AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Dasatinib for CML: Bench to ODAC

Robert Justice, MD, MS
DDOP/OODP/CDER/FDA

Topics

- Relevant laws and regulations
- Regulatory milestones in drug development and approval
- ODAC questions and votes

Laws and Regulations

- Federal Food, Drug, and Cosmetic Act of 1938 required drugs be shown to be safe prior to marketing
- Public Health Service Act of 1944 provided for the regulation of biological products
- Kefauver-Harris Drug Amendments of 1962 required proof of efficacy prior to marketing
- Code of Federal Regulations, Title 21
  - IND regulations: Part 312
  - NDA regulations: Part 314

Regulatory Milestones

- Pre-IND Meetings
- Investigational New Drug Application (IND)
- End-of-Phase 2 Meetings
- Special Protocol Assessments
- Pre-NDA Meetings
- Treatment Protocol or IND
- New Drug Application (NDA)

Pre-IND Meetings

- Purpose is to ensure adequacy of an IND submission
- Discuss questions posed by the drug sponsor regarding
  - Chemistry, manufacturing and controls (CMC)
  - Non-clinical pharmacology and toxicology studies
  - Previous clinical data, if any
  - Proposed clinical study or studies

Investigational New Drug Application (IND)

- Required to conduct clinical studies with an investigational drug involving interstate commerce
- IND submission contains information on CMC, non-clinical pharmacology and toxicology studies, previous clinical data (if any), and clinical protocols
- FDA has 30 days to review initial submission
- Subsequent clinical studies may begin as soon as the protocols are submitted
- FDA reviews all new protocols, protocol amendments, adverse event reports, study reports and annual reports

End-of-Phase 1 & 2 Meetings

- Requested by IND sponsor to discuss questions concerning CMC, non-clinical and clinical pharmacology, toxicology, and proposed studies
- Purpose is to ensure that the drug development plan is adequate to support a new drug application
- Particular emphasis is placed on reaching agreement on the design of studies intended to support approval

Special Protocol Assessment

- Requested by IND sponsor, generally after an end-of-phase 2 meeting
- Goal is to reach formal agreement on protocol design
- FDA has 45 days to review proposed protocol, statistical analysis plan, case report forms, and questions posed by the sponsor. FDA may take longer if an outside consultant is required.
- If agreement is reached, the SPA is a commitment by FDA that depending on the results the study will support filing of a new drug application
- Significant protocol amendments must be agreed to in writing by FDA and IND sponsor

Pre-NDA Meetings

- Requested by IND sponsor to discuss
  - Adequacy of CMC, non-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics information
  - Adequacy of clinical study results to support approval
  - Format and content of the application
  - Treatment Protocol/IND

Treatment Protocol/IND

- Makes available promising new drugs before commercial marketing begins
- Must be for a serious or immediately life-threatening disease
- No comparable or satisfactory alternative treatment for that stage of the disease in the intended patient population
- Drug is under investigation in a controlled clinical trial or all clinical trials have been completed
- Sponsor must be actively pursuing marketing approval of the investigational drug with due diligence

New Drug Application

- Contains proposed labeling and detailed technical sections:
  - CMC and microbiology (if applicable)
  - Non-clinical pharmacology and toxicology
  - Human pharmacokinetics and bioavailability
  - Clinical data, including study protocols and all amendments, study reports, case report forms and CRF tabulations
  - Statistical evaluation of the clinical data

Proposed Indications

- Treatment of adults with chronic, accelerated, or blast phase CML with resistance or intolerance to prior therapy including imatinib
- Treatment of adults with Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior therapy

New Drug Application

- NDA is reviewed by a multidisciplinary team of physicians, statisticians, chemists, pharmacologist/toxicologists, clinical pharmacologists, and microbiologists
- Manufacturing sites are inspected by FDA field personnel
- Selected clinical sites are inspected by DSI
- Trade name is reviewed by DMETS & DDMAC

Accelerated Approval

- For serious or life-threatening diseases
- Drug appears to provide benefit over available therapy
- Approval based on a surrogate that is reasonably likely to predict clinical benefit
- Applicant must verify and describe benefit
- Post-marketing studies usually underway
- The applicant must carry out such studies with due diligence

ODAC

- Most applications are either discussed with an FDA consultant or at a meeting of the Oncologic Drugs Advisory Committee (ODAC)
- ODAC is composed of hematologists/oncologists, a statistician, a consumer representative, a patient representative, and a non-voting industry representative
- ODAC discusses and votes on questions posed by FDA regarding approvability of the application

ODAC Question 1

1. The Agency has accepted durable responses in hematologic malignancies for approval for both chronic leukemias (accelerated approval) and acute leukemias (regular approval). The FDA granted Gleevec accelerated approval for chronic, accelerated, and blast crisis phases of CML based on durable major cytogenetic responses and major hematologic responses.

ODAC Question 1

1. (continued) Based on the magnitude and duration of responses, has the sponsor provided sufficient evidence of dasatinib's effectiveness for the following:
   - Chronic phase CML?
   - Accelerated phase CML?
   - Myeloid blast CML?
   - Lymphoid blast CML?

Vote: Yes 14, No 0, Abstain 0

ODAC Question 2

For the imatinib-resistant population (except ALL)

- The major toxicities observed with dasatinib include the following: gastrointestinal and hematological toxicities, fluid retention, bleeding, and myelosuppression. Less frequent, but serious, adverse events include cardiac toxicity and intracranial bleeding. Table 3 provides the dose reductions and interruptions occurring with dosing at 70 mg BID.

ODAC Question 2

2. (continued) Based on the phase 2 data, does the risk/ benefit profile support dasatinib's approval for the following:
   - Chronic phase CML?
   - Accelerated phase CML?
   - Myeloid blast CML?
   - Lymphoid blast CML?

Vote: Yes 14, No 0, Abstain 0

ODAC Question 3

For the imatinib-intolerant population (except ALL)

3. Imatinib intolerance was defined as either 1) imatinib-related toxicity leading to imatinib discontinuation, or 2) inability to tolerate imatinib. The number of intolerant patients enrolled per study (except for the Chronic phase CML studies) was less than 10%. Based on the data presented, has the sponsor provided evidence of an effect on a surrogate endpoint (major cytogenetic response) for Chronic phase CML patients intolerant to Gleevec?

Vote: Yes 13, No 0, Abstain 1

ODAC Question 3

(continued) Based on the data presented, has the sponsor provided sufficient evidence to warrant accelerated approval in CML patients intolerant to imatinib in either

- Accelerated
- Myeloid blast
- Lymphoid blast phases?

Vote: Yes 14, No 0, Abstain 0

ODAC Question 4

4. As stated above, the FDA has approved drugs to treat acute leukemias based on durable complete responses. The sponsor has presented data (major hematological responses) for Philadelphia-positive acute lymphoblastic leukemia patients who have experienced disease progression on imatinib and other therapies. Based on the data presented in the above tables, has dasatinib demonstrated sufficient evidence to warrant regular approval in either the imatinib-resistant or intolerant Philadelphia-positive ALL populations?

Vote: Yes 12, No 1, Abstain 1

ODAC Question 5

5. Accelerated approval requires a commitment to perform a confirmatory clinical trial to demonstrate clinical benefit. Please discuss future study designs to accomplish this goal. These trials could be either front-line or relapsed disease settings.

Discussion:

- Continued long-term follow-up on submitted trials
- Complete ongoing trial of 100 mg qd vs. 50 mg b.i.d. vs. 140 mg qd vs. 70 mg b.i.d.
- Randomized trial of dasatinib vs. imatinib
- In combination in Ph+ ALL, including pediatrics

NDA Final Steps

- Agreement on package insert and other labeling
- Agreement on phase 4 commitments, if any
- FDA has 6 months to take action on a priority application and 10 months for a standard action.

Regulatory History

- IND submission: March 2003
- End-of-Phase 1 Meeting: December 2004
- Pre-NDA Meetings: July & October 2005
- NDA Submission: December 28, 2005
- Treatment Protocol: February 2006
- ODAC Meeting: June 2, 2006
- FDA Action Date: June 28, 2006