Clinical Study Start-up Time Lines for Rare Orphan Diseases: Can We Do Better? The Example of Primary Biliary Cholangitis

Monika Varga¹, Afshawn Chakamian², Virginia Chow³, Pol Boudes¹
On behalf of the MBX8025-21528 Study Coordinators and Investigators
¹CymaBay Therapeutics, Newark, CA, ²PRA Health Sciences, San Diego, CA, USA, ³Liver Unit, University of Calgary, Calgary, Canada

Clinical Study Start-up Time Lines for Rare Orphan Diseases: Can We Do Better? The Example of Primary Biliary Cholangitis

Primary Biliary Cholangitis (PBC) is a rare autoimmune disease which primarily affects women of middle age.

A 12-week, double-blind, randomized, placebo-controlled, Phase 2 study, evaluated the effects of two doses of MBX-8025 in subjects with Primary Biliary Cirrhosis (PBC) and an inadequate response to ursodeoxycholic acid (UDCA) (NCT02609048/Eudra-CT 2015-002698-39). The outcome of this study will be presented during the late breaking session of the congress¹.

Participating clinical study sites ranged from private clinics to academic centers.

The recruitment of patients with rare diseases is challenging². One of the challenges is the time to study site activation.

Objectives

We report on study site activation and study start-up activities and their impact on study timelines.

Methods

Sites from Canada, Germany, Poland, United Kingdom and United States participated.

We collected the time to:
1) Health Authority or IND approval (United States): from first submission to written approval
2) Ethics Committee (EC) submission: from EC documents provided to site to first submission
3) EC approval: from first submission to first written approval
4) Complete contractual agreement: from first draft contract to site to full execution

We calculated the total time to activate sites (from site agreement to participate to site being able to screen a patient). We present the mean durations and correlations of study start up activities.

References


Introduction

The Liver Meeting 2016, AASLD, November 11 – 15, Boston, MA, USA

Results

Mean Time (days) to Approval or Task Completion

<table>
<thead>
<tr>
<th>Country</th>
<th>United States</th>
<th>United Kingdom</th>
<th>Germany</th>
<th>Poland</th>
<th>Canada</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites (N)</td>
<td>23</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>53</td>
</tr>
<tr>
<td>Health Authority or IND Approval</td>
<td>189</td>
<td>57</td>
<td>58</td>
<td>42</td>
<td>34</td>
<td>112</td>
</tr>
<tr>
<td>Time to EC Submission</td>
<td>48</td>
<td>26</td>
<td>41</td>
<td>116</td>
<td>86</td>
<td>52</td>
</tr>
<tr>
<td>EC Submission to Review and Approval</td>
<td>19</td>
<td>41</td>
<td>62</td>
<td>33</td>
<td>73</td>
<td>38</td>
</tr>
<tr>
<td>Contract Completion</td>
<td>84</td>
<td>155</td>
<td>133</td>
<td>115</td>
<td>200</td>
<td>116</td>
</tr>
<tr>
<td>Site Activation</td>
<td>105</td>
<td>173</td>
<td>188</td>
<td>189</td>
<td>214</td>
<td>152</td>
</tr>
</tbody>
</table>

Mean Duration of Site Activation Milestones

| Site Activation Duration is Correlated to Ethics Committee Approval Duration (r = 0.77) |
| Site Activation Duration is Correlated to Contract Completion (r = 0.87) |

Discussion

Health Authority approval, EC approval, contract execution, collection of regulatory documents from the study site and site training are on the critical path to study initiation. We observed that EC approval and contract execution had the greatest impact on site activations.

The UK has the shortest time to EC submission. This was due to the expertise of the UK PBC Network, an organization that fosters collaboration between patients, clinical researchers and industry.

A central EC was used by 43% of the United States sites and shortened the average time to study approval post submission.

The completion of research contracts was the most time consuming task for clinical study site activation and has the greatest impact on overall duration. The United States sites, which had the shortest average time to contract completion, had the shortest time to site activation.

Conclusions

Overall, site activations took close to half a year. Contracts completion and EC approvals were the most time consuming activities. Wide variation between countries and between sites helped to identify best and worst practices.

The primary targets to improve site activation timelines are the preparation for Ethics Committee submission and shortening the contract negotiation.

Close partnering with clinical sites and clear communication from the sponsor on timelines and expectations improve EC submission. Contract negotiation may be shortened. We have found that our sponsor practice to review and respond within 48 hours elicits smoother site contract negotiation.

Working with the same study sites on multiple studies should provide further time saving. CymaBay is working with a subset of the sites to initiate a new clinical study.