Deferasirox (ICL670): from bench to bedside

[haematologica reports]
2005;1(8):7-10

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This document accompanies the presentation by Dr Daniele Alberti, Clinical Program Leader, Novartis Pharma.

The presentation provides an overview of the drug development process and refers, by way of illustration, to a case history of a Novartis compound currently completing clinical development.

Identification of medical need

Medical need is a key inspiration and driver in the search for new medicines.

It may be established by:

- The emergence or discovery of a new disease eg AIDS, SARS;
- Absence of an effective treatment for an established disease eg cancer;
- A suboptimal, existing treatment for an established diseases eg iron overload.

Understanding the pathophysiology of disease

Basic and clinical research over many years builds understanding of the pathophysiology (molecular and cellular bases) of disease. This facilitates creation of therapeutic concepts which may lead to the identification of appropriate potential molecular targets and drugs to prevent, treat or cure medical conditions. This process is known as rational drug design. It is also worth noting that many important drug discoveries were the result of serendipitous research or a chance observation on the part of scientists.

New compound synthesis and screening

For any therapeutic target, hundreds or thousands of new chemical entities (NCEs) will be synthesized for testing. Test compounds are subjected to a series of assays in which they are added to enzymes, cell cultures or cellular substrates to ascertain whether they have an effect, or how they might be modified to achieve an effect.

In recent decades there has been significant automization of the screening process. For example, computer simulation of potential chemical structures and corresponding molecular, cellular or receptor targets is now routine. Drug discovery scientists utilize tools and systems such as bioinformatics databases, genomic sequencing, proteomic mapping together with combinatorial chemistry and high throughput screening to help analyze large numbers of potential drug candidates.

On identification of a potential candidate, sponsors will apply for patent protection. In general, patent exclusivity lasts for 20 years.

Preclinical studies

Before a drug can be tested in humans, sponsors are required to demonstrate that it is reasonably safe. For compounds that have not been studied or marketed previously, the data required for this process are produced by non-clinical in vitro and in vivo studies.

Preclinical studies are designed to develop and test for the following:

- pharmacologic profile of the compound and its ADME (absorption, distribution, metabolism and excretion);
- toxicity. This includes:
  - acute toxicity demonstrated in at least 2 species of animals
  - short-term toxicity shown in 2 week to 3 month studies (depending on predicted duration of product use in the clinical setting)
- teratologic effects, in longer term studies which may continue after commencement of clinical studies;
- oncologic effects, also in longer term studies.

Preclinical-clinical transition

In order to start clinical testing, sponsors must apply for permission from the regulatory authorities. This process is known as an Investigational New Drug (IND) submission.

In assessing the merits of an IND submission, the regulatory authorities review the data from preclinical studies.

Clinical development

In most cases, new drugs will undergo three stages of clinical development.

Phase I

These are the first studies of the drug in humans. The compound will be administered under controlled circumstances to small groups (usually 20-80) healthy volunteers or to patients (eg in oncology and AIDS indications).

Phase I studies are designed to determine the following:

- the pharmacologic activity and pharmacokinetics of the drug in humans;
- safety profile and side effects (also in association with dosing levels and regimens);
- early indications of efficacy.

Phase II

If the compound is considered to have a satisfactory safety profile in Phase I, it will be progressed to Phase II where it is tested in a relatively small number (several hundred) of patient volunteers. Phase II studies are sometimes called Proof of Principle (POP) trials because they are designed to provide evidence of the desired therapeutic effect.

Specifically Phase II studies seek to evaluate the following:

- efficacy in a particular indication or indications;
- optimum dose schedule;
- the pharmacologic activity and pharmacokinetics of the drug in humans;
- safety in terms of short-term side effects and risks associated with the drug.

The studies will usually focus on stable patients with moderate disease. If Phase II studies demonstrate that the compound is stable and well tolerated, is effective, has a satisfactory side-effect profile, and is worthy of further development, it will progress to Phase III.

Phase III

These are expanded controlled and uncontrolled studies, undertaken in large numbers (1,000-5,000) of patients to evaluate further the safety and efficacy of developmental compounds in comparison with placebo and appropriate active compounds. The design of Phase III studies may be similar those conducted in Phase II. However the patient populations will be more diverse in terms of age, range of disease and concomitant illnesses. Information from these trials will be used at a later stage in labelling.

The New Drug Application

On successful completion of Phase III trials, the sponsor will submit a New Drug Application (NDA) to the regulatory authorities. The NDA dossier will contain reports from all Phase I to III clinical trials, plus data from preclinical in vitro and in vivo studies.

If, on review of the supporting data, the regulatory authorities are satisfied that the drug is safe and effective, the sponsor will be granted a licence to market the drug for specific indications set out in the Product Licence.

Figure 1 shows the drug development and regulatory approval processes.

The US regulatory authority, the FDA, has established a number of alternative review and approval processes to accommodate the needs of particular patient groups.

1. The Accelerated Development Review process

This is reserved for fast-track approval of drugs which are expected to confer significant benefit over established treatments for serious diseases or life-threatening illnesses, or where there is no existing therapy. After approval sponsors are required to continue testing to demonstrate that the drug is effective. If not, the regulatory authorities may withdraw the product from the market.

2. The Treatment IND

This is designed to make investigational drugs available to desperately-ill patients as early as possible in the drug development process. Examples of diseases for which Treatment INDs may be granted include: advanced cases of AIDS, herpes simplex encephalitis, subarachnoid hemorrhage.

3. The Parallel Track policy

This was developed in response to AIDS. Under this scheme, patients whose condition would not permit inclusion in controlled clinical trials may receive investigational drugs.

Phase IV

After a drug is launched, the sponsor is required to continue collecting safety data for review by the regulatory authorities. If a compound proves subsequently to be less safe than originally thought, the regulatory authorities may restrict its use or revoke its licence agreement.

Phase IV studies are important because it is only at this stage that the drug will be taken by much larger, diverse groups of patients. The safety and efficacy profiles generated in the more tightly-controlled pre-marketing development phases may therefore change. For example, low incidence side effects not previously detected during clinical development may only be observed at this stage.

Sponsors will often establish Post-Marketing Surveillance Studies (PMS) to further evaluate the safety and performance of their drugs. Data are used to bolster those collected in Phase I-III clinical trials and to

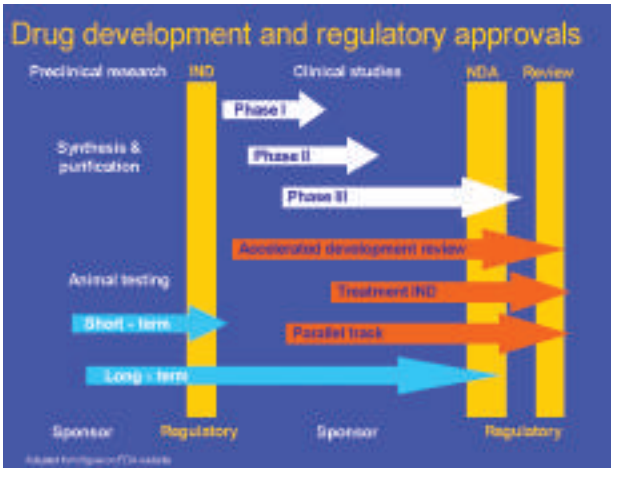

Figure 1. Drug development and regulatory approvals.

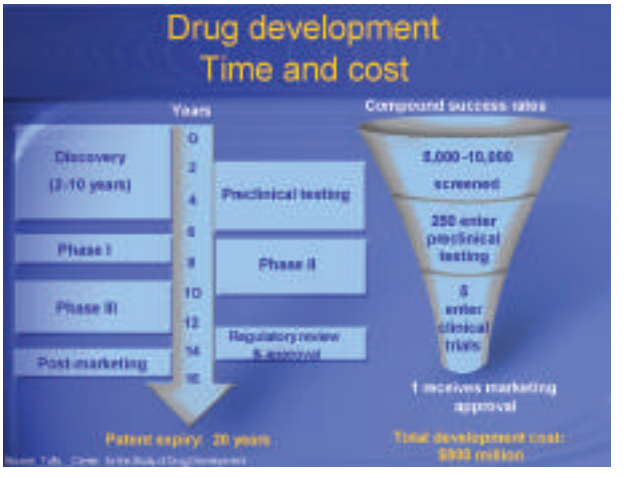

Figure 2. Drug development: time and cost.

refine and expand information about the drug for prescribers. These data may also be used to determine whether the drug may be effective in indications other than those contained in the Product Licence. If this is the case, the sponsors may plan further clinical trials to support an application to the regulatory authorities to extend the range of licensed indications for the drug.

Success and failure in drug development

On average, of 5,000-10,000 candidate compounds screened, only 250 will enter preclinical testing. Thereafter, only five will go forward into Phase II evaluation. One of these (20%) is likely to be approved for patient use.

The cost of drug development

Typically, it takes 12-15 years to discover and develop a new medicine.

Compounds are protected by patent for 20 years. Sponsors can therefore expect 5-8 years of market exclusivity for a new compound. After patent expiry, regulatory authorities may permit the introduction of generics.

The fully-capitalized cost of bringing a drug to market is estimated to be in the region of US$ 800 million. If post-marketing studies are included, the cost increases to US$ 900 million.

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), pharmaceutical companies typically reinvest 1 in 5 US dollars of revenue in R&D. The same organization estimates that only 3 of 10 marketed drugs produce revenues that match or exceed average R&D costs.

Deferasirox (ICL670, Exjade®): a drug development case history

Deferasirox is a once-daily oral iron chelator completing Phase III clinical development for the treatment of chronic iron overload.

The disease

Iron overload is a serious problem which arises from:

- management of transfusion-dependent anemias: thalassemia intermedia and major, sickle cell disease, myelodysplastic syndrome and aplastic anemia;
- diseases of abnormal iron absorption (e.g. hereditary hemochromatosis).

Clinical data for thalassemia major indicate that excess iron, if untreated, is associated with significant morbidity and early mortality.

Current standard-of-care

Desferal (deferoxamine) is a well-established, effective, first-line, life-saving treatment for iron overload.

However, due to poor oral activity, it must be administered by subcutaneous or intravenous slow infusion 5-7 nights per week. In addition to the inconvenience, treatment with Desferal is associated with infusion-site reactions and pain. Patient compliance, therefore, is frequently poor resulting in unnecessary morbidity and early mortality.

The unmet need

A significant unmet need was identified for a safe and effective oral iron chelator to improve management of excess iron. The aim was two-fold:

1. to prevent the morbidity and mortality associated with iron overload and improve patients' QoL;

2. to create opportunities for more effective therapeutic intervention for the underlying diseases. For example, the hemalogic status of patients with myelodysplastic syndrome could be improved with transfusion therapy if clinicians had a more effective treatment for the increased iron burden associated with the therapy.

The discovery process

Since the introduction of deferoxamine in the early 1960s there has been considerable research across many institutions to develop an orally active iron chelator.

Rational drug design, experience and intuition led to research with a new class of chelators, the bishydroxyphenyltriazoles. Novartis synthesized more than 40 derivatives of this series and these were assayed with more than 700 chelators from other chemical classes.

The result was the identification of deferasirox, a tridentate chelator which proved to be orally highly potent and well tolerated in animals.

The development program

After intensive preclinical research to evaluate the safety of the compound, deferasirox progressed into clinical development to establish its safety and efficacy in humans.

The deferasirox clinical programme has involved more than 1100 patients for one year or more; more than 800 patients received deferasirox.

Results from a Phase II trial, in which patients with beta-thalassemia and transfusional iron overload received 12 months of therapy with deferasirox, demonstrated the following rationale for progression to Phase III studies:

- no serious adverse events or clinically-relevant safety issues;
- pharmacokinetics to support once-daily dosing and dose-dependent fecal excretion;
- comparable efficacy (20 mg/kg/day) with deferoxamine (40 mg/kg/day) in decreasing liver iron content over the treatment period.

Phase III development

Phase III development of deferasirox has been completed successfully and according to planned schedule. Data from this phase of studies support use of the compound in transfusional iron overload to maintain and reduce iron burden.

In Phase III and throughout the clinical development programme, deferasirox has been well-tolerated in adults and children as young as 2 years of age.

The dossier was submitted to the regulatory authorities in April 2005.

Other clinical development objectives

Another key driver in the clinical program has been to evaluate methodologies for the assessment of iron overload.

Effective monitoring is important to ensure that chelation therapy can be adjusted to ensure *safe* tissue iron concentration, the primary therapeutic goal.

The reference standard for monitoring iron overload is liver biopsy. However, this is invasive and has risks. Serum ferritin analysis is a non-invasive, easy to perform, commonly-used indirect measure of iron burden, although results can fluctuate in the short term in response to inflammation and other factors. However, in different studies with deferasirox dose-dependent effects on serum ferritin were shown to be in line with those for LIC. These results demonstrate that repeated measurements of serum ferritin provide a reliable and useful tool for monitoring iron burden.

The deferasirox clinical development programme has yielded data on a number of techniques for the assessment of LIC, and has highlighted the importance of using a standardized methodology when preparing tissue. Research included evaluation of methodologies for preparation of liver biopsy samples and assessment of investigational non-invasive approaches such as Superconducting Quantum Interference Device (SQUID) and Magnetic Resonance Imaging (MRI).

Summary

The drug development process, from first identification of a potential candidate compound through to registration and launch, is lengthy, complex, highly-regulated and costly to pursue.

It is driven by leading-edge science and technology but also draws on scientific and technical expertise accumulated over many decades of basic and clinical research.