Stock Market Reaction to FDA Breakthrough Therapy Designation

An Event Study of Capital Market Responses to Pharmaceutical Companies' Breakthrough Therapy Designation Announcements from 2013 to 2015

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SUMMARY

Breakthrough Therapy Designation, created in 2012, is one of the programs the Food and Drug Administration administers to expedite the development of drugs intended to treat serious conditions. To receive a Breakthrough Therapy Designation, a candidate drug must be intended to treat a serious disease and show substantial improvement over available therapies. Pharmaceutical firms submit requests for Breakthrough Therapy Designation to accelerate clinical trials of a promising drug and expedite regulatory review required prior to commercialization.

In this study, I examine the securities market reaction to 74 announcements of Breakthrough Therapy Designation granted from the conception of the program (the first designation was granted in January 2013) to December 2015. Receiving a Breakthrough Therapy Designation appears to have a small positive effect on the price of equity on the day of the announcements. Thus, an FDA Breakthrough Therapy Designation enhances investor recognition of firm value. In addition, we demonstrate that this effect is more pronounced with smaller “sponsor” (i.e., pharmaceutical) firms.

I. INTRODUCTION

When the US Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law in July 9th 2012, a new program to expedite drug development called Breakthrough Therapy Designation (BTD) was created.

> "SEC. 902. BREAKTHROUGH THERAPIES
>
> IN GENERAL. The Secretary [of the US Department of Health and Human Services] shall, at the request of the sponsor of a drug, expedite the development and review of such drug if the drug is intended, alone or in combination with one or more other drugs, to treat a **serious or life-threatening disease** or condition and **preliminary clinical evidence** indicates that the drug may demonstrate **substantial improvement over existing therapies** on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."[1]

With the introduction of this new designation, the Food and Drug Administration (FDA) has four programs to facilitate and expedite the development and review of new drugs intended to treat serious or life-threatening conditions:

- Fast Track Designation
- Accelerated Approval
- Priority Review Designation
- Breakthrough Therapy Designation

All four expedited programs (see table 1) represent efforts to address an unmet medical need in the treatment of a serious condition. The FDA defines a disease or condition to be *serious* when the disease or condition is associated with morbidity that has substantial impact on day-to-day functioning.[2] Each expedited program has different qualifying criteria. For example, Fast Track Designation, introduced by the FDA Modernization Act of 1997, was created to accelerate the development of drugs that target an unmet medical need: a disease or condition that has no available therapy (or whose treatment or diagnosis is not addressed adequately by existing therapies).

Table 1: Comparison of Qualifying Criteria of FDA's Expedited Programs[3]

Fast Track	**Breakthrough Therapy**	**Accelerate Approval**	**Priority Review**
Designation	Designation	Approval Pathway	Designation
A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need	A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit	An application for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness

To qualify for the Breakthrough Therapy Designation program, a candidate drug must be intended to treat a serious disease or condition and show **substantial improvement over available therapies**. Available therapies are therapies approved or licensed in the United States for the same indication being considered for the new drug. Unlike the information that could support a Fast Track Designation, which could include nonclinical data (i.e., theoretical or

mechanistic rationale), Breakthrough Therapy Designation requires *preliminary clinical evidence* that may represent substantial improvement over available therapies for the treatment of a serious condition.[4] According to the FDA, preliminary clinical evidence means "evidence that is sufficient to indicate that the drug may demonstrate substantial improvement in effectiveness or safety over available therapies, but in most cases is not sufficient to establish safety and effectiveness for purposes of approval" (such evidence generally would be derived from phase 1 or phase 2 trials).[5]

A Breakthrough Therapy Designation offers numerous benefits to the pharmaceutical firm developing the candidate drug. The features of the program include "*Intensive Guidance on an Efficient Drug Development Program, Beginning as Early as Phase 1", "Organizational Commitment Involving Senior Managers",* rolling review and other actions to expedite development. According to the FDA, the development program for a drug granted breakthrough therapy status could be considerably shorter than for other drugs intended to treat the disease being studied. However, this compressed drug development program still must generate adequate data to demonstrate that the drug is safe and effective to meet standards for drug approval for commercialization.

It is important to recognize that not all products designated as breakthrough therapies ultimately will be shown to have the substantial improvement over available therapies suggested at the time of designation. Nor is the designation implicative of an increased chance of drug approval for commercialization. However, the increased communication between the FDA and a pharmaceutical company throughout the entire drug development and review process ensures that issues are resolved quickly, often leading to earlier drug approval.

Based on data from the Tufts Center for the Study of Drug Development (CSDD), the average development cost of a new drug in the early 2010's is $2,558 million, with a typical

development program spanning over 10 years.[6] Since a drug designated as Breakthrough Therapy could potentially come to market sooner than drugs without the designation, there is an implication that the sponsoring pharmaceutical companies could have substantial economic benefits from a drug that is granted Breakthrough Therapy Designation.

The expedited programs are of crucial importance for patients who are in need of a treatment for a serious or life threatening disease and who wait for new and promising drugs. Recent discoveries of new molecular pathways in cancer and other serious conditions have opened the door to the development of innovative potential therapeutic solutions. Breakthrough Therapy Designation holds the promise of facilitating the development process of these drugs, making the forthcoming therapies available as soon as possible.

In this paper, I assess whether or not capital markets react to the announcement of drug-specific designation of Breakthrough Therapy. Companies that receive Breakthrough Therapies Designations for their products receive significant positive press and interest. But what does all this mean for investors? The goal of this research study is to evaluate the effect of the Breakthrough Therapy Designation on the value of the sponsor firms.

From the literature reviewed, it is interesting to highlight a prior study Anderson and Zhang (2010), where they investigated how capital markets responded to pharmaceutical companies' announcements of FDA Fast Track designation. As the authors explain, this designation conveys little specific economic information about a drug's medical or commercial potential. However, they found that financial markets responded favorably in various dimensions studied, suggesting that the Fast Track designation reveals positive information and enhances investors' favorable views of the company.

II. METHODOLOGY

The event-study methodology is used in this study to examine the reaction of investors to drug-specific FDA designation of Breakthrough Therapy.

Model Description

An event study typically uses financial market data to measure the impact of a specific event on the value of a firm. First introduced by Fama, Fisher, Jensen and Roll (1969), the event study methodology is widely used in Economics and Finance to examine security price behavior surrounding specific events, such as stock split or earning announcements. The usefulness of an event study comes from the fact that, given rationality in the marketplace, the effects of an event will be reflected quickly in security prices (MacKinlay, 1997). Therefore, the economic impact of an event can be measured using the stock prices observed over a relatively short period (in contrast to direct productivity measures of the company that require many months or even years of observation).

An event study examines stock market return behavior of firms experiencing a common type of event. The first step for conducting an event study is to define the event of interest and identify the event window (the period over which the security prices of the firm will be examined). In this study, an *event* is defined as a pharmaceutical firm announcement of Breakthrough Therapy Designation granted to a development drug in its portfolio. These events take place at different points in calendar time, from January 6th 2013 to December 17th 2015.

The decision as to the size of the event window is subjective and may vary depending on the event of interest. Typically, events studies specify an event window surrounding the event of interest in order to capture the pre-event and post-event reaction (MacKinlay, 1997).

In this study, two event windows were considered: three-day, and seven-day windows. For example, the three-day window is formed by the day of the event plus the day before and the day after the event. Extending the event window permits us to examine the period surrounding the announcement and provides inferences as to any information leakage prior to the actual announcement.

The abnormal return ("AR") is the difference between the observed return and the expected return of a security. It is a direct measure of the change in the security price associated with the event of interest.

$$AR_{it} = R_{it} - E(R_{it} | X_t)$$

where AR_{it} = abnormal return, R_{it} = actual return, and $E(R_{it} | X_t)$ = expected return for time t.

There are several steps to calculate the ARs of the days in the event window for each firm. To begin, it is necessary to calculate expected (aka "normal") returns. There are various expected return models that are used in event studies: the single-index model (constant mean return model), the market model (used in this study) and the capital asset price model (CAPM) are the most widely used. The market model assumes a stable linear relation between the market return and the security return. In the market model, the expected firm return is a linear function of the market return using an Ordinary Least Squares beta (Dyckman et al., 1984). According to the market model, the factor determining the return on a stock i at time t, is the return of the market at time t, as showed in the following linear relationship:

$$R_{it} = \alpha + \beta_i R_{mt} + \varepsilon_{it}$$

where R_{it} and R_{mt} are the returns on security *i* and the market portfolio, respectively, during period t, and ε_{it} is the error term for security *i.*

With the estimates of α and β, one can predict a "normal" return during the days covered by the event window. In this study, the market model parameters (α intercept and β) were estimated running two different ordinary least squares (OLS) regressions: each security's daily holding period return against the daily returns on the S&P 500 Composite Index and against the daily returns on the NYSE Arca Pharmaceutical Index (DRG). For each of the firms in the sample, the least-squares regression parameters were estimated using a 90-day regression period of daily returns, from days -94 to -4 relative to the event day. I assume that the stock returns from more than a week prior to the announcement are not influenced by the event itself, and think of this window as a "normal" estimation period. The OLS regressions have been done separately for 74 firms to obtain firm-specific Beta coefficients. With the estimated values of α intercept and β, I compute the expected returns $E(R_{it}|\, X_t)$ in the event window and calculate ARs as the difference between actual and expected returns.

For each individual event, one can estimate the abnormal return and relevant test statistics for each day within the event window. However, in order to draw overall inference on abnormal returns for the type of event of interest, the abnormal returns must be aggregated. For any given number of events, the sampled aggregated abnormal returns (AAR) at each time *t* within the event window is computed as:

$$AAR_t = \frac{1}{n}\sum_{i=1}^{n} AR_{it}$$

where AAR_t = average abnormal return for time *t*, AR_{it}= abnormal return for company *i* at time *t*, and *n* = the sample size.

To ascertain the significance of the average abnormal returns for each day in the event window, testing is performed with t-statistics according to the following formula:

$$t_{AR} = \sqrt{n}\,\frac{AAR_t}{S_{AAR_t}}$$

where t = t-statistic, AAR_t = average abnormal return for time, *n* the sample size.

S_{AAR_t} is the standard deviation across firms at time *t*, calculated as:

$$S^2_{AAR_t} = \frac{1}{n-1}\sum_{i=1}^{n}(AR_{i,t} - AAR_t)^2$$

In order to test for the persistence of the impact of the event during a period, the abnormal returns can be added to obtain the cumulated abnormal returns (CAR). Firm-specific CARs are calculated in order to ascertain the magnitude of the sum of the abnormal returns over the entire event window.

$$CAR_T = \sum_{t=1}^{T} AR_t$$

We can also aggregate across time and events, calculating overall cumulative average abnormal returns as:

$$CAAR_T = \frac{\sum_{t=1}^{T} CAR_T}{n}$$

The significance of CAARs is ascertained via the calculation of a t-statistic as follows:

$$t_{CAAR} = \sqrt{n}\,\frac{CAAR_T}{S_{CAAR_T}}$$

where S_{CAAR_t} is the standard deviation of the cumulative abnormal returns across the sample and is calculated according to the following formula:

$$S^2_{CAAR_T} = \frac{1}{n-1}\sum_{i=1}^{n}(CAR_{i,T} - CAAR_T)^2$$

III. DATA

Breakthrough Therapy Designation announcements were collected from January 2013 to December 2015. Two major sources of data, described below, are the Food and Drug Administration (FDA) and the Center for Research in Security Prices (CRSP) database.

The FDA does not disclose information regarding sponsors that have submitted requests for or been granted (or denied) a Breakthrough Therapy Designation. Thus, the FDA does not provide an official listing of pharmaceutical firms that have received a Breakthrough Therapy Designation. Quarterly, the FDA releases a "Breakthrough Therapy (BT) Designation Requests" reports containing a count of breakthrough therapy designations requests received and the status of these requests. A summary of these reports can be seen in Table 2.

Table 2: Breakthrough Therapy Requests Received by Fiscal Year

Data as of December 31, 2015

Fiscal Year	Received	Granted	Denied	Withdrawn
Center for Drug Evaluation and Research (CDER)				
2016	36*	5	13	5
2015	93	32	43	18
2014	96	31	51	14
2013	92	31	52	9
2012	2	1	1	0
Center for Biologics Evaluation and Research (CBER)				
2016	7	2	4	1
2015	20	8	9	3
2014	26	7	19	0
2013	12	1	10	1
2012	0	0	0	0
Total	**384**	**118**	**202**	**51**

*Requests that are still pending a decision are included in the total requests received column.

SOURCE: U.S. Food and Drug Administration [7]

Sponsors, however, announced publicly almost all the designations granted: from 118 requests granted, information is not available for approximately 10 requests that have not been publicly announced by their sponsors. Thus, I relied on firm announcements of Breakthrough Therapy Designation approvals.

I supported my independent search of firm announcements with the listing of pharmaceutical firm Breakthrough Therapy Designation announcements maintained by "Friends of Cancer Research", an advocacy group based in Washington, DC (http://www.focr.org/breakthrough-therapies). This search resulted in a sample of 96 Breakthrough Therapy Designation announcements for sponsored drugs (see Table 3a and 3b). I determined selection criteria for the inclusion of a given firm in the study mainly based on data availability:

Inclusion criteria: US- traded, public companies listed on New York Stock Exchange (NYSE) and NASDAQ with stock-price data available in the Center for Research in Securities Prices (CRSP) database.

Table 3a: Sample characteristics: included events

Sponsored Drug	Company	Ticker	Market Listed	BTD Announced
Ivacaftor (Kalydeco)*	Vertex	**VRTX**	NASDAQ	01/06/13
Ibrutinib (Imbruvica)*	J&J/Pharmacyclics	**JNJ/PCYC**	NYSE/NASDAQ	02/12/13
Ceritinib (Zykadia)	Novartis	**NVS**	NYSE	03/15/13
Ibrutinib (Imbruvica)	J&J/Pharmacyclics	**JNJ/PCYC**	NYSE/NASDAQ	04/08/13
Palbociclib (Ibrance)	Pfizer	**PFE**	NYSE	04/10/13
Pembrolizumab (Keytruda)	Merck	**MRK**	NYSE	04/24/13
Daclatasvir	BMS	**BMY**	NYSE	04/25/13
Daratumumab	J&J	**JNJ**	NYSE	05/01/13
ABT-450 (Viekira Pak)	AbbVie	**ABBV**	NYSE	05/06/13
Sebelipase Alfa	Synageva	**GEVA**	NASDAQ	05/20/13
Asfotase Alfa	Alexion	**ALXN**	NASDAQ	05/28/13
Serelaxin	Novartis	**NVS**	NYSE	06/21/13
Drisapersen	GSK/Prosensa	**GSK**	NYSE	06/27/13
Sofosbuvir/ledipasvir combination	Gilead	**GILD**	NASDAQ	07/25/13
BYM338 (Bimagrumab)	Novartis	**NVS**	NYSE	08/20/13
Amifampridine phosphate (Firdapse)	Catalyst	**CPRX**	NASDAQ	08/27/13
Ofatumumab (Arzerra)	GSK/Genmab	**GSK**	NYSE	09/13/13

Grazoprevir/Elbasvir	Merck	**MRK**	NYSE	10/22/13
cPMP (ALXN1011)	Alexion	**ALXN**	NASDAQ	10/24/13
Sofosbuvir (Sovaldi)	Gilead	**GILD**	NASDAQ	10/25/13
Idelalisib (Zydelig)	Gilead	**GILD**	NASDAQ	11/18/13
Andexanet alfa (PRT4445)	Portola	**PTLA**	NASDAQ	11/25/13
Tafenoquine	GlaxoSmithKline	**GSK**	NYSE	12/20/13
Dabrafenib	GlaxoSmithKline	**GSK**	NYSE	01/13/14
Esketamine	J&J	**JNJ**	NYSE	01/21/14
Orkambi / Kalydeco combination	Vertex	**VRTX**	NASDAQ	01/29/14
Eltrombopag (Promacta)	GlaxoSmithKline	**GSK**	NYSE	02/03/14
Daclatasvir/asunaprevir combination	BMS	**BMY**	NYSE	02/24/14
Trumenba	Pfizer	**PFE**	NYSE	03/20/14
Bexsero	Novartis	**NVS**	NYSE	04/07/14
MYDICAR	Celladon	**CLDN**	NASDAQ	04/10/14
AZD9291	AstraZeneca	**AZN**	NYSE	04/24/14
Nivolumab (Opdivo)	BMS	**BMY**	NYSE	05/14/14
Elotuzumab	BMS	**BMY**	NYSE	05/19/14
Rociletinib (CO-1686)	Clovis Oncology	**CLVS**	NASDAQ	05/19/14
Arikayce	Insmed	**INSM**	NASDAQ	06/17/14
Blinatumomab (Blincyto)	Amgen	**AMGN**	NASDAQ	07/01/14
CTL019	Novartis	**NVS**	NYSE	07/07/14
Pirfenidone (Esbriet)	InterMune	**ITMN**	NASDAQ	07/17/14
Nuplazid (pimavanserin)	Acadia	**ACAD**	NASDAQ	09/02/14
Eylea (aflibercept)	Regeneron	**REGN**	NASDAQ	09/16/14
Nivolumab (Opdivo)	BMS	**BMY**	NYSE	09/26/14
AP26113	Ariad	**ARIA**	NASDAQ	10/02/14
Pembrolizumab (Keytruda)	Merck	**MRK**	NYSE	10/27/14
NBI-98854	Neurocrine Biosc.	**NBIX**	NASDAQ	10/30/14
Dupilumab	Regeneron/Sanofi	**REGN/SNY**	NASDAQ/NYSE	11/20/14
Obeticholic acid (OCA)	Intercept	**ICPT**	NASDAQ	01/29/15
LentiGlobin	BlueBird	**BLUE**	NASDAQ	02/02/15
Rindopepimut (Rintega)	Celldex	**CLDX**	NASDAQ	02/23/15
EBV-CTL	Atara and MSKCC	**ATRA**	NASDAQ	03/02/15
Rucaparib	Clovis	**CLVS**	NASDAQ	04/06/15
Grazoprevir/Elbasvir*	Merck	**MRK**	NYSE	04/08/15
Viaskin Peanut	DBV	**DBVT**	NASDAQ	04/09/15
Xalkori (crizotinib)	Pfizer	**PFE**	NYSE	04/21/15
Venetoclax	AbbVie/Roche	**ABBV/RO**	NYSE	05/06/15
Siroliums (Rapamune)	Wyeth (Pfizer)	**PFE**	NYSE	05/28/15
Olipudase alfa	Sanofi/Genzyme	**SNY**	NYSE	06/04/15
DX-2930	Dyax	**DYAX**	NASDAQ	07/07/15
BMS-663068	BMS	**BMY**	NYSE	07/21/15
Tafinlar and Mekinist combination	Novartis	**NVS**	NYSE	07/24/15
Ultratrace iobenguane I-131 (Azedra)	Progenics	**PGNX**	NASDAQ	07/28/15
Cabozantinib	Exelixis	**EXEL**	NASDAQ	08/24/15
Nivolumab (Opdivo)	BMS	**BMY**	NYSE	09/02/15
Nivolumab (Opdivo)	BMS	**BMY**	NYSE	09/16/15
Abemaciclib	Eli Lilly	**LLY**	NYSE	10/08/15
Inotuzumab Ozogamicin	Pfizer	**PFE**	NYSE	10/19/15
Pembrolizumab (Keytruda)	Merck	**MRK**	NYSE	11/02/15
SD-809 (deutetrabenazine)	Teva	**TEVA**	NYSE	11/09/15
Avelumab	Merck / Pfizer	**MRK / PFE**	NYSE/NYSE	11/18/15
KTE-C19	Kite	**KITE**	NASDAQ	12/17/15

* BTD granted to a drug under development intended to be use for the treatment of 2 different medical indications.

Table 3b: Excluded firms with corresponding exclusion criteria

Sponsored Drug	Company	BTD Announced	Exclusion Criteria
SD101	Scioderm	04/29/13	Private
Obinutuzumab (Gazyva)	Genentech-Roche	05/15/13	Listed abroad
Entinostat	Syndax	09/11/13	Private
Volasertib	Boehringer Ingelheim	09/17/13	Private
Alectinib	Roche	09/23/13	Listed abroad
Atezolizumab (MPDL3280A)	Roche	05/31/14	Listed abroad
Idarucizumab	Boehringer Ingelheim	06/26/14	Private
Nintedanib (Ofev)	Boehringer Ingelheim	07/16/14	Private
CRS-207 and GVAX	Aduro	07/21/14	IPO after BTD (04/15/2015)
SPK-RPE65	Spark Therapeutics	11/06/14	IPO after BTD (01/30/2015)
JCAR015	Juno Therapeutics	11/24/14	IPO after BTD (12/19/2014)
Ixazomib	Takeda	12/02/14	Listed abroad
Ranibizumab (Lucentis)	Genentech/Roche	12/15/14	Listed abroad
MPDL3280A	Genentech/Roche	02/01/15	Listed abroad
Ibalizumab (TMB355)	TaiMed	02/27/15	Listed abroad
ACTEMRA/RoACTEMRA	Genentech/Roche	06/10/15	Listed abroad
SER-109	Seres	06/12/15	Listed abroad
AR101	Aimmune	06/18/15	Listed abroad
Lenvatinib (Lenvima)	Eisai	07/29/15	Listed abroad
ACE910	Roche/Genentech	09/04/15	Listed abroad
RBX2660	Rebiotix, Inc.	10/12/15	Listed abroad
Pexidartinib (formerly PLX3397)	Daiichi Sankyo	10/30/15	Private
BI 1482694	Boehringer Ingelheim	12/18/15	Private

CRSP US Stock Database

Stock Market data was obtained from the CRSP database. The Center for Research in Security Prices (CRSP) is one of the most comprehensive providers of historical stock market data. The CRSP Daily Stock database was used to collect the data on securities Holding Period Returns and market information (Return on S&P Composite Index).

S&P 500 Composite Index

The S&P 500 Composite Index is based on the average performance of the common stock of the 500 largest US firms. It is often used as a benchmark indicator of the overall US

stock market performance.[8] The S&P 500 Index was used in this study as "the market" to calculate expected returns.

DRG Index Description

The NYSE Arca Pharmaceutical Index (DRG) is designed to represent a cross section of widely held, highly capitalized companies involved in various phases of the development, production, and marketing of pharmaceuticals. The DRG is market-capitalization weighted, using the U.S. primary market prices for component securities, and current shares outstanding. The DRG Index was used to create a second "market" index to estimate abnormal returns.

IV. EMPRICAL RESULTS

Following the methodology described in section III, two models have been used to run the regressions in this event study. In one model each company's security Holding Period Return (RET) is regressed on the market return of the S&P 500 Composite Index. In the second model, Holding Period Returns (RETs) were regressed against the return of the NYSE Arca Pharmaceutical Index (DRG). In both cases, the sample period for the OLS regression was ninety days before the event date. Exhibits 1 and 2 show the abnormal returns calculated for each model.

Table 4 reports very similar results for the two models studied. Table 5 shows the linear correlation matrix measuring the strength of the linear association between the variables. A correlation coefficient of 0.8195 indicates a strong linear association between the S&P500 and DRG returns. In addition, a multivariable regression model was done using both indexes as right hand variables. The abnormal returns obtained through this multivariable model were very similar to the S&P500 Model and the DRG Model. Thus, it was decided it was not worth to

continue with both models. Further analysis on this study was done using the S&P 500 Model only.

Table 4: Summary of results for each model. AAR (Average Abnormal Return), CAAR (Cumulative Average Abnormal Return).

				S&P 500			
Event Day	-3	-2	-1	0	1	2	3
AAR	-0.37%	0.00%	0.22%	1.30%	0.73%	0.06%	0.33%
t-test	-1.50	0.01	0.58	1.87	0.97	0.14	1.36
CAAR	-0.37%	-0.37%	-0.15%	1.14%	1.87%	1.93%	2.26%
				DRG Index			
Event Day	-3	-2	-1	0	1	2	3
AAR	-0.42%	-0.02%	0.15%	1.32%	0.85%	0.06%	0.37%
t-test	-1.82	-0.05	0.41	1.95	1.16	0.15	1.58
CAAR	-0.42%	-0.44%	-0.29%	1.03%	1.88%	1.94%	2.31%

Table 5: Correlation Coefficient Matrix *S&P vs. DRG*

		DRG	S&P
DRG	**R**	**1.**	
	R Standard Error		
	t		
	p-value		
	H0 (5%)		
S&P	**R**	**0.8195**	**1.**
	R Standard Error	0.0003	
	t	45.2811	
	p-value	0.	
	H0 (5%)	*rejected*	

Variable vs. Variable	*R*	*No# of valid cases*
S&P vs. DRG	0.8195	1005

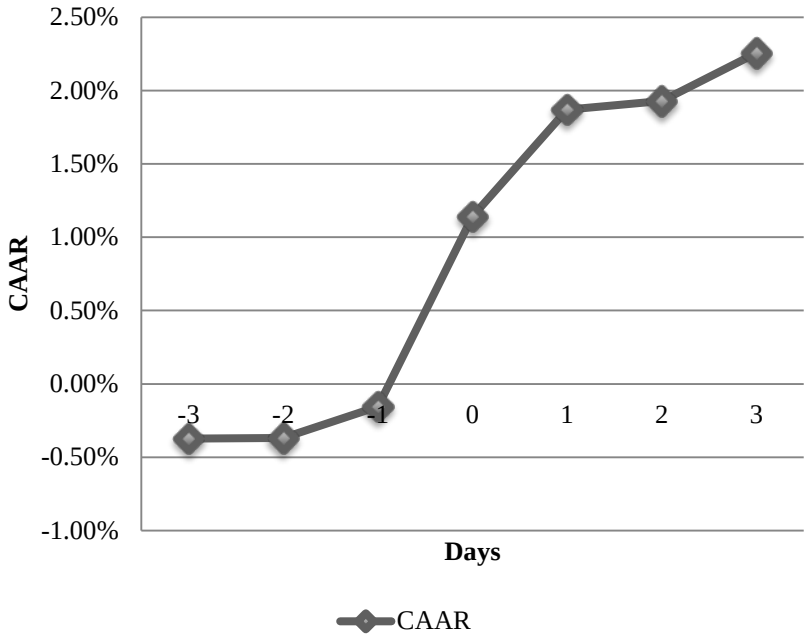
Using the S&P 500 Index, we examine the distribution of the 7-day Cumulative Abnormal Returns, 3-day Cumulative Abnormal Returns and Market Capitalization (in Millions) of the sample companies (see Table 6).

Table 6: Distribution Analysis of continuous variables

Variable Name	Mean	SD	Min	Max
7-day CAR	0.025	0.098	-0.21	0.47
3-day CAR	0.022	0.089	-0.17	0.43
Market Cap (US Millions)	$88,046.07	$80,066.17	$60.1	$262,478.4
Institutional Holding	70.39%	18.5%	0%	100%

Figure 1 shows the mean cumulative abnormal returns for days -3 to +3 relative to the announcement of Breakthrough Therapy Designation of a sponsored drug on day zero. We can notice evident abnormal stock returns that are coincidental with the announcement of Breakthrough Therapy Designation for a sponsored drug. On the announcement day (Event Day 0) the average abnormal return is +1.30%, indicating a slightly positive reaction of investors towards announcements of Breakthrough Therapy Designation.

Figure 1: Cumulative Average Abnormal Returns Surrounding Announcements of Breakthrough Therapy Designations



The highest abnormal return corresponds to Catalyst Pharmaceutical (Nasdaq: CPRX), a small pharmaceutical company specialized in the development of drugs targeting orphan neurological diseases. On August 13th 2013, CPRX announced that their lead investigational product, Firdapse, had received Breakthrough Therapy Designation by the FDA. CPRX stock showed an AR of +42.84% on the day this announcement was made, with a 3-day CAR of +39.70% and 7-day CAR +39.27%.

The second highest return corresponds to Acadia's Pharmaceutical (Nasdaq: ACAD). Acadia is also focused on the development of medicines to address unmet medical needs related to neurological disorders. On September 2, 2014, when it announced Breakthrough Therapy Designation granted to Nuplazid, ACAD showed an AR of 13.80%, with a 3-day CAR of +12.77% and 7-day CAR +10.52%.

Both of these examples showed t-statistics significant at the 1% level. Other companies showed minimal AR's, which are mostly insignificant (AR statistically not significantly different from zero).

These results could indicate that abnormal returns are higher for smaller firms. In addition, Acadia's Pharmaceuticals and Catalyst Pharmaceuticals both showed high abnormal returns with Breakthrough Therapies Designations for drugs that target conditions in the same therapeutic area. The therapeutic area of the drug that receives Breakthrough Therapy Designation could have an effect on the level of the abnormal return. To determine which characteristics affect the level of abnormal returns, we turn to cross-sectional regression analysis.

Cross-sectional Analysis

Cross-sectional tests examine how the stock price effects (CARs) of an event are related

to firm characteristics. For a cross-section of firms, abnormal returns are compared to (regressed against) firm characteristics (Khotari and Warner, 2006). CARs could vary cross-sectionally because the economic effect of the event differs by firm. CARs could also vary cross-sectionally because the degree to which the event is anticipated differs by firm.

The differential characteristics of the events used in the cross-sectional analysis are:

- *Firm size by market capitalization*: natural log of the market value of equity.

  A Breakthrough Therapy Designation might have a different effect depending on the size of the firm developing the candidate drug. We expect investors to react more strongly to a BTD announcement of a small firm (by market cap), such as a small research and development focused biotech firm, than to a BTD announcement of a bigger pharmaceutical company. The BTD announcement is likely to be relatively more important for a small firm's future profitability than would be true for a large firm.

- *Drugs in Market*: whether the firm has already marketed products to consumers (indicator variable equal to one if a firm has already marketed products to consumers and a zero if it hasn't).

  The value of a firm that has no products marketed to consumers is based on the company's research pipeline. A Breakthrough Therapy Designation granted to a firm that is entirely on a development stage may send a promising message about the strength of its pipeline, and, may cause a greater effect on the returns of the stock.

- *Therapeutic area (TA) of drug that receives Breakthrough Therapy Designation:*

  - Cancer
  - Rare Diseases
  - Cardiovascular

- Infectious Diseases

- Other

Breakthrough Therapies Designations have been granted to drugs intended to treat conditions that are classified based on their therapeutic target area. Areas such as Cancer (i.e., Immuno-oncology drugs) have seen fierce competition, and multiple pharmaceutical companies could be simultaneously developing drugs that have the same mechanism of action. A Breakthrough Therapy Designation granted to a firm that is developing a drug in a very competitive "hot" therapeutic area might have a stronger economic effect than a firm developing a drug in another therapeutic area.

- *Geographic location of headquarters* (East region, West and Other):

  In the United States, there are two major clusters of pharmaceutical companies: the East region (with popular regions such as Boston/Cambridge in MA, and other cities in CT and NY) and the West region (with clusters in the San Francisco Bay Area and San Diego, both in CA). By including a geographic location dummy, we explore the effect of a Breakthrough Therapy Designation granted to a firm headquartered in these different cluster regions.

- *Percentage of institutional holding:* natural log of the percentage of a firm's common equity held by institutions.

  On a previous study by Anderson and Zhang (2010) the authors observed higher abnormal returns for firms that were subject to lower levels of institutional ownership. Following this lead, we included a variable to explore differences of CARs related to differences on the level of institutional holdings. Arguably, institutions might have more advance information about the likelihood of a BTD announcement, which would mean that the likely positive effects of the

announcement would already be embedded in the price of a company's stock; consequently, the stock market's reaction on the day of the announcement (or even a few days before) would be more muted. (Because the logarithm of this variable is use in the cross-section regression, we replaced any observations that had a value of 0% with the value 1%).

- *Year that designation was received* (2013, 2014 or 2015):

  The FDA first introduced the Breakthrough Therapy Designation program in July 2012, and granted the first designations in 2013. With the evolution of this program, and as more designations were approved and denied, there was a better overall understanding of the program (i.e., qualifying criteria, FDA support to sponsoring firm and timelines to commercialization). Thus, a Breakthrough Therapy Designation granted to a firm in 2013 (during the first year of the program) might have a different effect than a designation granted in 2014 or 2015.

While searching for causes of the variation of the abnormal returns using cross-sectional analysis, we first look at the variance of the errors across observations. According to Saxonhouse, applying ordinary least squares to an equation with a heteroscedastic error structure (when the variance of the errors is not constant across observations) is an inefficient method (Saxonhouse, 1976). Since our OLS estimations of the ARs yields an estimate of the variance of each dependent variable, to deal with the issue of heteroscedasticity in our observations we run ordinary least square regressions weighting each observation (for all variables) used by the inverse of the estimated standard error of the dependent variable.

Table 6a reports estimated results for cross-sectional regressions of 3-day cumulative abnormal returns (CAR). The dependent variable is the 3-day CAR estimated using the S&P 500 Model. The number of observations equals 74 for all estimations. Table 6b shows cross-

sectional regressions results of 7-day CARs.

Table 6a: Regression Analysis of 3-day CARs

	Estimate	**t Ratio**	**Estimate**	**t Ratio**	**Estimate**	**t Ratio**	**Estimate**	**t Ratio**
Intercept	0.1811	1.8	0.1792	1.81	0.1800004	1.9	0.1864248	1.98
Drugs in Market[0]	-0.0017	-0.11	-0.0011	-0.08	-0.002372	-0.19	-0.001584	-0.11
TA Cancer[0]	0.0042	0.5	0.0038	0.47	0.0041583	0.51		
TA Rare Ds[0]	0.0036	0.28	0.0026	0.21	0.0034775	0.27		
TA Infectious Ds[0]	0.0004	0.04	-0.0002	-0.02	0.0004134	0.04		
TA Cardiovascular[0]	0.0115	0.6	0.0102	0.56	0.0116177	0.62		
G. Location East[0]	-0.0004	-0.06	-0.0003	-0.05			-0.000502	-0.08
G. Location West[0]	0.0008	0.06	0.0008	0.06			0.0009176	0.07
Ln[Market Cap]	-0.0155	-2.86	-0.0152	-2.92	-0.015466	-2.92	-0.015401	-3.12
Ln[Institutional Holding]	-0.0042	-0.22	-0.0039	-0.21	-0.003896	-0.22	-0.002276	-0.13
2013[0]	-0.0014	-0.2			-0.001316	-0.19	-0.001112	-0.16
2014[0]	0.0004	0.05			0.000461	0.06	-0.000578	-0.08
F-ratio	1.4570		1.8281		1.8367		**2.3107**	
p-value	0.1712		0.0801		0.0785		**0.0360**	
R-Square	0.2054		0.2045		0.2053		0.1968	
R-Square Adj	0.0644		0.0926		0.0935		0.1116	

	Estimate	t Ratio	Estimate	t Ratio	Estimate	t Ratio	Estimate	t Ratio
Intercept	0.1707	4.27	0.0221	2.4	0.1756	3.71	0.1790	2.2
Drugs in Market[0]			0.0219	2.38	-0.0022	-0.2		
Ln[Market Cap]	-0.0147	-4.19			-0.0153	-3.3	-0.0147	-4.15
Ln[Institutional Holding]							-0.0019	-0.12
F-ratio	**17.5275**		**5.6811**		**8.6664**		**8.6508**	
p-value	**2.0873**		**0.0198**		**0.0004**		**0.0004**	
R-Square	0.1958		0.0731		0.1962		0.1959	
R-Square Adj	0.1846		0.0603		0.1038		0.1732	

Table 6b: Regression Analysis of 7-day CARs

	Estimate	**t Ratio**	**Estimate**	**t Ratio**	**Estimate**	**t Ratio**	**Estimate**	**t Ratio**
Intercept	0.1330	1.09	0.1279	1.06	0.1723	1.49	0.1171	1.02
Drugs in Market[0]	0.0194	1.04	0.0173	0.95	0.0143	0.95	0.0206	1.13
TA Cancer[0]	-0.0049	-0.49	-0.0028	-0.29	-0.0040	-0.4		
TA Rare Ds[0]	0.0031	0.2	0.0061	0.41	0.0027	0.18		
TA Infectious Ds[0]	0.0024	0.2	0.0037	0.32	0.0035	0.3		
TA Cardiovascular[0]	0.0244	1.06	0.0267	1.21	0.0235	1.03		
G. Location East[0]	0.0078	0.99	0.0084	1.08			0.0066	0.86
G. Location West[0]	0.0116	0.7	0.0104	0.63			0.0113	0.7
Ln[Market Cap]	-0.0124	-1.89	-0.0130	-2.05	-0.0129	-1.99	-0.0107	-1.77
Ln[Institutional Holding]	-0.0012	-0.05	-0.0006	-0.03	-0.0079	-0.37	0.0048	0.22
2013[0]	-0.0033	-0.38			-0.0036	-0.42	-0.0005	-0.06
2014[0]	-0.0090	-0.98			-0.0093	-1.04	-0.0080	-0.91
F-ratio	1.5915		1.8648		1.8416		**2.2232**	
p-value	0.1236		0.0736		0.0776		**0.0432**	
R-Square	0.2202		0.2078		0.2057		0.1908	
R-Square Adj	0.0818		0.0964		0.0941		0.1049	

	Estimate	t Ratio	Estimate	t Ratio	Estimate	t Ratio	Estimate	t Ratio
Intercept	0.1847	3.68	0.0313	2.84	0.1548	2.63	0.1894	1.86
Drugs in Market[0]			0.033	3.00	0.0136	0.96		
Ln[Market Cap]	-0.0159	-3.62			-0.0123	-2.13	-0.0159	-3.58
Ln[Institutional Holding]							-0.0011	-0.05
F-ratio	**13.0772**		**9.0086**		**6.9961**		**6.4494**	
p-value	**0.0006**		**0.0037**		**0.0017**		**0.0027**	
R-Square	0.1537		0.1112		0.1646		0.1537	
R-Square Adj	0.1419		0.0989		0.1411		0.1299	

The F-ratio shows the model mean square divided by the error mean square. The F-Ratio is the test statistic for whether the model differs significantly from a model where all predicted values are the response mean. The *p*-value for the F-test measures the probability of obtaining an F-ratio as large as what is observed, given that all parameters except the intercept are zero. Small p-values indicate that the observed *F*-ratio is unlikely and is considered evidence that there is at least one significant effect in the model.

As Tables 6a and 6b show, the cross-sectional regressions indicate that abnormal returns

are inversely related to market capitalization. Combining Market Capitalization with any of the other variables attenuates the results. The coefficient on Ln Market Cap for the 3-day CAR regression is -1.47% (t-test -4.19) and for the 7-day CAR is -1.59% (t-test -3.62), both showing that there is a negative correlation between the size of the company and the 3-days CARs. We thus see that -- as expected -- smaller companies are more likely to show larger CARs.

V. CONCLUSIONS

Pharmaceutical companies request Breakthrough Therapy Designation to accelerate the development of a promising drug intended to treat a serious condition. When this designation is granted, the sponsor pharmaceutical company will receive various benefits such as extensive guidance from the FDA and actions to expedite development. In this study, I analyzed the economic impact of an announcement of Breakthrough Therapy Designation on the price of equity of the sponsor firm.

The summary of the findings of the present research study suggest the existence of a statistically significant positive abnormal return (AR) for the day of the events (announcement of Breakthrough Therapy Designation). In this study, we found positive average abnormal return of 1.30% on the announcement day, and a 7-day CAAR of 2.25%. These findings suggest that the grant of Breakthrough Therapy Designation conveys positive information about a drug's sponsor company and reveals positive information about the firm's growth opportunities.

Further, it appears that a Breakthrough Therapy Designation granted to a drug developed by a small company has a relatively larger security market reaction than a Breakthrough Therapy Designation granted to a drug developed by a large pharmaceutical firm. Thus, we would expect financial markets to respond favorably to Breakthrough Therapy Designation announcements of small market capitalization firms.

The results of this study are consistent with the results found in the literature reviewed. Anderson and Zhang (2010) studied the Security Market Reaction to FDA Fast Track Designations. They found that financial markets responded favorably to fast track announcements with abnormal stock returns that average about 9 percent across several alternative benchmarking techniques. Specifically, they studied 107 fast track announcements that occurred between 1998 and 2004. They also identified that the abnormal stock returns were highest among smaller firms, firms that have yet to commercialize a product, and firms with low levels of institutional ownership. The results of their study cannot be compared directly with the results of the present study; however, the similarity of the positive abnormal return suggest that being accepted into one of the FDA's Expedited Programs for Serious Conditions reveals positive information to investors.

VI. EXHIBITS

Exhibit 1: Calculated Abnormal Returns (AR) on the S&P 500 Model

	S&P 500						
Event Day	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**
AAR	-0.37%	0.00%	0.22%	1.30%	0.73%	0.06%	0.33%
t-test	-1.50	0.01	0.58	1.87	0.97	0.14	1.36
CAAR	-0.37%	-0.37%	-0.15%	1.14%	1.87%	1.93%	2.26%
1 VRTX	0.30%	4.09%	1.06%	3.96%	3.40%	-0.65%	-3.95%
2 JNJ	-0.42%	0.18%	-0.14%	0.36%	-0.29%	0.09%	0.44%
3 PCYC	-1.75%	-0.01%	1.09%	-0.80%	9.28%	3.93%	8.54%
4 NVS	0.73%	-1.53%	0.16%	1.28%	-0.78%	1.39%	1.06%
5 JNJ	-0.33%	0.06%	-0.36%	-1.61%	0.17%	-0.18%	0.03%
6 PCYC	-2.97%	-1.22%	-0.86%	0.54%	-2.88%	1.44%	-0.77%
7 PFE	0.15%	-0.52%	-0.62%	1.45%	1.96%	0.31%	1.56%
8 MRK	1.44%	0.60%	0.83%	-1.42%	-1.52%	1.19%	-0.56%
9 BMY	1.33%	-0.13%	-2.21%	-3.48%	0.09%	-1.68%	-0.87%
10 JNJ	-0.17%	0.00%	-0.69%	-0.81%	0.44%	-0.03%	-1.50%
11 ABBV	-0.57%	-4.51%	0.39%	-0.64%	-0.01%	-3.80%	1.76%
12 GEVA	-8.24%	1.19%	-1.13%	-2.32%	1.91%	3.45%	1.46%
13 ALXN	-1.09%	-0.27%	-0.54%	1.51%	-1.09%	1.65%	-1.94%
14 NVS	-0.67%	-1.09%	-1.53%	-0.78%	-1.20%	0.20%	0.50%
15 GSK	0.39%	-0.38%	0.70%	0.21%	-0.13%	0.17%	0.16%
16 GILD	-1.11%	-0.89%	1.67%	1.09%	2.52%	-0.50%	-0.69%
17 NVS	0.46%	-0.48%	0.44%	2.31%	-0.30%	0.18%	0.70%
18 CPRX	-5.10%	-2.81%	11.12%	42.84%	-14.26%	5.12%	2.36%
19 GSK	-0.60%	1.57%	0.13%	0.21%	-0.61%	-0.61%	-0.62%
20 MRK	-0.54%	-1.46%	-0.18%	-0.43%	0.56%	-0.91%	0.44%
21 ALXN	-2.46%	0.83%	2.39%	5.86%	6.54%	-1.06%	-0.99%
22 GILD	0.59%	1.88%	0.51%	-1.06%	-1.75%	0.09%	5.11%
23 GILD	-0.12%	-0.22%	0.50%	-0.87%	1.18%	2.48%	-0.67%
24 PTLA	-1.47%	-3.07%	-1.35%	4.38%	-2.41%	-0.41%	2.98%
25 GSK	-1.46%	-0.25%	0.48%	-0.60%	0.13%	0.64%	0.50%
26 GSK	-0.61%	0.21%	-0.27%	-1.02%	0.82%	1.28%	0.67%
27 JNJ	-0.36%	-0.06%	0.77%	-1.32%	0.26%	-0.92%	-0.52%
28 VRTX	-2.25%	0.12%	-0.83%	0.67%	2.84%	-2.97%	1.05%
29 GSK	-1.59%	-0.98%	-0.38%	0.54%	-0.77%	1.67%	0.27%
30 BMY	-1.28%	-0.13%	0.77%	-0.57%	-1.01%	-0.24%	0.00%
31 PFE	-0.33%	0.93%	-0.05%	0.05%	1.17%	-1.63%	0.63%
32 NVS	-0.25%	-1.34%	-0.06%	0.88%	0.69%	-0.29%	1.51%
33 CLDN	-5.30%	-0.86%	17.97%	6.89%	2.69%	-10.31%	2.10%
34 AZN	8.38%	-3.73%	1.46%	1.54%	0.10%	11.75%	-0.42%
35 BMY	0.73%	0.48%	0.35%	0.50%	-4.92%	-0.72%	0.73%
36 BMY	0.48%	-4.93%	-0.74%	0.70%	-0.34%	-1.07%	-0.08%
37 CLVS	0.08%	17.39%	-5.91%	1.08%	1.22%	-4.81%	5.74%
38 INSM	-1.11%	-1.03%	3.26%	-2.08%	42.01%	6.11%	-0.02%
39 AMGN	0.08%	-0.62%	0.01%	0.75%	0.63%	0.80%	-1.45%
40 NVS	0.44%	-0.12%	-0.57%	-1.04%	-0.42%	0.17%	-0.07%
41 ITMN	1.16%	-2.31%	-4.24%	0.30%	-0.02%	4.18%	2.75%
42 ACAD	-2.22%	0.53%	0.47%	13.80%	-1.50%	-0.28%	-0.29%
43 REGN	-1.37%	-0.70%	-0.08%	1.73%	0.72%	0.31%	-1.15%
44 BMY	-0.09%	0.57%	1.05%	-1.82%	1.51%	-0.68%	0.84%
45 ARIA	2.44%	-5.66%	1.27%	11.02%	-4.23%	-5.13%	1.00%
46 MRK	1.56%	0.69%	0.99%	-1.79%	-2.35%	0.83%	1.33%
47 NBIX	0.77%	3.04%	-1.48%	0.14%	-1.37%	-2.16%	-2.71%
48 REGN	0.81%	2.52%	0.47%	-2.70%	-1.07%	0.53%	0.72%
49 SNY	1.92%	1.51%	-0.33%	-3.17%	1.02%	0.27%	0.93%
50 ICPT	5.49%	7.45%	-5.79%	-0.03%	19.79%	-7.27%	-1.07%

51 BLUE	-2.22%	1.24%	-5.31%	-4.34%	-7.79%	-1.92%	-1.05%
52 CLDX	1.28%	-2.51%	-2.04%	16.06%	2.06%	-2.43%	-0.49%
53 ATRA	-3.90%	0.13%	-7.16%	2.99%	7.25%	20.28%	7.24%
54 CLVS	-0.36%	-4.13%	-3.04%	-2.40%	7.80%	2.14%	-2.73%
55 MRK	0.20%	-0.30%	0.62%	-0.64%	0.20%	-0.65%	-0.54%
56 DBVT	-1.28%	-0.38%	6.68%	5.28%	-3.43%	-4.43%	0.32%
57 PFE	-0.11%	0.37%	-0.95%	-0.34%	-0.41%	0.93%	-0.55%
58 ABBV	-1.83%	0.24%	0.23%	0.71%	0.76%	-0.78%	0.60%
59 PFE	-0.06%	0.38%	-0.27%	0.49%	1.43%	-0.75%	-0.14%
60 SNY	-0.54%	1.06%	2.35%	0.57%	-2.50%	0.57%	-0.24%
61 DYAX	-0.73%	-1.95%	0.73%	-1.00%	-2.67%	0.91%	2.56%
62 BMY	-0.67%	-0.30%	0.84%	-1.24%	0.88%	-1.17%	-2.38%
63 NVS	-0.13%	0.37%	-0.43%	0.05%	-0.50%	-0.78%	0.79%
64 PGNX	0.19%	8.51%	-0.63%	0.94%	-11.94%	0.09%	2.47%
65 EXEL	1.10%	-1.40%	4.01%	5.38%	5.13%	-2.26%	1.23%
66 BMY	-0.37%	-1.01%	0.86%	0.62%	-1.53%	-0.90%	0.47%
67 BMY	0.35%	0.35%	0.25%	1.65%	1.22%	5.14%	-2.97%
68 LLY	-3.28%	-2.69%	-1.34%	-1.47%	2.46%	-8.20%	0.65%
69 PFE	0.64%	1.60%	0.48%	0.21%	-1.33%	-1.02%	-2.11%
70 MRK	1.79%	-0.32%	0.20%	-0.43%	-0.25%	1.20%	-0.69%
71 TEVA	-0.74%	-0.98%	-1.26%	-0.17%	0.10%	-1.24%	-0.57%
72 MRK	1.32%	-0.33%	0.24%	-0.76%	0.29%	-0.69%	0.04%
73 PFE	0.84%	-1.97%	-0.75%	-0.44%	-2.96%	-0.78%	-2.53%
74 KITE	-2.98%	-0.32%	1.68%	-1.96%	1.00%	-0.72%	-2.69%

Exhibit 2: Calculated Abnormal Returns (AR) on the DRG Index Model

	DRG Index						
Event Day	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**
AAR	-0.42%	-0.02%	0.15%	1.32%	0.85%	0.06%	0.37%
t-test	-1.82	-0.05	0.41	1.95	1.16	0.15	1.58
CAAR	-0.42%	-0.44%	-0.29%	1.03%	1.88%	1.94%	2.31%
1 VRTX	2.34%	3.20%	0.95%	3.27%	2.36%	-0.99%	-3.98%
2 JNJ	0.23%	0.12%	0.31%	0.24%	-0.19%	0.24%	0.15%
3 PCYC	-0.22%	-0.04%	2.17%	-1.07%	9.53%	4.31%	7.78%
4 NVS	0.46%	-1.32%	0.16%	1.09%	-0.31%	1.01%	0.62%
5 JNJ	-0.69%	0.31%	-0.24%	-1.46%	0.26%	-0.34%	-0.43%
6 PCYC	-3.93%	-0.75%	-0.87%	0.94%	-2.68%	1.56%	-1.40%
7 PFE	0.39%	-0.24%	-0.46%	1.14%	1.07%	0.14%	-0.17%
8 MRK	0.83%	0.82%	0.48%	-0.44%	-0.76%	1.04%	-1.03%
9 BMY	1.61%	-0.20%	-1.38%	-2.75%	-0.11%	-1.93%	0.56%
10 JNJ	-0.32%	-0.20%	0.32%	-0.40%	0.51%	0.43%	-0.52%
11 ABBV	-0.46%	-4.17%	1.15%	0.38%	0.07%	-3.59%	1.59%
12 GEVA	-8.47%	1.48%	0.46%	-1.99%	1.03%	1.88%	1.48%
13 ALXN	-2.20%	-0.24%	-0.87%	1.60%	-0.27%	1.66%	-1.63%
14 NVS	-0.45%	-0.56%	-0.51%	-0.81%	-0.77%	0.29%	-0.15%
15 GSK	0.86%	-0.29%	-0.03%	0.23%	0.49%	0.11%	0.25%
16 GILD	-1.41%	-1.29%	1.14%	1.09%	2.24%	-0.81%	-0.44%
17 NVS	0.41%	-0.42%	0.02%	2.25%	0.07%	0.50%	0.64%
18 CPRX	-2.51%	-1.16%	12.19%	42.84%	-12.35%	6.99%	3.63%
19 GSK	-0.74%	1.07%	0.24%	0.33%	-0.74%	-0.68%	-0.88%
20 MRK	-1.21%	-0.99%	-0.11%	-1.09%	0.41%	-1.06%	0.37%
21 ALXN	-2.35%	-0.36%	2.00%	5.60%	6.46%	-1.31%	-0.94%
22 GILD	-0.59%	1.47%	0.26%	-1.12%	-2.00%	0.17%	5.17%
23 GILD	0.33%	-0.18%	0.40%	-0.99%	0.80%	1.86%	-0.23%
24 PTLA	-2.21%	-2.57%	-1.64%	4.36%	-1.57%	0.43%	2.05%

25 GSK	-1.29%	-0.75%	0.33%	-0.31%	0.20%	0.74%	0.28%
26 GSK	-0.91%	-0.29%	-0.51%	-1.30%	0.45%	1.59%	0.35%
27 JNJ	0.14%	-0.48%	0.64%	-1.39%	0.69%	-1.19%	-0.13%
28 VRTX	-1.42%	0.65%	-1.53%	0.99%	2.21%	-2.80%	0.34%
29 GSK	-1.47%	-1.28%	-0.32%	0.06%	-0.85%	1.41%	0.75%
30 BMY	-1.20%	-0.73%	0.94%	-0.62%	-1.60%	-0.20%	0.02%
31 PFE	-0.20%	0.87%	0.12%	1.08%	1.70%	-1.03%	-0.04%
32 NVS	-0.36%	-0.89%	-0.16%	1.11%	1.25%	-1.13%	1.89%
33 CLDN	-5.43%	-0.67%	17.92%	6.89%	2.68%	-10.48%	2.01%
34 AZN	7.15%	-4.77%	1.49%	2.13%	-0.30%	10.45%	-0.29%
35 BMY	1.05%	1.11%	0.08%	0.09%	-5.44%	-0.28%	1.78%
36 BMY	0.07%	-5.45%	-0.30%	1.76%	-0.71%	-1.01%	0.07%
37 CLVS	-0.33%	16.93%	-5.43%	2.34%	0.90%	-4.88%	5.88%
38 INSM	-1.80%	-0.56%	2.97%	-1.81%	42.21%	6.05%	-1.12%
39 AMGN	-0.10%	-0.24%	0.18%	0.67%	0.03%	1.45%	-1.09%
40 NVS	0.29%	-0.49%	-0.27%	-0.77%	-0.23%	0.33%	-0.41%
41 ITMN	1.23%	-1.45%	-3.55%	-0.79%	0.34%	4.18%	2.81%
42 ACAD	-1.36%	0.34%	0.72%	10.39%	-0.22%	0.23%	-0.32%
43 REGN	-1.38%	-1.37%	-0.35%	1.75%	0.41%	0.21%	-1.03%
44 BMY	0.16%	0.16%	0.36%	-1.19%	1.32%	-0.69%	0.41%
45 ARIA	1.96%	-5.75%	-0.01%	12.12%	-3.93%	-4.93%	1.38%
46 MRK	0.65%	0.44%	0.43%	-1.70%	-0.55%	0.99%	-0.33%
47 NBIX	0.88%	5.23%	-1.29%	-1.67%	-0.35%	-2.05%	-3.58%
48 REGN	0.13%	1.38%	0.48%	-1.62%	-0.90%	0.94%	0.35%
49 SNY	1.33%	0.35%	-0.24%	-2.31%	0.97%	0.53%	0.67%
50 ICPT	5.10%	5.73%	-5.78%	-0.28%	20.84%	-6.42%	0.09%
51 BLUE	-3.54%	2.09%	-6.31%	-2.87%	-6.09%	-2.13%	-0.23%
52 CLDX	1.53%	-2.86%	-2.59%	15.64%	2.26%	-2.66%	-0.95%
53 ATRA	-3.61%	0.04%	-8.01%	2.85%	6.42%	18.79%	6.66%
54 CLVS	0.78%	-4.02%	-2.87%	-2.00%	6.94%	1.35%	-3.09%
55 MRK	0.26%	-0.12%	-0.04%	-1.34%	-0.17%	-1.18%	0.20%
56 DBVT	-1.09%	-0.90%	6.16%	5.02%	-3.80%	-3.87%	0.03%
57 PFE	0.19%	-0.18%	-0.25%	-1.19%	0.07%	0.79%	-0.30%
58 ABBV	-2.01%	0.07%	0.60%	1.15%	1.20%	-1.55%	-0.03%
59 PFE	0.21%	0.45%	-0.52%	0.03%	1.69%	-0.73%	0.02%
60 SNY	-0.52%	1.26%	2.22%	0.42%	-1.95%	0.48%	-0.06%
61 DYAX	-1.00%	-2.05%	0.81%	-0.92%	-3.00%	0.47%	1.81%
62 BMY	-0.46%	0.07%	0.59%	-0.82%	0.99%	-1.85%	-1.95%
63 NVS	-0.05%	0.28%	-0.10%	0.23%	-0.45%	-0.61%	0.42%
64 PGNX	-0.95%	8.46%	-1.97%	1.46%	-11.16%	0.44%	1.41%
65 EXEL	0.09%	-1.78%	2.40%	3.03%	4.76%	-0.19%	3.15%
66 BMY	0.26%	-0.33%	0.52%	0.58%	-0.96%	-0.87%	0.38%
67 BMY	0.46%	0.44%	0.31%	1.74%	0.16%	4.71%	-0.92%
68 LLY	-1.51%	-1.38%	-0.81%	-1.22%	2.29%	-8.08%	1.84%
69 PFE	-0.47%	0.86%	-0.60%	0.68%	0.77%	-0.22%	-0.33%
70 MRK	1.28%	0.24%	0.05%	-0.79%	0.36%	1.21%	-0.61%
71 TEVA	-0.59%	-0.87%	-0.52%	0.28%	-0.12%	-1.10%	0.16%
72 MRK	0.16%	0.29%	-0.48%	-0.70%	0.40%	-0.79%	0.83%
73 PFE	-0.28%	-1.48%	-1.50%	-0.56%	-2.83%	-0.93%	-1.67%
74 KITE	-3.14%	-1.34%	1.03%	-1.99%	0.34%	-0.67%	-2.59%

Exhibit 3: Clinical Research Phase Studies[9]

Phase I
Purpose: Safety and dosage
During Phase 1 studies, researchers test a new drug in normal volunteers (healthy people). In most cases, 20 to 80 healthy volunteers or people with the disease/condition participate in Phase 1. However, if a new drug is intended for use in cancer patients, researchers conduct Phase 1 studies in patients with that type of cancer.
Phase 1 studies are closely monitored and gather information about how a drug interacts with the human body. Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can tolerate and what its acute side effects are.

As a Phase 1 trial continues, researchers answer research questions related to how it works in the body, the side effects associated with increased dosage, and early information about how effective it is to determine how best to administer the drug to limit risks and maximize possible benefits. This is important to the design of Phase 2 studies.

Phase II
Purpose: Efficacy and side effects
In Phase 2 studies, researchers administer the drug to a group of patients with the disease or condition for which the drug is being developed. Typically involving a few hundred patients, these studies aren't large enough to show whether the drug will be beneficial. Instead, Phase 2 studies provide researchers with additional safety data. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols.

Phase III
Purpose: Efficacy and monitoring of adverse reactions
Researchers design Phase 3 studies to demonstrate whether or not a product offers a treatment benefit to a specific population. Sometimes known as pivotal studies, these studies involve 300 to 3,000 participants. Phase 3 studies provide most of the safety data. In previous studies, it is possible that less common side effects might have gone undetected. Because these studies are larger and longer in duration, the results are more likely to show long-term or rare side effects.

Phase IV
Purpose: Safety and efficacy
Phase 4 trials are carried out once the drug or device has been approved by FDA during the Post-Market Safety Monitoring.

VII. END NOTES

[1] Food and Drug Administration Safety and Innovation Act, January 2013.

[2] US Food and Drug Administration, Guidance for Industry, Expedited Programs for Serious Conditions, May 2014.

[3] Adapted from "US Food and Drug Administration, Guidance for Industry, Expedited Programs for Serious Conditions, May 2014".

[4] US Food and Drug Administration, Guidance for Industry, Expedited Programs for Serious Conditions, May 2014.

[5] US Food and Drug Administration, Guidance for Industry, Expedited Programs for Serious Conditions, May 2014.

[6] Cost of Developing a New Drug, Tufts Center for the Study of Drug Development (CSDD). R&D Cost Study Briefing; November 18, 2014.

[7]http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/ucm373559.htm

[8] http://www.businessdictionary.com/definition/Standard-Poor-s-500-composite-index-S-P-500.html#ixzz3yNcqhZyn

[9] http://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm

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