Research and Development Related to dasatinib (Sprycel™)

KEI Research Note 2008:3

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1. Introduction

The following is a report on research and development related to dasatinib, a product sold by Bristol-Myers Squibb under the trade name Sprycel.[3]

Dasatinib has been approved by the US FDA for two indications: (1) to treat adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy, and (2) to treat chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy, including imatinib.

1 Boston University School of Law. David Serafino also contributed to this research note.
2 Revised 1 August 2008.
3 This research note was prepared in response to a request from Korean NGOs who are concerned about the price of Sprycel in Korea. The research note was earlier shared with Brian Henry at BMS. BMS declined to provide any comment on the specifics of this report, or provide any information on the company R&D outlays on Sprycel, but did offer more general comments, which are reported at the end of this research note.

FDA Application No. (NDA): 022072
Active Ingredient: DASATINIB
Company: BRISTOL-MYERS SQUIBB (BMS)
Approval Date: June 28, 2006
Chemical Type: 1. New molecular entity (NME)
Review Classification: P (Priority review drug) ; O (Orphan drug)
Approval history/number: NDA 021986
Orphan designation: 11/28/05
Marketing Exclusivity (approval): 6/28/2006

The U.S. FDA , the EMEA (European Union) and Switzerland granted orphan designation and marketing approval for dasatinib.

Based upon the data publicly available regarding clinical trials, it is estimated that BMS spent from $6.5 to $26 million USD on clinical trials related to the FDA approval of the BMS version of dasatinib, for the indications ALL and CML.

2. Patents

Bristol-Myers Squibb currently owns three patents with regards to dasatinib. All of the patents are expected to expire by June 2020 (see Table 1).

Table 1: Patent Rights in Dasatinib

Patent number	6596746	7125875	7153856
Filing date	Apr 13, 2000	Mar 24, 2003	May 26, 2005
Issue date	Jul 22, 2003	Oct 24, 2006	Dec 26, 2006
Expiration date	Jun 28, 2020	Apr 13, 2020	Apr 28, 2020
Inventors	Jagabandhu Das, Ramesh Padmanabha, Ping Chen, Derek J. Norris, Arthur M. P. Doweyko, Joel C. Barrish, John Wityak	Jagabandhu Das, Ramesh Padmanabha, Ping Chen, Derek J. Norris, Arthur M. P. Doweyko, Joel C. Barrish, John Wityak, Louis J. Lombardo, Francis Y. F. Lee	Joel C. Barrish, John Wityak, Jagabandhu Das, Ping Chen, Derek J. Norris, Gary Schieven
Assignee	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company

3. Orphan Drug Status and Benefits

The United States (FDA) and the European Union (EMEA) provide various benefits for drugs designated as orphan drugs. The orphan drug status for dasatinib in the United States and Europe is as follows:

November, 28, 2005	FDA: orphan drug designation for ALL and CML[4]
December 23, 2005	EMEA: orphan drug designation for ALL and CML[5]
June 28, 2006	FDA: marketing authorization
November 20, 2006	EMEA: marketing authorization throughout EU
January 1, 2008	Switzerland: orphan designation & marketing approval

Orphan Drug Status in the United States
In the United States, an Orphan Product is defined as a treatment for an indication that afflicts 200,000 individuals or less in the United States. The U.S. government normally allows tax credits for 50 percent of the cost of qualified clinical testing expenses[6], seven-year marketing exclusivity from the date of approval, research design assistance by the FDA and grants of up to $200,000 per year.

The U.S. Orphan Drugs Tax Credit
The U.S. tax credit for orphan designated products is 50 percent of qualifying clinical testing expenses. The tax credit includes contract research expenses as well as in-house research expenses, but does not include government-funded clinical trial expenses. Under the Orphan Drug Act, the tax credit is limited to clinical testings conducted in the United States, although it is available for foreign-conducted trials "if there is an insufficient testing population in the United States." (See Section 45C (d)(2) of the Orphan Drugs Act.)

After U.S. orphan drug designation, BMS was eligible to receive a 50% tax credit for its clinical trial expenses incurred in connection with the development of dasatinib. Several of the clinical trials (see clinicaltrials.gov) were conducted outside the U.S., mostly in Europe; however, the trials may still qualify under the Section 45C, if there isn't a sufficient testing population in the U.S. BMS did not receive grants from the U.S FDA Orphan Drug program.

Orphan Drug Status in the European Union
In the European Union, an Orphan Product is defined as a treatment for diseases that affect no more than 5 in 10,000 people in the EU. The EMEA operates a fee-reduction policy for orphan-designated medical

4 ALL (acute lymphoblastic leukemia) affects about 3,000 people per year and CML (chronic myeloid leukemia) affects about 4,600 per year, in the United States.
5 ALL (EU/3/05/338) affects 0.71/10,000 of the EU population. CML (EU/3/05/339) affects 0.9/10,000 of the EU population. See http://www.emea.europa.eu/pdfs/human/comp/opinion/38678105en.pdf
6 26 U.S.C. SEC. 45C. Clinical Testing Expenses for Certain Drugs for Rare Diseases or Conditions.

products, protocol assistance for sponsors intending to develop an orphan designation for marketing authorization, ten-year marketing exclusivity from the date of approval, and grants from community and member state programs and initiatives supporting research and development, including the Community Framework programs.

We are unable to determine if BMS received grants from the European Union following dasatinib's orphan designation by EMEA.

Orphan Drug Status in Japan
Products which receive an orphan drug designation in Japan are eligible for tax incentives. However, if a product that receives such benefits earns more than 100 million yen[7], it must share future profits with the government. BMS declined to ask for orphan drug status in Japan.

4. Non-Patent Exclusivity from the US FDA

The US FDA has granted five types of non-patent exclusivity to BMS for dasatinib, including:

Type	Exclusivity Code	Exclusivity Expiration
Test data, for new chemical entity	NCE[8]	Jun 28, 2011
Test data, for dose	D-109[9]	Nov 6, 2010
Test data, for dose	M-70[10]	Nov 6, 2010
Orphan Drug indication	ODE[11]	Jun 28, 2013
Orphan Drug indication	ODE	Jun 28, 2013

5. Clinical Trials

According to c*linicialtrials.gov*, there were twenty-five clinical trials involving dasatinib that started before or on June 2006—the date of FDA approval.

Of the twenty-five trials, twelve trials were sponsored by BMS while the other thirteen trials were NIH- and/or university-sponsored. The twelve trials sponsored by BMS involved 1,349 unique persons. 664

7 As of July 11, 2008, 1 JYP (yen) is worth 0.00942711 USD (100,000,000 JYP = 942,711 USD).
8 NCE: New Chemical Entity.
9 D-109: provide for the use of a lower dose for the treatment of adults with chronic phase chronic myeloid leukemia (cml) with resistance or intolerance to prior therapy, including imatinib mesylate.
10 M-70: provision of information of the results of a phase 2 randomized trial of Sprycel 70mg twice daily or imatinib 800mg daily.
11 ODE: Orphan Drug Exclusivity.

patients also participated in follow-on trials. One of the trials involving 60 patients was terminated.

Table 2: 25 Clinical Trials Started before June 2006 FDA Approval

NCT ID	Title	Recruitment	Sponsors	Phases	Enrollment	Start Date
NCT00036738	Fludarabine and Total-Body Irradiation Followed By Donor Peripheral Stem Cell Transplant in Treating Patients With Acute Lymphoblastic Leukemia or Chronic Myelogenous Leukemia That Has Responded to Treatment With Imatinib Mesylate, Dasatinib, or Nilotinib	Recruiting	Fred Hutchinson Cancer Research Center|National Cancer Institute (NCI)	Phase I| Phase II	25	July 2001
NCT00064233	BMS-354825 in Treating Patients With Chronic Phase Chronic Myelogenous Leukemia That Is Resistant to Imatinib Mesylate	Active, not recruiting	Jonsson Comprehensive Cancer Center| National Cancer Institute (NCI)	Phase I	50	November 2003
NCT00099606	Phase I (PH I) Mad Refractory Solid Tumor Study	Completed	Bristol-Myers Squibb	Phase I	60	July 2004
NCT00070499	Imatinib Mesylate or Dasatinib in Treating Patients With Chronic Phase Chronic Myelogenous Leukemia	Recruiting	Southwest Oncology Group|National Cancer Institute (NCI)|Eastern Cooperative Oncology Group	Phase II	335	August 2004
NCT00101647	Study of Dasatinib (BMS-354825) in Patients With Accelerated Phase Chronic Myeloid Leukemia	Completed	Bristol-Myers Squibb	Phase II	197	December 2004

NCT ID	Title	Recruitment	Sponsors	Phases	Enrollment	Start Date
NCT00101816	Dasatinib (BMS-354825) in Subjects With Myeloid Blast Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate	Completed	Bristol-Myers Squibb	Phase II	126	December 2004
NCT00101595	Dasatinib (BMS-354825) in Subjects With Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia	Completed	Bristol-Myers Squibb	Phase II	100	January 2005
NCT00110097	BMS-354825 in Treating Patients With Blastic Phase Chronic Myelogenous Leukemia or Acute Lymphoblastic Leukemia That Did Not Respond to Previous Imatinib Mesylate	Active, not recruiting	Jonsson Comprehensive Cancer Center| National Cancer Institute (NCI)	Phase II		January 2005
NCT00108693	BMS-354825 in Treating Patients With Accelerated Phase Chronic Myelogenous Leukemia That Did Not Respond to Previous Imatinib Mesylate	Active, not recruiting	Jonsson Comprehensive Cancer Center| National Cancer Institute (NCI)	Phase II		January 2005
NCT00108719	BMS-354825 in Treating Patients With Blastic Phase Chronic Myelogenous Leukemia That Did Not Respond to Previous Imatinib Mesylate	Active, not recruiting	Jonsson Comprehensive Cancer Center| National Cancer Institute (NCI)	Phase II		January 2005

NCT ID	Title	Recruitment	Sponsors	Phases	Enrollment	Start Date
NCT00101660	Study of BMS-354825 in Patients With Chronic Myeloid Leukemia Who Are Either Resistant or Intolerant to Imatinib	Completed	Bristol-Myers Squibb	Phase II	424	February 2005
NCT00103844	Dasatinib (BMS-354835) Versus Imatinib Mesylate in Subjects With Chronic Myeloid Leukemia	Completed	Bristol-Myers Squibb	Phase II	165	February 2005
NCT00112801	BMS-354825 in Treating Patients With Chronic Phase Chronic Myelogenous Leukemia That Did Not Respond to Previous Imatinib Mesylate	Active, not recruiting	Jonsson Comprehensive Cancer Center| National Cancer Institute (NCI)	Phase II		March 2005
NCT00112775	BMS-354825 or Imatinib Mesylate in Treating Patients With Chronic Phase Chronic Myelogenous Leukemia That Did Not Respond to Previous Imatinib Mesylate	Active, not recruiting	Jonsson Comprehensive Cancer Center| National Cancer Institute (NCI)	Phase II		March 2005
NCT00123487	Advanced Chronic Myelogenous Leukemia (CML) - Follow On: Study of BMS-354825 in Subjects With CML	Active, not recruiting	Bristol-Myers Squibb	Phase II	264	June 2005
NCT00337454	Study of BMS-354825 in Subjects With CML Who Are Resistant to or Intolerant of Imatinib or Ph+All in Japan	Completed	Bristol-Myers Squibb	Phase I |Phase II	48	July 2005
NCT00123474	Chronic Myelogenous Leukemia (CML) - Follow on: Study of BMS-354825 in Subjects With CML	Active, not recruiting	Bristol-Myers Squibb	Phase III	400	July 2005
NCT00162214	Study of Dasatinib in Patients With Advanced Solid Tumors	Terminated	Bristol-Myers Squibb	Phase I	60	August 2005

NCT ID	Title	Recruitment	Sponsors	Phases	Enrollment	Start Date
NCT00345826	Dasatinib in Treating Patients With Chronic Myelogenous Leukemia or Acute Lymphoblastic Leukemia	Completed	Jonsson Comprehensive Cancer Center| National Cancer Institute (NCI)	Phase I	54	November 2005
NCT00254423	Study of Dasatinib in Patients With Chronic Myelogenous Leukemia	Recruiting	M.D. Anderson Cancer Center| Bristol-Myers Squibb	Phase II	100	November 2005
NCT00255346	Dasatinib as Therapy for Myeloproliferative Disorders (MPDs)	Active, not recruiting	M.D. Anderson Cancer Center| Bristol-Myers Squibb	Phase II	145	November 2005
NCT00298987	A Study of Dasatinib in Patients With Chronic Myelogenous Leukemia Who Are Resistant or Intolerant of Imatinib Mesylate	Completed	Bristol-Myers Squibb	Phase II	400	February 2006
NCT00316953	Dasatinib in Treating Young Patients With Recurrent or Refractory Solid Tumors or Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia or Chronic Myelogenous Leukemia That Did Not Respond to Imatinib Mesylate	Recruiting	Children's Oncology Group|National Cancer Institute (NCI)	Phase I	48	March 2006
NCT00306202	Study of BMS-354825 in Children and Adolescents With Relapsed or Refractory Leukemia	Recruiting	Bristol-Myers Squibb|ITCC	Phase I |Phase II	72	March 2006
NCT00570401	Dasatinib in Treating Patients With Advanced Lung Cancer That Is No Longer Responding to Erlotinib or Gefitinib	Recruiting	Memorial Sloan-Kettering Cancer Center| National Cancer Institute (NCI)	Phase II	37	June 2006

Source: clinicaltrials.gov

Of the twelve BMS-sponsored pre-approval trials, one was conducted in Japan, and others were conducted in multiple countries, including the United States. All government-funded trials were conducted in the United States.

Including trials started before and after the FDA approval, clinicaltrials.gov lists a total of 90 clinical trials on dasatinib, including 38 for leukemia. Table 3 provides a breakdown of the number of trials by condition and source of funding.

Table 3: Clinical Trial Sponsorship

Condition	All Trials	Industry Funded	NIH Funded	% Industry	% NIH
ALL	90	55	29	61	32
Leukemia	38	25	12	66	32
Leukemia/CML	18	17	1	94	6
Leukemia/ALL	16	10	5	63	32

Source: Search of clinicaltrials.gov on July 3, 2008.

6. Cost of Clinical Trials Related to 2006 FDA Approval for Marketing for CML and ALL

Calculating the cost of clinical trials is difficult for many reasons. There are several important variables such as the phase of the trial, the number of patients[12] and the intensity, duration and location of the care and testing during the trial. Another important consideration is the degree to which these costs are covered by insurance.

For Bristol-Myers Squibb, the period of testing for the pre-approval clinical trials relating to the registration of dasatinib was relatively short. The first BMS-funded trial started on July 2004, less than 24 months before the June 28, 2006 FDA approval for CML and ALL. In contrast, according to the Tufts University CSDD, for the industry in general the average time from the start of clinical testing to marketing approval is approximately 90.3 months.[13]

We do not have data on the costs per patient for the BMS-funded clinical trials, but there are extensive data on the average costs of similar trials. Fast Track Systems reported that in 2006, the per patient cost

12 The actual number of patients in the trials related to the FDA approval could be less than 1,349 since some of the twelve trials are still recruiting. Also, the FDA approval letter indicates that the approval was based on four single arm studies involving approximately 400 patients, much smaller than 1,349. See FDA label on Sprycel: http://www.fda.gov/cder/foi/label/2007/021986s001lbl.pdf, viewed July 10, 2008.

13 Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, "The price of innovation: new estimates of drug development costs," *Journal of Health Economics* 22 (2003), *164-165*.

of clinical trials for oncology were $9,631 per patient in the U.S., Canada and Western Europe.[14]

If one considers the 1,349 patients (the total number of unique patients in trials, including terminated trials) in BMS-sponsored clinical trials related to the June 2006 approval for CML and ALL, we can estimate the BMS costs according to two assumptions:

Assumption 1: The cost per patient was **twice the average** cost reported by Fast Track Systems, and BMS claimed zero Orphan Drug tax credits. With these assumptions, the BMS total outlay on the trials would be $26 million.[15]

Assumption 2: The cost per patient was **equal to** the $9,631 fast track average, less the full 50 percent Orphan Drug tax credit. In this case, the outlay would be $6.5 million.

7. Evidence from the Orphan Drug Tax Credit Regarding Costs of Trials for FDA Approvals

Table 5 provides IRS data from the U.S. Orphan Drug Tax Credit. The amount of the tax credit is compared to the total number of FDA approvals for orphan indications. This data provides a useful benchmark when considering estimates of the costs of trials for dasatinib.

The amount of money claimed under the Orphan Drug Tax Credit has increased dramatically. There was a sharp increase from $30.62 million to $109.4 million from 1996 to 1999, followed by a somewhat more modest rate of increase for the next five years. From 2000 to 2005, the claimed tax credit rose from $112.95 million to $232.19 million, an increase of 106 percent.

As reported in Table 5, the amount of the Orphan Drug Tax Credit per FDA marketing approval for orphan indications was $1.28 million in 1996, rising sharply to $12.90 million in 2005.

14 *Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007.* Page 112.

15 Some industry sources claim that internal indirect costs and analysis are roughly equal to direct third party costs of trials.

Table 5: Orphan Drug Tax Credits Compared to FDA Marketing Approvals for Orphan Indications

Years	Orphan Drug Tax Credit *(millions)*	FDA Orphan Product Indication Marketing Approvals	Credit per Approved Orphan Indication
1996	$30.62	24	$1.28
1997	$61.36	18	$3.41
1998	$80.12	21	$3.82
1999	$109.44	18	$6.08
2000	$112.95	12	$9.41
2001	$134.85	6	$22.47
2002	$146.90	14	$10.49
2003	$173.85	12	$14.49
2004	$209.49	13	$16.11
2005	$232.19	18	$12.90
All 2000 to 2005	**$1,010.23**	**75**	**$13.47**

The data from the Orphan Drug Tax Credit provide interesting data points, but require some clarification. First, there are more Orphan Drug indications than there are orphan drugs. For example, Dasatinib has received FDA approval for two indications – CML and ALL. Since dasatinib received two indications, the relevant comparison would be twice the credit per approved orphan indication.

On the other hand, the Orphan Credit is given to products early in the R&D process, including products and product indications that fail and never receive FDA marketing approval. In other words, the credit per approved indication is a risk-adjusted number, and takes into account all of the costly trials that fail. Since the beginning of the Orphan Drug program in the United States, there have been approximately five times more designations of Orphan Drug Indications by the FDA than Orphan Drug Indication marketing approvals.

It is reasonable to assume that more money is invested in products that succeed than in products that fail, for no other reason than that failures sometimes come earlier. In any event, the amount of credit per approval overstates the amount invested in the approved products themselves, because it includes both successes and failures.

The Orphan Drug Tax Credit is granted for 50 percent of qualifying clinical testing expenses. So, on a risk-adjusted basis, for the period 2000 to 2005, the Orphan Drug Tax Credit was $13.47 million per FDA approved indication for outlays of $26.94 million before the tax credit. For two indications, this would be $53.88 million before the credit, and $26.94 million after the credit, counting both successful and unsuccessful products.

8. Comparison to Early Estimated Costs of Trials for dasatinib

Earlier we presented two assumptions regarding the costs of trials for dasatinib for the orphan indications for CML and ALL. These were an estimate of $26 million, using high per patient costs, and not taking into account the benefits of the Orphan Drug Tax Credit, and $6.5 million, using average per patient costs, and assuming the full benefit of the credit. These estimates are consistent with the data from the orphan drug tax credit, which suggest pre-tax credit investments of $53.88 million for **two** orphan indication approvals, taking into account both successes and failures, in a situation where the expected rate of success is roughly 20 percent.

9. Price of dasatinib (Sprycel)

The average CML patient takes 100 mg of dasatinib per day. In the United States and the United Kingdom, 100 mg per day is priced at $174 USD, or $63,481 USD per year. In the Republic of Korea, the yearly cost of 100 mg per day of dasatinib is $40,150 USD.

Table 6: Price of dasatinib

Type/Country	United States	United Kingdom	Republic of Korea
20 mg tablet	$44.61	£21.7 (=$42.3)	
50 mg tablet	$86.96	£43.5 (=$84.8)	55,000 won (=$55)
70 mg tablet	$86.96	£43.5 (=$84.8)	55,000 won (=$55)

Source: LCLabs.com, CMSSupport.org.uk

Note that the average price of dasatinib in A7 countries (US, UK, Switzerland, Japan, France, Germany, Italy) is higher than in ROK.

10. Sales from dasatinib

In 2007, BMS earned $158 million USD by selling dasatinib, and its revenue from dasatinib sales has increased every quarter by at least $10 million USD. By the first quarter of 2008, cumulative sales were $224 million USD, or roughly ten times the high estimate of the cost of the clinical trials for the 2006 approval for CML and ALL.

Table 6: Worldwide Net Sales Profit from Sprycel (dasatinib)

Quarter	Net Sales	Change
2007 (1st quarter)	21	
2007 (2nd quarter)	35	+14
2007 (3rd quarter)	46	+11
2007 (4th quarter)	56	+10
2008 (1st quarter)	66	+10

11. Bristol-Myers Squibb Response to Research Note

KEI provided a copy of this research to Brian Henry of BMS on July 11, 2008. On July 22, 2008, Brian Henry provided this response:

> Subject: Re: <report on R&D cost of Sprycel>
> From: "Brian Henry"
> Date: Tue, July 22, 2008 1:42 pm
> To: Jacqueline Lee
> ---
>
> We do not disclose specific costs of clinical trial programs.
>
> Our response is below:
>
> Sprycel is a valuable medicine for adults with all phases of chronic myeloid leukemia, as well as for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia resistant or intolerant to prior therapy including imatinib. The effectiveness of SPRYCEL is based on hematologic and cytogenetic response rates from a number of clinical trials. At the time of its approval, Sprycel was the only therapy approved for the treatment of these patients once their disease had developed resistance to imatinib.
>
> We price our medicines based on the cost to develop them, the scientific innovation they represent, and the value they deliver to patients and physicians. The price of SPRYCEL reflects the company's robust research and development program for this drug moving forward and competitive market pressures that affect our pricing considerations.
>
> Bristol-Myers Squibb is committed to ensuring that patients who need SPRYCEL have access to the drug. We have programs in place to assist patients in facilitating reimbursement. Patients will also continue to have access to SPRYCEL through clinical

trials where the drug is provided at no charge.

In regards to cost of R&D of Sprycel:

In 2007, the company's overall investment in R&D totaled $3.28 billion, an increase of 10% over $2.99 billion in 2006. The increase reflects the Company's strategy with continued investment in late-stage compounds and developing a pipeline in disease areas that address significant unmet medical need.