Combining Crowdsourced Protocol Design and Digital Study Execution

CTTI Expert Meeting: Legal & Regulatory Issues Affecting the Adoption of Mobile Clinical Trials

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July 11, 2017

Reinventing Drug Development
Agenda

1. TLS Corporate Introduction
2. Kiacta Project Overview
3. FDA Interactions Breakdown
   • Pre-IND Meeting
   • IND Submission
4. Conclusions on Regulatory Climate
Leader in Digital Drug Development Services

for biopharma sponsors, TLS radically improves quality, cost, and delivery of clinical trials

+ patient digital phenotypes
+ crowdsourced protocol design
+ digital study execution

TLS maximizes value of sponsors’ drug development projects

✓ biopharma partners recognize value
✓ FDA endorses and encourages TLS model
Clinical Trial Design via Crowdsourcing

TLS Protocol Builder collects, curates input from global community of patients, MDs, researchers

**Approach**

- Protocols crowdsourced in CNS, GI, cancer, autoimmune
- Results of prostate project published in *JNCI*
- Dozens to hundreds of patients and MDs involved per protocol
- Strong support from FDA
- Multiple TLS trial designs approved by major U.S. academic IRB’s

**Impact**

- Protocols crowdsourced in CNS, GI, cancer, autoimmune
- Results of prostate project published in *JNCI*
- Dozens to hundreds of patients and MDs involved per protocol
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site.tls Supports Diverse Patient Monitoring Scenarios

- **patient / MD engagement, recruitment**
  - TLS Protocol Builder
  - disease foundations
  - social media, online patient communities

- **patient monitoring**
  - telemedicine
  - smartphone apps/ePRO, wearables
  - mobile nurses
  - sub-site 1...n

- **virtual study hub**
  - study coordinator / patient views
  - cloud CRF’s, databases

- **instant visualizations**
TLS builds patient digital phenotypes in diverse, relevant indications

**Approach**

- remote and continuous biometric monitoring and ePRO

**Impact**

- maintains relationships with patients before, during and after randomized clinical trials
- better patient stratification
- more effective clinical trials
- builds valuable data store that can be monetized separately
- opportunity to engage patient communities via foundations
Kiacta in Sarcoidosis

**KIACTA™** is an orally bioavailable small molecule, currently being investigated in a Phase III pivotal study in patients with AA Amyloidosis, an orphan indication that results from long-standing inflammatory conditions.

*sarcoidosis* is a disease involving abnormal collections of inflammatory cells (granulomas) that can form as nodules in multiple organs, most often in the lungs.
Sarcoidosis Trial – Major Questions

all trials conducted in sarcoidosis to date have failed, mostly due to design / operational reasons:

- inclusion criteria
- treatment duration
- steroid tapering
- criteria for success
- clinically relevant endpoints
- acceptability of telemedicine
Remote Spirometry Opportunity
Protocol challenge (Kiacta™ in sarcoidosis)

Once patients have been taking 20mg of prednisone for three months, we will incrementally reduce the dose to 5mg over a six-week period.

Drawing from your knowledge of prednisone treatment, what are important elements to consider when reducing prednisone?

Crowd input - patients

“I have attempted various taper doses with about 10mg being the lowest I can go and still feel OK.”
- Patient X

“Taper down, watch for symptoms of rebounding inflammation…”
- Patient Y

250 patients, 50 researchers co-designing TLS protocol catalyze rapid, thorough response to key design issues
Crowdsourcing Impact – Round 1

- adjusted primary endpoint to 10% improvement
- adjusted PFTs, administration of PFTs
- refined steroid taper
- added walk test, QoL questionnaire
- adjusted process flow and documentation for better execution, comprehension
Randomization: ≥12% decline in FVC or FEV1 @ visit 3 compared to visit 1

The primary endpoint is a comparison of proportion of patients with at least a 10% increase over baseline (Visit 4) in FVC and/or FEV1 between eprodisate and placebo groups at 12 months (Visit 8) or end of study.
FDA Responses to Pre-IND Meeting

On one hand…
• Full endorsement of distributed model and telemonitoring
• Concur with suitability for Phase 2, plus agency encouragement to redesign this study as Phase 2/3

On the other hand…
• Pushback on run-in
  • Standard of care issue
  • Steroids should be offered and patients remain enrolled
• Push back on endpoint
  • Endorses FVC and FEV1, but best used at end of study
  • Notes that endpoint is at sponsor’s discretion in phase 2
Revised Study Flow

- N = 100 patients with pulmonary sarcoidosis
- Interim analysis to re-estimate sample size, possibility to convert into Phase2/3 trial
- Primary endpoint: Change from Baseline in FVC
- Method of imputation for rescue patient: Worst observation (FVC) carried forward
# Pulmonary Sarcoidosis - Key Study Criteria

<table>
<thead>
<tr>
<th><strong>Primary Objective:</strong></th>
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<tbody>
<tr>
<td>The primary objective of the study is to evaluate the safety and efficacy of Eprodisate administered orally to subjects with active pulmonary sarcoidosis.</td>
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<table>
<thead>
<tr>
<th><strong>Secondary Objective:</strong></th>
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<tbody>
<tr>
<td>The secondary objective of the study is to:</td>
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<tr>
<td>- Assess feasibility of telemedicine techniques for monitoring subjects with pulmonary sarcoidosis.</td>
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<table>
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<tr>
<th><strong>Study Design:</strong></th>
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<tbody>
<tr>
<td>This is a phase 2/3, multi-center, randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of Eprodisate administered orally to subjects with active pulmonary sarcoidosis. Using an adaptive design approach, between up to 200 subjects will be randomized to Eprodisate or placebo in a 1:1 ratio.</td>
</tr>
<tr>
<td>The Eprodisate dose will be assigned based on predefined creatinine clearance (CrCl) levels.</td>
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</tbody>
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Structure for All-Digital Study

20 patients at Mt. Sinai

Q2 / 2017

screen

80-180 patients virtual

Q3 / 2019

screen

virtual visit

in-person visit
# FSR Direct-to-Patients Feasibility Study

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>“I can see myself enrolling in a trial of this type and duration”</td>
<td>138</td>
</tr>
<tr>
<td>“I could enroll in a trial of this type and duration upon receiving more information”</td>
<td>177</td>
</tr>
<tr>
<td>“I do not see myself enrolling in a trial of this type and duration”</td>
<td>65</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>380</strong></td>
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broad geographical spread of patients highlights opportunity for fully distributed study
Pulmonary Sarcoidosis - Clinical Trial Supplies

**CSM**
- experienced in direct-to-patient shipments
- assures on-demand availability of Kiacta/placebo and prednisone
- allows for rapid dose adjustments

**ThermoFisher**
- exploring Fisher Clinical Services as an alternative

On-time, regulatory compliant, error-free delivery of drug supplies to patients is an essential step for success of “siteless” trial
Safety Patient Monitoring – Pharmacovigilance

pharmacovigilance process similar to current practice in clinical trials
• safety reporting done by medical monitor
• process facilitated by real-time access to data

Data Safety Monitoring Board
• two pulmonary medicine experts, one statistician
• via TC once per quarter

FDA acknowledges that remote monitoring of patients via digital tools affords better detection of safety problems
Key Regulatory Conclusions

IND clearance to proceed received April 21, 2017

Distributed care (telemonitoring patients, digital trials) fully supported by the FDA (Office of Medical Policy)

TLS has tested this approach with the Agency…
• by conducting distributed care study in IBD patients with Genentech
• by opening IND and initiating the execution of clinical study in MS
• at pre-IND meeting for sarcoidosis program
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