2

LAI: Liposomal amikacin for inhalation

Non-CF Bronchiectasis

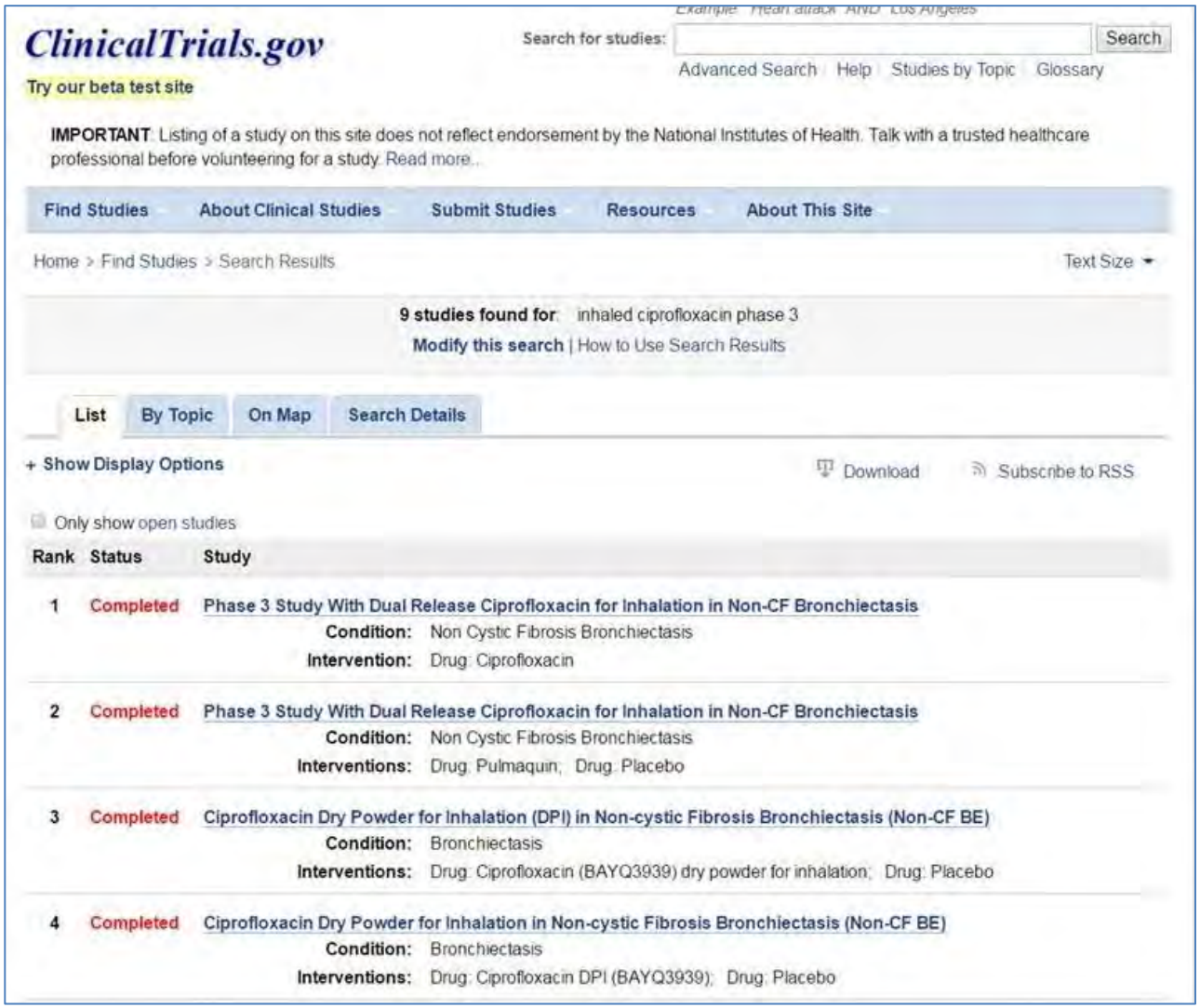
- There are no FDA-approved antibacterial drugs for the treatment of NCFB
- There is interest in developing antibacterial drugs for this clinical condition
- We recognize the need for new therapies given the increasing incidence and impact on patients
- Some inhaled antibacterial drugs have failed to show a treatment benefit in randomized controlled clinical trials: aztreonam, colistin

McCoy KS et al. Am J Respir Crit Care Med 2008;178:921-8
Haworth CS et al. Am J Respir Crit Care Med 2014;189(8):975-82
Chalmers et al. Expert Opinion on Pharmacotherapy, 16:6, 833-850

Trial Considerations

- Trial Design: Superiority trial; test drug plus Standard of Care (SOC) vs. SOC
- Endpoints: Time to first pulmonary exacerbation; Frequency of pulmonary exacerbations
- Approaches so far have followed the CF paradigm with cyclical on/off treatment regimens
- If intended use is long term, studies will need to evaluate longer treatment durations

Phase 3 Trials of Inhaled Antibacterial Drugs in NCFB



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Rank	Status	Study
1	Completed	Phase 3 Study With Dual Release Ciprofloxacin for Inhalation in Non-CF Bronchiectasis **Condition:** Non Cystic Fibrosis Bronchiectasis **Intervention:** Drug: Ciprofloxacin
2	Completed	Phase 3 Study With Dual Release Ciprofloxacin for Inhalation in Non-CF Bronchiectasis **Condition:** Non Cystic Fibrosis Bronchiectasis **Interventions:** Drug: Pulmaquin; Drug: Placebo
3	Completed	Ciprofloxacin Dry Powder for Inhalation (DPI) in Non-cystic Fibrosis Bronchiectasis (Non-CF BE) **Condition:** Bronchiectasis **Interventions:** Drug: Ciprofloxacin (BAYQ3939) dry powder for inhalation; Drug: Placebo
4	Completed	Ciprofloxacin Dry Powder for Inhalation in Non-cystic Fibrosis Bronchiectasis (Non-CF BE) **Condition:** Bronchiectasis **Interventions:** Drug: Ciprofloxacin DPI (BAYQ3939); Drug: Placebo

https://clinicaltrials.gov/ct2/results?term=inhaled+ciprofloxacin+phase+3&Search=Search

Endpoints

- Primary Outcome Measures:
- RESPIRE 1 and RESPIRE 2:
  - Time to First Exacerbation Event Within 48 Weeks [Time Frame: Up to Week 48]; time to first exacerbation was defined as the time from randomization until the visit at which the first qualifying exacerbation is recorded by the investigator. Exacerbation events are defined as exacerbations with systemic antibiotic use and presence of fever or malaise / fatigue and worsening of at least three signs/symptoms.
- ORBIT 3 and ORBIT 4:
  - Time to first pulmonary exacerbation (from baseline) [Time Frame: 48 weeks]
- Secondary outcomes also listed for RESPIRE 1 and 2

https://clinicaltrials.gov/ct2/show/NCT01764841?term=inhaled+ciprofloxacin+phase+3&rank=4
https://clinicaltrials.gov/ct2/show/NCT02104245?term=inhaled+ciprofloxacin+phase+3&rank=2

Ventilator-Associated Bacterial Pneumonia

- Trial design for such products will be superiority, assessing the superiority of the adjunctive treatment plus standard of care compared to standard of care; some examples:
  - Inhaled Amikacin Solution BAY41-6551 as Adjunctive Therapy in the Treatment of Gram-Negative Pneumonia (INHALE 1) https://clinicaltrials.gov/ct2/show/NCT01799993?term=amikacin+inhaled&rank=3
  - Aerosolized Amikacin and Fosfomycin in Mechanically Ventilated Patients With Gram-negative Pneumonia (IASIS) https://clinicaltrials.gov/ct2/show/NCT01969799?term=amikacin+fosfomycin&rank=1

Endpoints

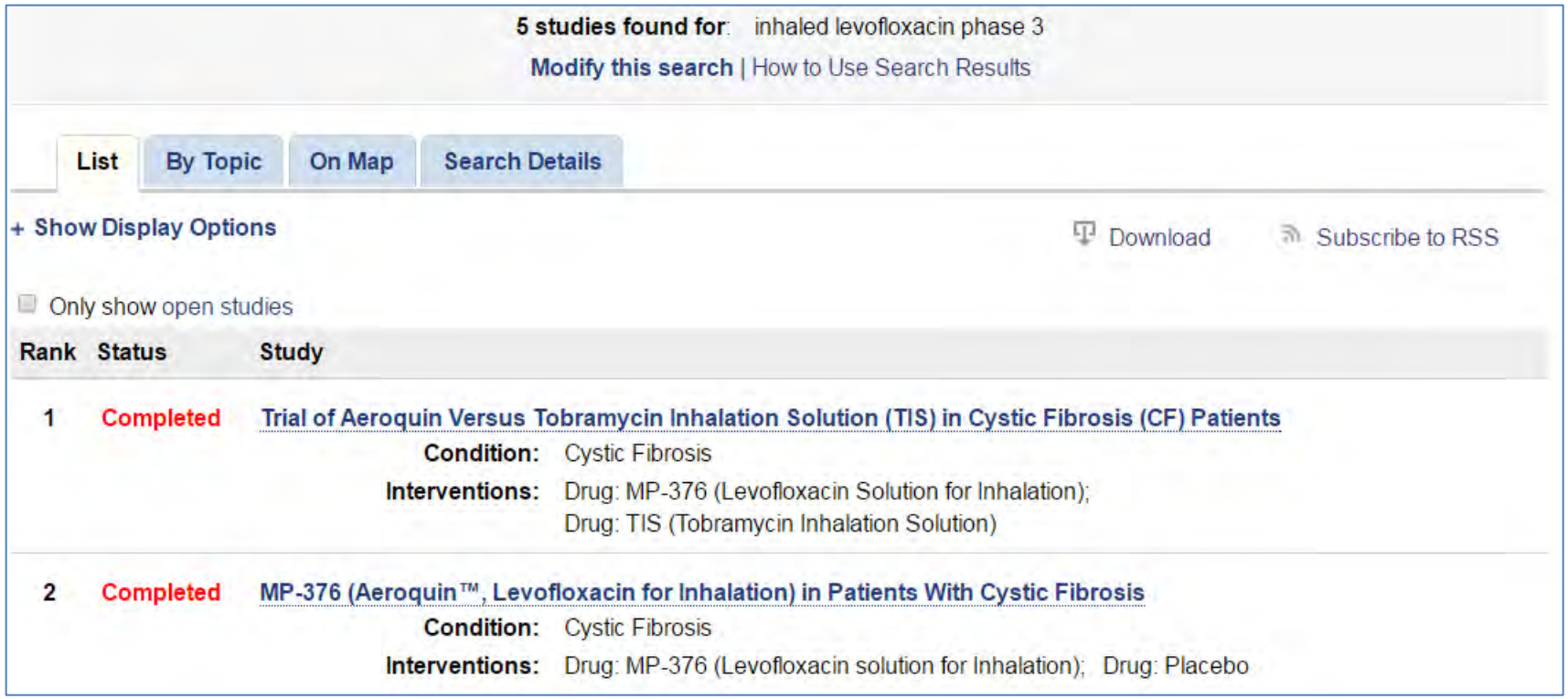
- Primary Outcome Measures
- Inhale 1 Trial:
  - Proportion of patients deemed to be clinical successes in the BAY41-6551 treatment group divided by the proportion of cured patients in the placebo treatment group.
    [Time Frame: Late follow-up (LFU) visit (day 28-32)]
- IASIS Trial:
  - Change from baseline in Clinical Pulmonary Infection Score (CPIS) during the planned 10-day treatment period.
    [Time Frame: 10 day treatment period]
- Several secondary outcome measures evaluated

https://clinicaltrials.gov/ct2/show/NCT01799993?term=amikacin+inhaled&rank=3
https://clinicaltrials.gov/ct2/show/NCT01969799?term=amikacin+fosfomycin&rank=1

Cystic Fibrosis

- Some inhaled antibacterial drugs are approved for the management of CF
- Approved therapies had demonstrated superiority against placebo on endpoints including FEV1; benefit also demonstrated on other endpoints such as use of IV antibacterial drugs for pulmonary exacerbation; improvement in respiratory symptoms
- Long-term placebo-controlled trials are no longer feasible for drugs with activity against *P. aeruginosa*; might still be possible for drugs with activity against methicillin-resistant *S. aureus* (MRSA)
- NI trials are likely not appropriate as treatment effect of available therapies is difficult to demonstrate in a treatment-experienced population

Phase 3 Trials of Inhaled Antibacterial Drugs in CF



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Rank	Status	Study
1	Completed	Trial of Aeroquin Versus Tobramycin Inhalation Solution (TIS) in Cystic Fibrosis (CF) Patients **Condition:** Cystic Fibrosis **Interventions:** Drug: MP-376 (Levofloxacin Solution for Inhalation); Drug: TIS (Tobramycin Inhalation Solution)
2	Completed	MP-376 (Aeroquin™, Levofloxacin for Inhalation) in Patients With Cystic Fibrosis **Condition:** Cystic Fibrosis **Interventions:** Drug: MP-376 (Levofloxacin solution for Inhalation); Drug: Placebo

Stuart EJ et al. J Cyst Fibros. 2015 Jul;14(4):507-14.; Flume PA et al. J Cyst Fibros. 2016 Jul;15(4):495-502.

Other Important Considerations

- Important that device issues be addressed early in development; the Division seeks input from
  - The Center for Devices and Radiologic Health for device-specific issues
  - The Division of Medication Error Prevention and Analysis for issues related to human factors
  - Patient Labeling Team in the Office of Medical Policy for review of Instructions for Use (IFU)
- Chemistry, Manufacturing, and Controls (CMC):
  - We encourage early interactions to discuss issues related to CMC e.g., PIND/EOP2, pre-NDA meetings

Generating Antibiotic Incentives Now (GAIN)

- Provides incentives for the development of certain antibacterial and antifungal drug products designated as Qualifying Infectious Disease Products (QIDP)
- QIDP refers to an antibacterial or antifungal human drug that is intended to treat serious or life-threatening infections, including…
- Sponsor may request QIDP designation at any time before submission of a marketing application for the drug
- So far, FDA has granted 131 QIDP designations for 69 new molecules

http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf

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GAIN – Incentives

- **Additional 5 years marketing exclusivity** granted at the time of approval for products that have been granted a QIDP designation
- **Priority review** for marketing applications for products that have a QIDP designation
- Products that have been granted a QIDP designation are eligible for **fast track** designation

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Expedited Programs for Serious Conditions

	Fast-Track Designation*	Priority-Review Designation*	Breakthrough-Therapy Designation	Accelerated-Approval Pathway
Criteria	• Nonclinical or clinical data demonstrate potential to address unmet medical need	• Provides significant improvement in safety or effectiveness over existing therapies	• Preliminary clinical data demonstrates substantial improvement over existing therapies	• Provides meaningful advantage over existing therapies • Demonstrates effect on a surrogate endpoint or intermediate clinical endpoint
Features	• Frequent FDA feedback • Rolling review	• 6 month review period (instead of 10 months)	• All benefits of Fast-Track Designation • Intensive guidance beginning Phase 1 • Organizational commitment involving senior FDA managers	• Approval based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict an effect on IMM or other clinical benefit

*Products with QIDP designation are eligible for fast track designation and priority review

IMM: Irreversible morbidity or mortality; Guidance on Expedited Programs for Serious Conditions, May 2014

Summary

- Trials of inhaled antibacterial drugs for the clinical conditions discussed are challenging
- Role of inhaled antibacterial drugs in the management of some of these clinical conditions is unclear
- Data from ongoing/recently completed trials will be helpful in understanding some of the issues including the patient population, duration of therapy, appropriate endpoints
- Knowledge gained will help to further refine clinical trial designs

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Thank You!


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