FDA Releases First Clinical Study Report in Data Transparency Pilot Program

By Zack Budryk & Conor Hale

The FDA published its first batch of clinical data summary documents under a transparency pilot program launched earlier this year. By making portions of CSRs publicly available, the FDA hopes to increase stakeholder understanding of the basis for the agency’s approval decisions, and enhance the accuracy of information used in scientific publications, said CDER Director Janet Woodcock. The FDA plans to post up to nine total CSRs from recently approved NDAs volunteered by participating sponsors across a range of disease areas.

“As an added benefit, our pilot program can help with global alignment, as our counterparts at the European Medicines Agency are similarly working to make information about their approvals more accessible and easier to understand,” Woodcock said.

The EMA launched its clinical data transparency program, which publishes clinical study reports and protocols from all new drug submissions, regardless of approval status, in October 2016 (CWWWeekly, Oct. 24, 2016). At the one-year anniversary of the EMA’s initiative, the agency had published more than 3,000 clinical documents covering 50 medicines, totaling 1.3 million pages. The publicly available database also registered more than 3,600 users.

The data from the FDA’s first release covers the pivotal trial for Janssen Biotech’s Erleada (apalutamide) — approved in February as the...
House Republicans Pass Right-to-Try Bill
The House passed its version of federal right-to-try legislation, sending it for reconsideration by the Senate, which passed a similar bill last August. The bill, H.R. 5247, had failed to garner enough votes on the floor last week to fast-track the bill under suspension of the House rules. Republicans that favor the legislation said they believe terminally ill patients, that have exhausted all other treatment options, should be able to try unproven therapies as a last resort. “For those patients caught between the traditional drug approval delays, a clinical trial process for which they do not qualify, and limited time, this right-to-try establishes the freedom for patients to try therapies in situations where the benefits far outweigh the risks,” said bill sponsor Rep. Brian Fitzpatrick (R-Pa.). Most Democrats opposed the bill, arguing that it would hinder the FDA’s oversight of investigational treatments — and contending that patients already have a program through which they can request access to experimental treatments. In addition, four former FDA commissioners — Robert Califf, Margaret Hamburg, Mark McClellan and Andrew von Eschenbach — as well as over 80 patient advocacy organizations opposed the bill because it would remove agency protections from the process.

FDA, EMA & the National Kidney Foundation Hold Workshop on CKD Meta-analysis
The National Kidney Foundation, the FDA and the EMA held a joint scientific workshop to review a multi-year meta-analysis examining an enormous compilation of data on chronic kidney disease — including data on nearly two million participants — to support the use of earlier markers of kidney disease progression as clinical trial endpoints for early stages of CKD. The analysis explored whether surrogate biomarkers measuring kidney damage and function — such as changes in albuminuria or changes in glomerular filtration rate — can be used as predictors of a treatment’s effect on progression to kidney failure. “This extensive meta-analysis of endpoints for chronic kidney disease builds upon previous research which recommended a 30 or 40 percent decline in GFR as the endpoint for clinical trials in some CKD populations,” said Kerry Willis, chief scientific officer for the National Kidney Foundation. “However, we’ve found that these recommended endpoints are less applicable to the clinical development of drugs targeted at earlier stages of kidney disease and for many drugs with possible hemodynamic effects...How to overcome these obstacles was the driving force behind today’s scientific workshop and this multi-year research project.” The research was conducted at Tufts Medical Center, Johns Hopkins University, the University of Utah and Groningen University in the Netherlands. The groups plan to publish the meta-analysis and workshop recommendations in a series of articles later this year.

Oncology Accelerated Approvals Showed Benefit
Most oncology treatments that received the FDA’s accelerated approval pathway in the past 25 years later demonstrated benefits in clinical trials, according to a review by agency officials published in JAMA Oncology. Between the program’s creation in 1992 and May 2017, the FDA granted 64 accelerated approvals for cancer treatments, including for 53 new molecular entities and in 93 new indications. Seventy-two percent of these indications were studied in single-arm clinical trials, 87 percent of which used response rate as their endpoint. For drugs with completed postmarket requirements, the most common study endpoint was progression-free survival and time to progression. Of the 93 indications, 51 fulfilled their postmarket requirements and verified clinical benefit in a median of 3.4 years after the initial designation, while another 37 have not yet completed confirmatory trials or verified benefit. The remaining five have been withdrawn from the market. The article is available here: www.jamaoncology/article-abstract/2673837.

Oncology Will Again Be The Top Clinical Trials Sector in 2018
Oncology will continue to be the top sector for clinical trials planned to be launched this year, according to the analytics firm GlobalData. Novartis and GlaxoSmithKline were listed as the top two industry sponsors, while MD Anderson Cancer Center led among non-industry sponsors. Immuno-oncology drugs were the most frequent. The largest number of clinical trials were planned for Merck’s Keytruda (pembrolizumab), with Bristol-Myers Squibb’s Opdivo (nivolumab) taking second. Both target PD-1. Across all diseases and phases, phase II trials account for 44 percent, according to the report. Phase I and III trials made up 26 percent and 21 percent, respectively. Postmarket phase IV trials meanwhile accounted for just 8 percent. Among sites, North America was ranked as the top location, followed by Europe and Asia-Pacific, with all three regions accounting for more than 90 percent of trial locations. “The dominance of industry sponsorship is most prominent in phase I, II and III trials, whereas non-industry sponsorship is most prominent in phase IV trials,” said Revati Tateke, global director of databases and analytics at GlobalData, adding that about two-thirds of trials are sponsored by pharmaceutical companies.

CWW2212
Data Transparency (continued from page 1)

first drug to treat non-metastatic, castration-resistant prostate cancer, and the first to use the endpoint of metastasis-free survival.

The released portions of Janssen’s clinical study report include complete summaries of the trial’s results, as well as its protocol, amendments and statistical plan, totaling about 1,000 pages.

The pilot program redacts or excludes confidential commercial information, trade secrets and personal privacy information, as well as patient-level data, Woodcock said. Previously, the FDA’s drug approval packages and clinical trial snapshots typically included the agency’s review letters and product labeling, as well as breakdowns of participant demographics.

“I am impressed with the release of such a data set so soon after Scott Gottlieb’s announcement of FDA’s proposal,” said David Forster, chief compliance officer of WIRB-Copernicus Group.

During his announcement of the project in January, FDA Commissioner Gottlieb said the disclosures can help sponsors address challenges in development, identify areas that may require additional postmarket research and generate the data necessary for approval.

In addition, the agency hopes to use the pilot to streamline CDER’s clinical review processes, by consolidating disparate staff review documents into a single memo (CWWeekly, Jan. 22).

In the Phase III trial, Erleada, an antiandrogen, showed a robust effect in its novel primary endpoint of prolonging the time until metastasis or death, according to Richard Pazdur, director of the FDA’s Oncology Center of Excellence. “This demonstrates the agency’s commitment to using novel endpoints to expedite important therapies to the American public,” he said. Erleada was granted priority review.

The placebo-controlled, multi-center trial — launched in October 2013, with last patient, last visit being completed in May 2017 — randomized a total 1,207 patients 2:1, demonstrating a median metastasis-free survival of 40.5 months in the Erleada arm, compared to 16.2 months in the placebo arm.

Erleada’s full approval package is available here: www.accessdata.fda.gov/drugsatfda_docs/nda/2018/Erleada_210951_toc.cfm.

Rare Disease Clinical Trials May Require Paradigm Shift Away From Traditional P-Values to More Adaptive Models, Experts Say

The future of clinical trials in rare diseases and precision medicine may require a paradigm shift away from traditional study methods. The shift trends toward the use of new and adaptive tools to squeeze every ounce of information from data gathered in shrinking patient populations, according to experts.

At a meeting on statistical methods and study designs in rare disease drug development, convened last week by Duke University under a cooperative agreement with the FDA, representatives from academia, the agency and industry sought to address the main challenges in the setting. Their feedback could form the basis of formal guidance documents, the university said.

One method to increase efficiency would be to borrow prior data from early phase trials and incorporate them into phase III designs, which traditionally begin de novo.

“Realistically, we’ve been using phase II borrowing for years,” to design subsequent trial dosing and regimens, for example, said Laura Lee Johnson, an acting division director in CDER’s Office of Biostatistics. “When you don’t, it goes haywire.”

However, this would go farther when formally incorporated into a Bayesian clinical trial approach, which aims to estimate the probability that a treatment is more effective, in a move away from the traditional reliance on acquiring two P-values of less than 0.05, described Karen Price, a research advisor at Eli Lilly & Co.

Evaluating, weighting and using data from a wide range of potential prior sources — including expert opinions; historical controls; natural history studies; summary-level data from randomized controlled trials or observational studies; pharmacokinetic and pharmacodynamic findings; and individual-level data from patient registries — can allow for greater flexibility in modeling and prediction in a completely transparent manner, Price said. Dynamic methods can allow sponsors to borrow more when current data are similar to historical data, and protect against over-borrowing.

Sponsors would need to assess the relevance and exchangeability of historical data compared to new data, Price said, including the similarity of indications, patient population and endpoints, as well as the time since collection. Data could be borrowed from either control or treatment arms, or both.

But borrowing historical data needs to be carefully considered. “The investigational sites may not be exactly the same, but are the regions the same?” added John Scott, acting director of CBER’s Division of Biostatistics. “If the regions aren’t the same, are there any substantial differences in the background care that patients are receiving? That can make huge differences in comparability.”

From the FDA’s perspective, the question of how much to borrow for phase III trials can become very complicated, said Scott, in addition to the practical trial constraints in the rare disease setting, with few patients available to participate in studies.

“I think that we have a moral obligation, especially in this setting, to use information as wisely as possible,” he said, as well as an obligation to not make erroneous conclusions of effectiveness.

Sponsors should plan their borrowing prospectively whenever possible, including when designing early-phase studies, and always ask if the external data were intended to be used in clinical research.

“If you have an overall development strategy that includes borrowing, it’s going to encourage collecting data in a way that fosters more homogeneity — and it can also help avoid some blind alleys where you might run a risk of fooling yourself,” Scott said.
Trial Designs (continued from page 1)

about what they will and will not consider when evaluating a product for approval.

“The number of comments I hear about what the FDA definitely will not accept — that have never been stated by anybody who has actually been employed or formerly employed by the FDA — is just phenom- enal,” said Roger Lewis, a professor at the UCLA David Geffen School of Medicine, during an FDA meeting to gather stakeholder input on the pilot.

Those rumors may proliferate because of the agency’s legal restrictions from discussing confidential product and protocol information while under review, they said.

“The FDA is tied with what they can talk about,” said Lisa LaVange, associate chair of the Department of Biostatistics at UNC Chapel Hill and formerly director of CDER’s Office of Biostatistics from 2011 to 2017. “Until the drug is approved, you’re not going to know that the FDA accepted that design,” a process that can take years, she said.

As an example, during the negotiations for PDUFA VI, there were concerns that the FDA would not accept adaptive trial designs that require computer simulations, over concerns of type I error rates, said LaVange.

“It’s very easy to ding that design… So how do sponsors get in the door?” she said, adding that real-world evidence, Bayesian trials and other methods are also real possibilities, both in and outside of the pilot.

Sponsors have questioned the public disclosure of possibly competitive study information through the pilot program, said John Zhong, senior director of biostatistics at Biogen. While most companies are open to disclosing statistical elements of the study design, aspects such as the names of the product and company should be redacted, he said.

“A lot of companies are not even comfortable with disclosing the disease they are targeting,” Zhong said. “That kind of information is not necessary… You can also say it is a continuous endpoint, an ordinal endpoint, or a common endpoint. You can disclose information like that.”

“We hope to disclose as much as possible, but it has to comply with the sensitiv- ity and confidentiality of the companies,” he said.

However, Lewis described how the nature of those details is fundamental to the design of adaptive studies.

“This is an area of clinical trial design where the clinical details are supposed to inform the design, because the design is sup- posed to be customized to those details,” he said. “When you anonymize them, you break the link between the very information that is intended to design and the design itself.”

“A lot of people are looking for very specific examples of something that was a successful design effort,” Lewis said.

LaVange said disclosures would be decided upon on a case-by-case basis, and said the pilot’s procedures would be more fully explained in the future Federal Register announcement.

“It may be that nothing about the drug, or the sponsor, or even the disease needs to be disclosed,” she said. “It may be just the elements of an adaptation or something else. On the other hand, if there is use of a patient registry, then you’ll have to disclose something about the disease.”

“Put yourself in the FDA’s shoes, and think about what would be most beneficial to the world of drug development for us to disclose,” LaVange said.

“Maybe it’s the fact that we are seriously considering a design with this particular adaptation, at these particular times, based on this information, these decision-making criteria, and this level of evidence.”

LaVange said she hopes the pilot project will spur more discussion about certain trial designs, including at industry meetings and through white papers.

“I have sat in meetings where sponsors have put up on the screen all these different types of adaptive designs — some of which are not complicated at all — and said, ‘This is what the FDA doesn’t like, because they called them less-well understood in their 2010 guid- ance.’ And I wanted to say, ‘No! No, we didn’t mean that!’” LaVange said. “I think we’re just trying to move the needle in this way.”

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Genentech Releases Results for Phase III Lung Cancer Study

Genentech announced that the Phase III IMpower131 study met its co-primary endpoint of progression-free survival (PFS) and demonstrated that the combination of TECENTRIQ plus chemotherapy (carboplatin and ABRAXANE) reduced the risk of disease worsening or death (progression-free survival; PFS) compared with chemotherapy alone in the initial treatment of people with advanced squamous non-small cell lung cancer (NSCLC). The study enrolled 1,021 people who were randomized equally (1:1:1) IMpower131 is a Phase III, open-label, multicenter, randomized study evaluating the efficacy and safety of TECENTRIQ in combination with carboplatin and nab-paclitaxel or TECENTRIQ in combination with carboplatin and paclitaxel versus chemotherapy alone in people with stage IV squamous NSCLC. During the treatment-induction phase, people in Arm A received four or six cycles of TECENTRIQ plus carboplatin and paclitaxel, given on day one of each 21-day cycle. During the treatment-induction phase, people in Arm B received four or six cycles of TECENTRIQ, carboplatin and nab-paclitaxel. During the treatment-induction phase, people in Arm C received four or six cycles of carboplatin and nab-paclitaxel. IMpower131 met its PFS co-primary endpoint per study protocol.

Cidara’s Lead Antifungal Med Flunks Trial

Cidara Therapeutics reported that the randomized, controlled Phase II RADIANT clinical trial in acute vulvovaginal candidiasis (VVC) did not show sufficient efficacy to justify further development of the tested topical formulations. RADIANT was designed to evaluate gel and ointment topical formulations of the novel echinocandin antifungal CD101 in women with moderate-to-severe acute VVC. RADIANT was a multicenter, randomized, open-label, active-controlled, dose-ranging trial that enrolled 125 patients into three treatment cohorts. In the first cohort, 50 patients were treated with CD101 Gel; a second cohort of 50 patients was treated with CD101 Ointment. The third cohort comprised 25 patients treated with oral fluconazole. The trial included women with and without a history of recurrent VVC (RVVC). The study found that the gel and ointment topical formulations of CD101 evaluated in RADIANT were similar in efficacy to each other but lower in clinical and mycological cure rates compared to oral fluconazole.

Alexion Announces Positive Paroxysmal Nocturnal Hemoglobinuria Trial

Alexion Pharmaceuticals announced that the pivotal Phase III study of ALXN1210, the Company’s investigational long-acting C5 complement inhibitor, demonstrated non-inferiority to Soliris in complement inhibitor treatment-naïve patients with paroxysmal nocturnal hemoglobinuria (PNH). This Phase III, randomized, open-label, active-controlled, multinational, and multicenter study evaluated the efficacy and safety of ALXN1210 compared to Soliris administered by intravenous (IV) infusion to adult patients (≥ 18 years of age) with PNH. The study enrolled 246 adult patients with a confirmed diagnosis of PNH. The study demonstrated non-inferiority on all four key secondary endpoints: percentage change from baseline in LDH levels, change from baseline in quality of life, proportion of patients with breakthrough hemolysis and proportion of patients with stabilized hemoglobin levels. In addition, numeric results for all six endpoints favored ALXN1210. Although ALXN1210 did not achieve superiority, a numeric trend in favor of ALXN1210 was observed for breakthrough hemolysis (4.0 percent [0.6 percent, 7.4 percent] vs. 10.7 percent [5.2 percent, 16.3 percent] for Soliris) with a p-value of 0.074. The study also confirmed that ALXN1210 provides immediate and complete (>99 percent) inhibition of the complement C5 protein that is sustained over the entire 8 week dosing interval.

Array BioPharma Announces Data on Melanoma Trial

Array BioPharma announced results of its multicenter, open-label, randomized Phase III COLUMBUS trial for the treatment of patients with BRAF-mutant advanced, unresectable or metastatic melanoma. In the analysis of the primary endpoint, the median progression-free survival (mPFS) for patients treated with the combination of encorafenib, 450 mg daily, plus binimetinib, 45 mg twice daily (COMBO450) was 14.9 months versus 7.3 months for patients treated with vemurafenib, 960 mg twice daily [hazard ratio (HR) 0.54, 95 percent CI 0.41-0.71; p<0.0001]. The combination of encorafenib and binimetinib was generally well-tolerated. The median duration of treatment was 51.2 weeks (27.1-79.7) for encorafenib and 50.6 weeks (26.1-79.7) for binimetinib. The median dose intensity was 100 percent (93-100) of planned doses of encorafenib and 99.6 percent (80-100) of planned doses of binimetinib.

AOBiome Therapeutics Reports Results for Therapy for Seasonal Allergic Rhinitis Trial

AOBiome Therapeutics announced clinical findings from Part 1 of a Phase Ib/IIa clinical trial of the company’s first-in-class Ammonia Oxidizing Bacteria (AOB) product candidate for intranasal delivery. AOBiome’s candidate is a single strain of beneficial AOB, Nitrosomonas eutropha, that converts naturally occurring ammonia to nitric oxide, a signaling molecule well known to regulate inflammation and vasodilation. In Part 1 of the double-blind, multi-dose, vehicle-controlled Phase Ib/IIa trial, AOBiome’s candidate demonstrated promising safety and tolerability when delivered intranasally to healthy volunteers (N=24, randomized 1:1:1 high dose AOB, low dose, and vehicle) over a period of two weeks. Based on these promising results, AOBiome announced that it has initiated Part 2 of its Phase Ib/IIa trial to assess preliminary efficacy in subjects with seasonal allergic rhinitis (SAR).
AstraZeneca Presents New Data on FARXIGA for Type 2 Diabetes
AstraZeneca announced the results of DERIVE, a Phase III study that evaluated the efficacy and safety of FARXIGA® (dapagliflozin 10 mg), in patients with type 2 diabetes (T2D) with moderate renal impairment (chronic kidney disease [CKD] stage 3A with eGFR of 45-59 mL/min/1.73m2). The DERIVE trial randomized 321 patients with T2D (hemoglobin A1C [HbA1C] between 7-11 percent; mean 8.2 percent) and stage 3A CKD (mean estimated glomerular filtration rate [eGFR] 53 mL/min/1.73m2) from eight countries and treated them with either dapagliflozin 10 mg or placebo over 24 weeks. Dapagliflozin 10 mg significantly decreased mean HbA1C (-0.37 percent) vs placebo (-0.03 percent) from baseline to week 24 (difference -0.34 percent, p < 0.001). The study met its primary and secondary efficacy endpoints.

Heron Announces Positive Results From Pivotal Phase III Clinical Trials
Heron Therapeutics announced positive topline results from its completed Phase III studies of the investigational agent HTX-011 in subjects undergoing bunionectomy (Study 301/EPOCH1) and hernia repair (Study 302/EPOCH2). EPOCH1 was a randomized, placebo- and active-controlled, double-blind, Phase III clinical study evaluating the efficacy and safety of locally administered HTX-011 at 60 mg compared to the standard dose of bupivacaine solution (50 mg) and placebo for post-operative pain control following bunionectomy surgery in 412 subjects. HTX-011 achieved all primary and key secondary endpoints in both Phase III trials, demonstrating statistically significant reductions in both pain intensity and the use of opioid rescue medications through 72 hours following surgery. The primary endpoint was pain intensity as measured by the Area Under the Curve (AUC) score from 0 to 72 hours post-surgery (AUC 0-72) compared to placebo. HTX-011 was well tolerated in both studies, with a safety profile comparable to placebo and bupivacaine solution. There were no drug-related serious adverse events or discontinuations due to drug-related adverse events in HTX-011-treated patients, and there were fewer opioid-related adverse events in HTX-011-treated patients.

Antibe Therapeutics Announces Successful Phase IIB Gastrointestinal Safety Study
Antibe Therapeutics announced that its lead drug, ATB-346, met its primary endpoint in the Phase IIB gastrointestinal (“GI”) safety study. The double-blind study was conducted in 244 healthy volunteers and was designed to demonstrate the superiority of ATB-346 in GI safety compared to naproxen, the most prescribed nonsteroidal anti-inflammatory drug (“NSAID”) in the USA. Subjects on ATB-346 exhibited an ulceration rate of 2.5 percent versus an ulceration rate of 42.1 percent for subjects on naproxen at the end of the 2-week treatment period, with a very high degree of statistical significance (p<0.001). Subjects received either 250 mg of ATB-346 once-daily, a dose previously shown to be very effective in reducing osteoarthritis-associated pain, or 500 mg of naproxen twice-daily. The primary endpoint for the study was the incidence of gastric or duodenal ulcers of at least 3 mm diameter with unequivocal depth, considered the gold standard in assessing the GI safety of NSAIDs.

Arena Pharmaceuticals Reports Positive Results for Ulcerative Colitis Study
Arena Pharmaceuticals announced positive topline Phase II results from the OASIS trial for etrasimod, an investigational, once-daily, orally administered, selective sphingosine 1-phosphate (S1P) receptor modulator in development for the treatment of ulcerative colitis (UC). Patients receiving the 2 mg dose of etrasimod achieved statistically significant improvements versus placebo in the primary, all secondary, and clinical remission endpoints. OASIS was a randomized, double-blind, placebo-controlled, parallel-group, dosage-ranging study to assess safety and efficacy of two orally administered doses (1 mg and 2 mg) of etrasimod in patients with ulcerative colitis (UC) across 71 sites in 16 countries. Relative to placebo, there was a statistically significant (p = 0.009) 0.99 point improvement in a 3-component (stool frequency, rectal bleeding and findings on endoscopy) Mayo Clinic Score (ranging from 0 to 9) with etrasimod 2 mg at week 12. In the 1 mg group, there was a 0.43 point improvement in 3-component Mayo Clinic Score at week 12 relative to placebo, which was not statistically significant (p = 0.146). More patients in the etrasimod 2 mg group achieved endoscopic improvement compared with placebo (41.8 percent vs. 17.8 percent, p = 0.003).
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Accelovance operates three core divisions: a global CRO, patient recruitment and a clinical call center that assists in recruitment, retention, long-term follow-up and post-marketing surveillance.

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Concentrics has conducted over 1,100 clinical studies. Core staff includes four nurses, two study coordinators, two research assistants, 10 physicians and four dental hygienists.

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<th><strong>PRA Health Sciences</strong>&lt;sup&gt;️&lt;/sup&gt;</th>
<th><strong>Splash Clinical</strong>&lt;sup&gt;️&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raleigh, NC</td>
<td>Wauwatosa, WI</td>
</tr>
<tr>
<td>(919) 786-8200</td>
<td>(414) 443-3280</td>
</tr>
<tr>
<td><a href="mailto:prahhealthsciences@prahs.com">prahhealthsciences@prahs.com</a></td>
<td><a href="mailto:matt@splashclinical.com">matt@splashclinical.com</a></td>
</tr>
</tbody>
</table>

With 13,000+ employees covering 80+ countries, PRA provides a global presence combined with an in-depth knowledge of local regulations, standards of care and cultural customs.

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<tr>
<th><strong>PSI Pharma Support America Inc.</strong>&lt;sup&gt;️&lt;/sup&gt;</th>
<th><strong>Techorizon</strong>&lt;sup&gt;️&lt;/sup&gt;</th>
</tr>
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<tr>
<td>King of Prussia, PA</td>
<td>Verona, Italy</td>
</tr>
<tr>
<td>(919) 249-2660</td>
<td>+39 045 8222888</td>
</tr>
<tr>
<td><a href="mailto:natania.barron@psi-cro.com">natania.barron@psi-cro.com</a></td>
<td><a href="mailto:silvio.severini@techorizon.com">silvio.severini@techorizon.com</a></td>
</tr>
</tbody>
</table>

PSI is home to 1,400 employees around the world, of which 250 hold medical degrees, with capabilities across all phases of clinical development from Phase I –IV.