

## ORGANIZATION AND MANAGEMENT OF RESEARCH AND DEVELOPMENT

The Company's research, development and pharmaceutical operations are managed in a matrix-based organization and in accordance with the procedures defined in its quality system, which was granted ISO 9001:2000 certification in 2005, renewed yearly since then (see Section 4.3.1 of this Reference Document).

The Company's research and development activities are organized in programs corresponding to a drug candidate or family of drug candidates targeting a given cell receptor and to development for an indication or a group of related clinical indications. Each program is overseen by a program manager and makes use of skills from various research and development groups defined by branch (e.g., cell immunology, chemistry, protein chemistry). The resources from the different research and development groups involved in a program are defined on a case-by-case basis and are subject to regular evaluations and reallocation, generally on a quarterly basis. Successive phases are distinguished in carrying out a program, defined in reference to milestones M0 to M3. The milestone following milestone M3 is the first marketing authorization.



- M0: initial definition of a program;
- M1: selection of a drug candidate and of an indication;
- M2: first administration to humans;
- M3: first clinical efficacy data in humans (proof-of-concept).

These milestones correspond to a set of prerequisites determined on the basis of standard industry practices, notably for the early milestones (M0 and M1), and on regulatory validation steps for the subsequent milestones (M2 and M3). Declaring that a development milestone has been reached and the resulting decision to change phases are decisions made by the Company's Executive Committee, which carries out periodic reviews of the programs and allocates resources accordingly. The different program phases result from different economic and management rationales.

Before M0: this is the "exploratory research" phase when there is no defined program but a set of possible projects identified internally or outside, through collaborative work or scouting. The objectives are to build a scientific rationale for pharmacological intervention on a molecular or cell target in a group of indications and to create or consolidate intellectual property elements. Projects in the exploratory research phase may lead to the implementation of a research and development program when the prerequisites of milestone M0 are met (validation of the contemplated molecular or cellular target and intellectual property).

Between M0 and M1: the program is in the "feasibility/validation" research phase. This phase aims at characterizing a drug candidate and demonstrating its efficacy through pre-clinical studies in cellular or animal models. From an economic and organizational point of view, the passage to milestone M1 is an essential step and a veritable change of scale for the program, insofar as the beginning of pharmaceutical development represents a very significant share of the early research and development costs.

Between M1 and M2: the program is in the "pre-clinical development" phase. In the pre-clinical phase, the drug candidate is defined and studies are carried out according to a regulatory reference system. For pharmaceutical development aspects, this notably consists in implementing a production method, producing pilot industrial batches, defining temporary product specifications and setting up analytical controls. Concurrently, non-clinical studies are carried out in pharmacology, toxicology and pharmacokinetics as required for the file presented to the regulatory agencies for the start of clinical trials. This phase of the program largely involves subcontractors. It should be pointed out that pre-clinical studies and pharmaceutical development studies continue throughout the program, notably depending on regulatory requirements and any changes of scale in industrial production of the drug candidate. However, the production process must be precisely defined at the start of the Phase IIb/III pivotal studies.

Between M2 and M3: the program is in the "clinical development for proof-of-concept" phase. The first administration to humans, which is milestone M2, is subject to authorization by the competent regulatory authorities. Milestone M3 corresponds to the end of one or more Phase IIa studies. A summary of results is generally submitted to the regulatory authorities at the end of the Phase IIa.

After reaching milestone M3, a decision is made whether to continue development with large scale studies aimed at obtaining marketing authorization (Phase IIb and Phase III). The Company will weigh the important decision to continue these studies with its own resources or through a partnership, sharing costs by sharing the commercial rights if the program is successful.