

Megatrial program for acute coronary syndromes; orphan indication with a direct thrombin inhibitor

From large to small: ACCOVION staff contributed to a megatrial program (phase 2 dose ranging with 900 subjects; phase 3 with 10,000 subjects) for a leading international manufacturer of plasma proteins, who tested a recombinant protein (anticoagulant) in acute coronary syndromes. In addition, ACCOVION staff supported the successful product registration (USA and EU) in an orphan (niche) indication.



Proven Experience

The sponsor intended to develop this anticoagulant as an improvement to standard therapy with heparin. Based on a series of smaller trials, the program was focused on a high-volume indication (unstable angina pectoris [UAP]) and an orphan indication (heparin induced thrombocytopenia type II [HIT] – a rare but life-threatening side effect of repeated heparin treatment).

The UAP program consisted of a dose ranging (phase 2) study with 900 subjects and a large randomized, double blind, confirmatory (phase 3) trial with more than 10,000 subjects recruited worldwide. The primary efficacy endpoint was the incidence of cardiovascular death and new occurring myocardial infarctions.

The HIT orphan indication was supported by two smaller studies (with 82 subjects). The primary efficacy endpoint was the incidence of new thromboembolic complications, limb amputations or death. Due to ethical considerations, no placebo treatment could be envisaged; regulatory authorities accepted the comparison to a historical registry of 91 cases receiving a variety of unlabelled treatments.



Reliability & Safety

Working as a cross-functional team, ACCOVION and the sponsor developed the study protocols and the case report forms.

In the UAP program, a very large network of investigators was selected, altogether covering 360 centers in 16 countries worldwide. The trial execution was assigned to a steering committee (under the leadership of the principal investigator), while safety and interim reports were overseen by an independent data and safety monitoring board (DSMB). ACCOVION staff were invited to support and contribute to the tasks of these committees.

Sponsor

A world leader in the development and marketing of plasma proteins.

Scope

- Selection of investigator networks
- 10,414 subjects (Phase 3 UAP)
- 360 active centers in 16 countries (UAP)
- 82 subjects (HIT)
- Historical registry (HIT)
- Site initiation after case diagnosis (HIT)

Operational Services

- Study protocol
- Study management
- Data management
- Case report form
- Site monitoring
- Pharmacovigilance
- Statistical analysis
- Study reports
- Medical writing
- Contributions to Steering Committee and DSMB Meetings (UAP)
- Liason with Regulatory Authorities

In the HIT program, the study administrative structures were less complex, but recruitment proved to be very challenging: investigational sites could only be contacted after a HIT case became known via a central laboratory diagnostic site (headed by the principal investigator).

Pharmacovigilance activities were an important part of both programs. After finalization of the study reports, the sponsor asked ACCOVION staff to support the HIT registration. This included the clinical parts of the dossier and the participation in a Committee for Proprietary Medicinal Products (CPMP) hearing.



Service Excellence

The development of this anticoagulant recombinant protein constituted a particular challenge in many respects. Knowledge of the regulatory environment regarding recombinant proteins was essential for the statistical support of the design, conduct and reporting of the studies. This was also necessary for the special attention that needed to be paid to the potential induction of antibodies by the study drug itself. In the HIT indication, the proper identification and documentation of historical cases was a key element to the success of the project.

All study management, coordination of data management, final analyses, final study reporting, presentations at the steering committee and DSMB meetings, and the successful registration for the orphan indication were performed to the complete satisfaction of the client.

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