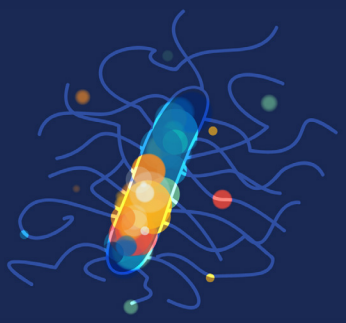
Case Study:

PIVOTAL PATHOGEN SPECIFIC HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA (HABP) / VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA (VABP) TRIAL



A pivotal Phase III registration trial, the first pathogen-targeted therapy being studied for the treatment of adults with hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* (ABC) complex.

200 PATIENTS

~100 SITES

17 COUNTRIES

TOP PERFORMING REGION:

(avg. pat per site per month)

EUROPE

TOP PERFORMING COUNTRIES:

(average pat per site per month)

ISRAEL AND HUNGARY

TRIAL REGIONS:

EUROPE | NORTH AMERICA | ASIA PACIFIC | LATIN AMERICA

CHALLENGES

Patient Recruitment

- Challenges for patient recruitment primarily related to the different entry points within the sites for identifying potential study subjects.
  - Patients could present at different Intensive Care Units (ICUs) within a hospital or even at other departments, could be identified based on alerts by the local microbiology lab (respiratory samples positive for ABC), or by the pharmacy (prescription of antibiotics). Sites had to react very quickly to confirm the pathogen and to ensure that study subjects did not receive more than 48 hours of effective empiric treatment before randomization.
- The study was actively recruiting during the height of the global COVID-19 pandemic and was not the highest priority of the sites during that time.

Study Blinding

- The different frequency and duration of IV dosing administration of Investigational Product (IP) and comparator did not allow for a double-blind study design. Therefore, the study was open label at the site level, except for the site's blinded assessor. This design was requested by regulatory authorities before study start that the study data be collected and handled as if it were a blinded study.
  - The blinded assessor, the Sponsor, and the Sponsor's designees involved in medical and safety monitoring, data management, operations, and other aspects of the study (e.g., interpretation of the results) should remain blinded to treatment assignment.
  - Given the complexity of the regimens, the Principal Investigator, other care givers at site, the Clinical Research Associate (CRA), and other site personnel (study coordinators and pharmacy staff) were all unblinded.
  - Patients should not be informed of their treatment assignment, and patients had to be kept naive of their treatment throughout the course of the study.

Creatine Clearance Calculations

- Potential renal toxicity of IP, comparator and combination therapy required daily assessment of creatine clearance to adjust the dose based on renal function. Uniform CrCl calculation had to be ensured across all sites.

Supply Logistics

- Provision of ancillary supplies (saline bags, infusion lines, etc.) and equipment (rapid test device and kits, infusion pumps) during times of global shortages across several countries with differing medical standards and requirements.

Quality of Microbiology Analysis

- A consistent high standard and timely respiratory sample processing and analysis had to be established across all sites and local microbiology laboratories to produce evaluable microbiological data for outcomes.
- The study protocol required sample processing which was not necessarily routine or an established method at each local microbiology lab. For example, local labs had to have the capability to perform colistin susceptibility testing using a broth based method.
- Close monitoring of local microbiology and central microbiology data was required to ensure that a sufficient number of patients were enrolled that met criteria for the mMITT population (120 patients, mMITT= Microbiologically Modified Intent-to-Treat).

THE SOLUTIONS

Patient Recruitment

- Implemented patient identification pathway worksheet for the study and obtained the information during SIV and routine review to ensure process and site contact information is updated. CRA and Study Coordinator quickly followed-up with the appropriate site personnel to ensure the patient is enrolled in the study within the short timeline.
- Had calls between Medical Monitors and site personnel covering all time zones and geographical areas to discuss patient eligibility and profile within the randomization timelines.
- Weekly touch base with site staff by CRA via phone calls and emails during COVID-19 to ensure sites received the support they needed (e.g., establishing the possibility for remote monitoring, providing additional ancillary supplies). This allowed us to maintain continuity and the majority of sites were still able to recruit during the pandemic. Those who had to stop because they suffered from shortage of personnel or beds, quickly returned to actively recruit for the trial as soon as the situation improved.
- Tiered sites by recruitment potential and worked closely with Sponsor to implement action items (e.g., Sponsor-site calls, MM calls, etc.).
- Provided study specific materials (i.e., magnet, flyers) to help increase visibility.

Study Blinding

- Developed a Study Blinding Plan that defined how the unique blinding requirements would be met at the system level (CTMS, EDC, IRT etc.), at sites and with Medpace and Sponsor project teams. All internal and external stakeholders (internal: Clinical Trial Management, Monitoring, Data Management, Biostats, Safety, QA; external: Sponsor, central labs, PK lab) worked closely and creatively together to develop the process and procedures to ensure data integrity.
- Developed a very detailed site-specific blinding plan, which was discussed and agreed before site activation with the sites to ensure that site personnel understood their role and allowed/disallowed communication pathways.
- Constant training of Medpace personnel, particularly CRAs, during monthly monitoring plan meetings to ensure blinded and unblinded communication pathways were followed.
- Training of the site personnel at Investigator Meetings, Site Initiation visits, Remote Monitoring Visits, and centrally via newsletter and email blasts.
- Defined in advance what would happen in case of an accidental unblinding. Actions taken depended on the extent of the unblinding and who was unblinded, thus enabling the team to quickly react and minimize impact of unblinding.
- The addition of an unblinded Medpace Medical Monitor allowed the study team and site personnel to discuss protocol-related, subject specific medical questions that involve treatment information, always ensuring patient safety and data integrity.

Creatine Clearance Calculations

- Constant reminders to measure serum creatinine daily at the local laboratory were provided by CRA during their routine site contacts and in email blasts and study newsletter.
- Sites were provided a validated calculator for calculation of the Ideal bodyweight and the CrCl using the Cockroft Gault formula. The validated calculator allowed the investigator to calculate the CrCl in one step, without the need to decide which body weight was to be used for the calculation (ideal body weight, adjusted body weight, or actual body weight). This ensured the correct calculation of the renal function, making the possibility of overdosing very unlikely.

- Actual Study drug doses were calculated in one step by IRT using validated calculators and pharmacist was informed about the dose.

Supply Logistics

- Worked very closely together with Medpace logistics team to set up a solid process for supply provision before site activation.
- Medpace contracted with vendors to organize procurement, storage, and distribution of ancillary supplies and equipment. Local purchase was always preferable, but if that was not feasible, thorough planning and monitoring ensured that import/export and local depot requirements were met and that sufficient supplies were available at the time of site activation and throughout study conduct.
- Medpace assessed equipment availability (e.g., refrigerated centrifuges) during the site selection period. Medpace has experience working with medical equipment vendors and could arrange for equipment rental on behalf of Sponsor.

Quality of Microbiology Analysis

- The Data Integrity Unit (DIU) team of microbiology experts was involved from the beginning of feasibility to ensure that only sites who had access to a local microbiology lab capable of performing the protocol required cultures and tests were selected. DIU team was available as a partner for the CTMs, CRAs, and for the site microbiology lab team to train and support them during the trial.
- Performed ongoing, real-time review of microbiology data to monitor study populations and identify trends and issues in data quality.
- DIU was a liaison between sites, Sponsor, and central microbiology laboratory.

RESULTS

Primary and secondary endpoints were met, and drug received FDA approval.

Close cooperation with DIU and central microbiology ensured that 120 evaluable patients in the mMITT population was met without over-recruiting.

There were no major findings at site inspections.

The unique blinding process, which was accepted by the FDA, can serve as a template and example for trials with a similar blinding set-up or requirement.

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