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The VALOR Trial

• Phase 3 randomized, controlled, double-blind, multinational trial in patients with first relapsed or refractory acute myeloid leukemia (AML)
• Evaluates the efficacy and safety of vosaroxin plus cytarabine versus placebo plus cytarabine

(vosaroxin is a first-in class anticancer quinolone derivative, or AQD, under development by Sunesis Pharmaceuticals, Inc.)
Part I: Design Considerations

- Primary endpoint is overall survival (OS)
- Design for 90% power; 5% significance level
- Plan for 24 month enrollment; 30 month trial
- Base Case Scenario
  - 5 vs. 7 month median on Ctrl vs. Trtm (HR=0.71)
  - 375 events and 450 patients @ 19/month
- Alternative Scenario
  - 5 vs. 6.5 month median on Ctrl vs. Trtm (HR=0.77)
  - 617 events and 732 patients @ 31/month
  - Requires larger upfront investment of resources and patients
Sponsor Favors Staged Commitment of Resources and Patients

Initial investment in base case scenario with commitment to invest additional resources if interim results are promising.
Sponsor’s Dilemma

<table>
<thead>
<tr>
<th>True HR</th>
<th>Power if designed with base case assumption (HR=0.71)</th>
<th>Power if designed with alternative assumption (HR=0.77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.71</td>
<td>91%</td>
<td>99%</td>
</tr>
<tr>
<td>0.74</td>
<td>83%</td>
<td>97%</td>
</tr>
<tr>
<td>0.77</td>
<td>71%</td>
<td>90%</td>
</tr>
<tr>
<td>Population Needed</td>
<td>450 patients; 375 events</td>
<td>732 patients; 616 events</td>
</tr>
</tbody>
</table>

- Sponsor conducted robust Phase 2 (N=69), though with inherent limitations of: small sample relative to Phase 3; non-randomized data; US-only conduct
- The true HR is not known but expected to be between 0.71 and 0.77
  - Trial would be underpowered if designed for HR=0.71 but true HR > 0.71
  - Trial would be overpowered if designed for HR=0.77 but true HR < 0.77
- Preferred decision: to invest additional patients, resources, and time on larger study only if warranted, based on interim results, rather than upfront
Adaptive Design Strategy

- Base case design (HR=0.71; 375 events; 450 patients)
- One interim analysis after 50% of information
  - Stop early if overwhelming evidence of efficacy
  - Stop early for futility
  - Increase number of events and sample size (by 50%) if interim results are promising
Adaptive Decision Rule: I (Example)
Adaptive Decision Rule: II
(Example)

% increase in number of events

0%  X%  50%  Y%  100%

Conditional Power

Unfavorable Zone

Promising Zone

Favorable Zone
Statistical Methodology

Use well established method of combining independent increments from the two stages with pre-specified weights

\[ Z_{j,chw}^* = \frac{\sqrt{w^{(1)}} Z^{*(1)} + \sqrt{w^{(2)}} Z^{*(2)} + \ldots + \sqrt{w^{(j)}} Z^{*(j)}}{\sqrt{w^{(1)}} + w^{(2)} + \ldots + w^{(j)}} \]

where

\[ Z^{*(j)} = \frac{\sqrt{D_j^* LR_j} - \sqrt{D_{j-1}^* LR_{j-1}}}{\sqrt{D_j^* - D_{j-1}^*}} \quad \text{and} \quad w^{(j)} = \frac{D^{(j)}}{D^{(K)}} \]

Reference: Lehmacher and Wassmer, 1999; Cui, Hung and Wang, 1999
Evaluate Properties by Simulation: (Example)

### Survival Superiority Trials: Two Sample Test - Logrank Test: Given Accrual Duration and Study Duration

<table>
<thead>
<tr>
<th>Input Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptation at Look L</td>
<td>1</td>
</tr>
<tr>
<td>Max. Events if Adapt (multiplier; total #)</td>
<td>1.50</td>
</tr>
<tr>
<td>Max. # of Subjects if Adapt (multiplier; total #)</td>
<td>1.50</td>
</tr>
<tr>
<td>Upper Limit on Study Duration</td>
<td>90.00</td>
</tr>
<tr>
<td>Shape Parameter for Re-estimating # of Events</td>
<td>0.99</td>
</tr>
<tr>
<td>Promising Zone: Min CP:</td>
<td>0.50</td>
</tr>
<tr>
<td>Max CP:</td>
<td>0.90</td>
</tr>
<tr>
<td>HR Used in CP Computations</td>
<td>Estimated HR</td>
</tr>
<tr>
<td>Accrual Rate After Adaptation</td>
<td>No Change</td>
</tr>
</tbody>
</table>

#### Output for all Trials

<table>
<thead>
<tr>
<th>Show Summary for</th>
<th>Promising</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentile</td>
<td>Study Duration</td>
</tr>
<tr>
<td>5%</td>
<td>37.0</td>
</tr>
<tr>
<td>25%</td>
<td>37.7</td>
</tr>
<tr>
<td>50%</td>
<td>38.3</td>
</tr>
<tr>
<td>75%</td>
<td>38.9</td>
</tr>
<tr>
<td>95%</td>
<td>39.7</td>
</tr>
<tr>
<td>Average</td>
<td>38.3</td>
</tr>
</tbody>
</table>

#### Simulation Results by Zone

<table>
<thead>
<tr>
<th>Zone</th>
<th>Simulations Rejecting H0</th>
<th>Simulations Rejecting H1</th>
<th>Total Simulations</th>
<th>Avg. Study Duration</th>
<th>Avg. Number of Events</th>
<th>Avg. Accrual Duration</th>
<th>Avg. Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>Row %</td>
<td>Count</td>
<td>Row %</td>
<td>Count</td>
<td>Column %</td>
<td></td>
</tr>
<tr>
<td>Unfavorable + Futility</td>
<td>1394</td>
<td>40.06%</td>
<td>2086</td>
<td>59.94%</td>
<td>3480</td>
<td>34.80%</td>
<td>28.3</td>
</tr>
<tr>
<td>Promising: 0.500 ≤ CP &lt; 0.900</td>
<td>2295</td>
<td>92.43%</td>
<td>188</td>
<td>7.57%</td>
<td>2483</td>
<td>24.83%</td>
<td>38.3</td>
</tr>
<tr>
<td>Favorable + Efficacy</td>
<td>3844</td>
<td>95.22%</td>
<td>193</td>
<td>4.78%</td>
<td>4037</td>
<td>40.37%</td>
<td>25.6</td>
</tr>
<tr>
<td>All Trials</td>
<td>7533</td>
<td>75.33%</td>
<td>2467</td>
<td>24.67%</td>
<td>10000</td>
<td>100.00%</td>
<td>29.7</td>
</tr>
</tbody>
</table>
### Benefit of Adaptive Design

<table>
<thead>
<tr>
<th>True HR</th>
<th>Base Case Design</th>
<th>Adaptive Design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>450 Patients, 375 Events</td>
<td>675 Patients, 563 Events</td>
</tr>
<tr>
<td>0.71</td>
<td>91%</td>
<td>98%</td>
</tr>
<tr>
<td>0.74</td>
<td>83%</td>
<td>96%</td>
</tr>
<tr>
<td>0.77</td>
<td>71%</td>
<td>90%</td>
</tr>
<tr>
<td>0.80</td>
<td>58%</td>
<td>84%</td>
</tr>
</tbody>
</table>

- VALOR’s adaptive design gains substantial additional power over non-adaptive IF interim outcome falls in the Promising Zone (~35% chance)
Part II: Operational Considerations

• Statistical methodology for controlling type-1 error is well established (Cui, Hung and Wang, 1999, East-SurvAdapt, 2011)
• Logistical and operational issues associated with trial execution are less well established
• We have implemented a web solution for handling the two main issues of concern to regulatory agencies: operational bias and trustworthiness
"A well-trusted firewall established for trial conduct beyond those established for conventional group sequential trials can help provide assurance that statistical and operational biases have not been introduced."

*FDA Guidance on Adaptive Design (2010)*
Operational Bias and Trustworthiness

• Operational Bias
  – Can knowledge that the sample size was increased (or not increased) affect the integrity of the study?

• Trustworthiness
  – Who saw what data, and when?
  – Can a non-invasive audit trail of the entire data handling process be implemented?
ACES: Access Control Execution System

- Web based technology to control flow of information and access to confidential documents
- Prevents operational bias by including the actual adaptive algorithm only in restricted appendix to Data Monitoring Committee (DMC) charter and tracking access to this document
- Establishes trustworthiness through secure password protected access to documents, execution of algorithms, and audit trail
Traditional Process

Sponsor

Create Documents (Protocol, SAP, DMC Charter)

Store/Archive Documents

Enroll Subjects & Collect Responses

Send Response Data to ISC

 ISC

Send Analysis to DMC

Perform Analysis and Create Reports

Create and Test Analysis Programs

DMC

Send Recommendation to Sponsor/Steering Committee

Make Recommendation

After decision...
1. DMC notified
2. Drug Supply notified
3. IVRS notified

Steering Committee

Make Decision About Trial

Request additional information
ACES Process

Sponsor

Create Documents (Protocol, SAP, DMC Charter)

Store/Archive Documents in ACES

Enroll Subjects & Collect Responses

Send Response Data to ISC

ISC

Send Analysis to DMC in ACES

Perform Analysis and Create Reports in ACES

Load Final Analysis Programs into ACES

Create and Test Analysis Programs

Request additional information

DMC

Send Recommendation to Sponsor/Steering Committee

Make Recommendation

Make Decision about Trial

After decision...
1. DMC notified
2. Drug Supply notified
3. IVRS notified

Steering Committee
Welcome to ACES. Please enter your User ID and Password to sign in.

User ID: 
Password: 

Sign In

Forgot your password?

By logging into ACES I accept and agree to the following terms. I understand that my use of ACES authenticates me as the official requestor and user of this ACES account. I understand that access to ACES is restricted to authorized personnel.
Execution Cycle

Interim Analysis begins… Responses Generated… Reports Generated.
# Audit Trial: Document Access Log Summary

### Document Access Log Summary: 12

<table>
<thead>
<tr>
<th>Document</th>
<th>Accessed on</th>
<th>Accessed by</th>
<th>Uploaded by</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Dependency Report</td>
<td>09-Feb-2011 15:40 UTC</td>
<td>Albert Einstein</td>
<td>SYSTEM</td>
<td>ACCEPTED</td>
</tr>
<tr>
<td></td>
<td>09-Feb-2011 15:45 UTC</td>
<td>David Gilmour</td>
<td>SYSTEM</td>
<td>ACCEPTED</td>
</tr>
<tr>
<td>Alcohol Dependency Report</td>
<td>10-Feb-2011 17:23 UTC</td>
<td>Albert Einstein</td>
<td>SYSTEM</td>
<td>ACCEPTED</td>
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<tr>
<td></td>
<td>10-Feb-2011 17:29 UTC</td>
<td>David Gilmour</td>
<td>SYSTEM</td>
<td>ACCEPTED</td>
</tr>
<tr>
<td></td>
<td>11-Feb-2011 18:50 UTC</td>
<td>David Gilmour</td>
<td>SYSTEM</td>
<td>ACCEPTED</td>
</tr>
<tr>
<td>Alcohol Dependency Report</td>
<td>11-Feb-2011 18:48 UTC</td>
<td>Albert Einstein</td>
<td>SYSTEM</td>
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</tr>
<tr>
<td>SAP Document</td>
<td>14-Feb-2011 21:45 UTC</td>
<td>Stephen Hawking</td>
<td>Stephen Hawking</td>
<td>ACCEPTED</td>
</tr>
<tr>
<td>DMC Charter</td>
<td>14-Feb-2011 21:45 UTC</td>
<td>Stephen Hawking</td>
<td>Stephen Hawking</td>
<td>ACCEPTED</td>
</tr>
</tbody>
</table>
Review: What Problems did ACES Address?

• DMC Portal
  – secure centralized storage of documents
  – customized access for DMC, Independent Statistical Center (ISC), and Sponsor

• ACES Engine Generates Interim Reports
  – analysis programs pre-tested and loaded to ACES
  – blinded dataset uploaded to ACES

• Non-Invasive Audit Trail
  – who sees what and when is time stamped
  – dataset and analysis program available for review
Concluding Remarks

• Adaptive design reduces risk of failing to detect a smaller clinically meaningful effect
• Pragmatic approach; wait to see data before committing additional patients and resources
• Statistical methodology well understood
• Operational challenges and trustworthiness are regulatory concerns that are handled well by the ACES system
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