EVENT STUDY ON DRUG APPROVALS - IMPACT OF ORPHAN DRUG APPROVALS ON THE SHAREHOLDER VALUE OF PHARMACEUTICAL COMPANIES

JAN-LUCA ROLF, B.A.

Jan-Luca Rolf follows a Master's program at Heinrich Heine University in the field of public health. He works in market access at a biopharmaceutical company.
Institution 1

GIANFRANCO MAROTTA, DBA, M.Sc.

(ORCID Code: 0000-0002-1135-511X)
Gianfranco is a Ph.D. student at UCAM University. He works as Head of Finance and is a lecturer at IU University.
Institution 1+2

ALEXANDER ZURECK, Prof. Dr.

Alexander Zureck is a Professor at FOM University.
Institution 1

Institution:

1 FOM University of Applied Sciences, ISF - Institute for Strategic Finance, Herkulesstr. 32, 45127 Essen, German

2 Universidad Católica San Antonio de Murcia (UCAM), Avda. de los Jerónimos, 135, 30107 - Guadalupe (Murcia), Spain

ABSTRACT

The pharmaceutical industry is controversially discussed. Nevertheless, there is a con-sensus that the need for new medicines is undeniable. In particular, the treatment of rare diseases with orphan drugs is characterized by a high unmet medical need. Regulatory incentive schemes seek to stimulate orphan drug research and development (R&D). This is also reflected in the increasing approvals during the last two decades. Orphan drugs have gained relevance and become a more attractive business for pharmaceutical compa-nies (Blonda et al., 2021, p. 2)

Keywords: #Event-Study; Pharmaceutical Industry; # Rare Diseases; #Shareholder Value

1.0 INTRODUCTION

The pharmaceutical industry is controversially discussed. Nevertheless, there is a con-sensus that the need for new medicines is undeniable. In particular, the treatment of rare diseases with orphan drugs is characterized by a high unmet medical need. Regulatory incentive schemes seek to stimulate orphan drug research and development (R&D). This is also reflected in the increasing approvals during the last two decades. Orphan drugs have gained relevance and become a more attractive business for pharmaceutical compa-nies (Blonda et al., 2021, p. 2).

Patients and physicians are the primary beneficiaries of newly approved drugs for treat-ing rare diseases (Weber & Grüters-Kieslich, 2017, p. 477). The question arises of whether the unique value of orphan drugs is also reflected in investors' views.

To answer this question, this paper analyzes the impact of orphan drug approvals on the shareholder value of pharmaceutical companies. The specific objectives of the authors lie in answering the following questions:

I.   First, do orphan drug approvals have an impact on the stock prices of phar-maceutical companies?

II. Second, can we observe relationships between abnormal return (AR) and specific characteristics of pharmaceutical manufacturers?

An event study on European approvals of orphan drugs was conducted to answer these research questions. The Association of Research-Based Pharmaceutical Companies (vfa) and the European Medicines Agency (EMA) website provide the data on drug approv-als, including their exact approval date and the respective pharmaceutical company. Fi-nancial data were drawn from the Refinitiv database. Regarding the event study, an event period of three days was defined to analyze the influence on a company's share price, for which an AR was subsequently calculated using the Market Model (MM). The results were tested for significance with a parametric testing procedure and interpreted accordingly.

2.0 THEORETICAL BASELINE

2.1 Theoretical Background of Orphan Drug Approvals

2.1.1 Drug Development: From Target to Approval

The drug development process is cumbersome. The process can take up to 15 years and is connected to several substantial uncertainties and development risks. The uncertainty derives from the fact that only a small number of drugs that make it to the clinical stud-ies reaches the final approval for market entry at the end of the process (Tamimi & Ellis, 2009, pp. 125–126). Generally, the drug development process has five phases (Chuang-Stein & Kirby, 2017, p. 3; Réda et al., 2020, p. 241).

1. Preclinical phase
2. Clinical studies: Phase I
3. Clinical studies: Phase II
4. Clinical studies: Phase III
5. Regulatory review & drug approval

The European system builds on the collaboration between the different national authori-ties in the EU member states and the EMA, whereby the EMA, as an umbrella organiza-tion, coordinates scientific resources and has a network of experts (Peterson & Shackle-ton, 2012, p. 233). Prior to the market entry, drugs in the EU need to be reviewed by the EMA. As the central regulatory agency, the EMA evaluates medical products like drugs in the EU (Gupta, 2011, p. 73).

For the scope of this paper, it is essential to distinguish between Orphan Designation and Marketing Authorization. The latter solely describes the acceptance of an orphan status of a drug, and market authorization enables the manufacturer to offer the drug on the market (EMA, n.d.-g, n.d.-e). This paper often uses the generic term drug approvals when discussing marketing authorization. When approving drugs, it is differentiated between the centralized and the decentralized procedure (Peterson & Shackleton, 2012, p. 233). The centralized authorization process allows a medicinal product to be approved for the whole EEA. The centralized approach is binding for most novel drugs, medicinal products derived from biotechnological processes, and orphan drugs (Scholz, 2015, p. 13).

Before an application is submitted to the EMA for centralized approval procedures, a pre-submission meeting is usually arranged with the EMA to clarify open questions. Af-ter that, the manufacturer shares a letter of intent, providing advance information about plans for official approval. As a basis for the approval decision, the EMA receives an approval application from the manufacturer containing data on toxicology, pharmacolo-gy, and human testing (Ng, 2015, pp. 4–5). The information usually amounts to more than 500,000 pages submitted via DVD or secured internet servers (vfa, 2018). In col-laboration with the respective committee, the EMA then prepares a recommendation for the European Commission (EC), which is issuing a final decision within 67 days.

This risky, costly, and cumbersome development pathway underpins research interest in the impact of regulatory approval on the shareholder value of pharmaceutical companies.

2.1.2 Characteristics of Rare Diseases

For a drug to be classified as an orphan drug, it must fulfill specific criteria defined by the European EMA. The drug should be intended to treat or prevent chronically debili-tating or life-threatening diseases. In addition, the patient number is a decisive factor. The status also depends on the low probability that the drug's marketing does not com-pensate for the high investment costs that pharmaceutical companies must put in R&D (EMA, n.d.-g). The latter includes tropical diseases or diseases that affect people, espe-cially in developing countries. What they have in common with rare diseases is their ne-glect and the high level of patient need. Thus, not only drugs for the therapy of rare dis-eases can obtain an orphan drug designation (Wastfeld et al., 2006, p. 3). Finally, a drug cannot obtain orphan status if a treatment for the specific disease already exists, and the drug-seeking orphan designation cannot show an additional benefit against the compara-tor therapy (EMA, n.d.-g).

Concerning the patient number, a rare disease is typically defined as a disease that af-fects only a few people compared to other diseases common in the population. Estima-tions go up to 8.000 rare diseases worldwide, although these are estimates (Richter et al., 2015, p. 907; Wetterauer & Schuster, 2008, p. 519; Wilson, 2013, p. 10). About 80% of rare diseases are attributed to a genetic origin, and in 50-75% of the cases, children are affected. Every third child born with a rare disease does not live beyond five before dying (Wright et al., 2018, p. 253). Even though rare diseases come in various forms, their characteristics are often similar, as shown in the figure below.

Figure 1: Characteristics of Rare Diseases
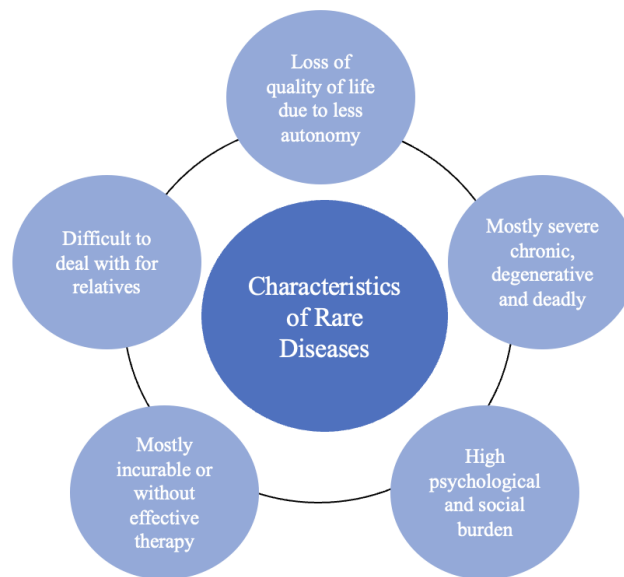
Own illustration based on (Mücke & Conrad, 2021, p. 15)

Apart from the general description of rare diseases, their characteristics, and challenges, it is to be mentioned that the definition of a rare disease in numbers varies between dif-ferent regions since some diseases are more common in certain areas but less common in others (Graf von der Schulenburg & Frank, 2015, p. 113).

Table 1: International Comparison of Rare Disease Classifications

	Affected patients in region	Relative prevalence
EU	< 230,000	< 5 patients per 10,000 inhabitants
USA	< 200,000	< 7.5 patients per 10,000 inhabitants
Australia	< 2,000	< 1.2 patients per 10,000 inhabitants
Japan	< 50,000	< 4 patients per 10,000 inhabitants

Own table based on Hübel et al., 2012, p. 33; Orphanet, n.d., n.d.

The diagram below can be used to understand the disease areas in which orphan drugs have already been approved.

Figure 3: Orphan Drug Approvals by Therapeutic Area in the EU
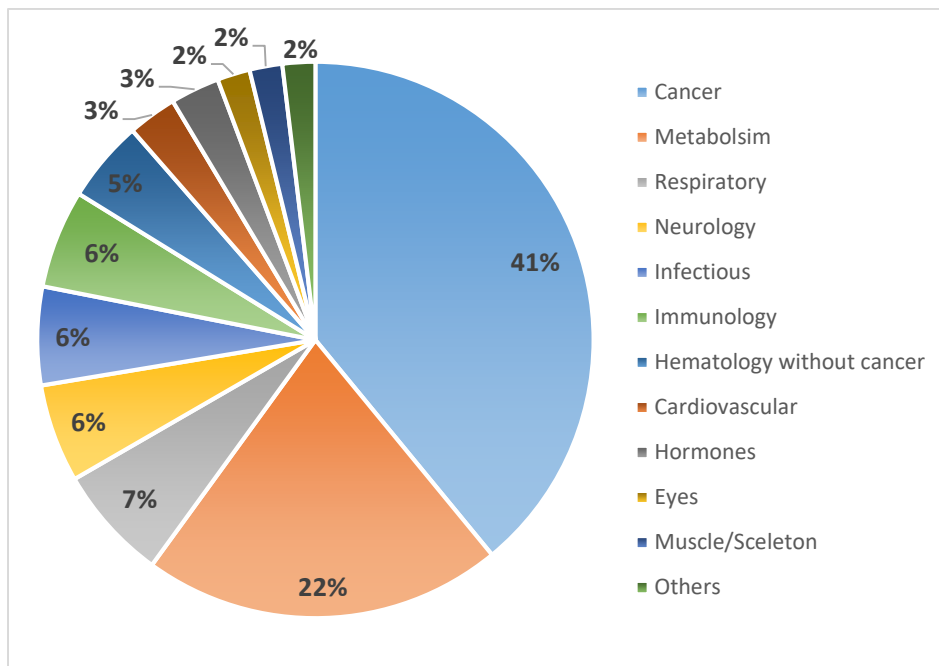
Own illustration based on vfa, n.d.

The diagram shows that orphan drugs are primarily approved for the oncological area (41%), followed by metabolism (21%). The relative orphan drug approvals for the re-maining disease are below 10%, with immunology, infectious diseases, and neurology still having the most treatment options, with 6% each of the European market.

Patients with apparent symptoms can be treated in a targeted and efficient manner. In contrast, in the case of patients with rare diseases, it is often unclear what the patient is suffering from. Consequently, the patient must undergo unnecessary assessments and numerous setbacks until a diagnosis (Weber & Grüters-Kieslich, 2017, p. 477). Today, there is still a large knowledge gap on the clinical side, as only a few centers conduct concentrated research on rare diseases. Critical problems for researchers include assem-bling patient cohorts to conduct clinical trials and funding research, typically sparse for rare diseases (Stoller, 2018, pp. 1310–1311). The dilemma is the uncertainty from pa-tients and physicians and the economic component when treating rare diseases. There are small target markets due to low patient numbers, and the industry faces high devel-opment costs and challenges in generating evidence. As a result, therapies for rare dis-eases are costly for the healthcare system (Taylor et al., 2018, p. 117).

2.1.3 Literature Review of Investors' Perspectives on Orphan Drugs

As argued, the development of orphan drug research is highly valued by physicians, regulatory boards, and patients. However, investors' perspective regarding orphan drugs is still to be examined more deeply.

In general, research shows that the valuation of SMEs is mainly influenced by the de-velopment phase of the company's portfolio. It applies that the further the products are in the development stage, the lower the risk of failing to enter the market. According to Michaeli et al., economic and clinical incentives for companies to do R&D for orphan drugs create an attractive risk-

return profile for investors (Michaeli et al., 2022, pp. 315–319). Another study in the American area analyzed the effect of the generally good conditions for orphan drug developments on investor behavior. It was found out that the orphan drug incentives of market exclusivity, tax credits, the lowering of R&D costs, and a short-term balance sheet all together send positive signals to investors even though it was not possible to measure which incentive showed the most substantial im-pact (Gorry & Useche, 2017, p. 17).

A study on orphan drug designation analyzed investor behavior related to the Food and Drug Administration's (FDA) publication of orphan drug designation. Regarding posi-tive FDA decisions, the investors reacted instantly, significantly increasing the compa-ny's value. Even though these results were primarily found for smaller companies and oncological drugs, they show a tendency of the investors' positive reaction to a compa-ny obtaining orphan status for their drug (Miller, 2017, pp. 3–6). For completeness, it must be mentioned that said results on investors' perception of orphan drugs are linked to the American market. Nonetheless, the results give an idea of the general investor interest in orphan drugs.

According to the presented research, it can be concluded that investors, in general, have a positive attitude toward orphan drugs. Consequently, this paper further assesses whether the study results are still valid today and if orphan drugs, respectively, their approval in the European region leads to an increase in a company's value.

3.0 METHODOLOGY

3.1 Framework Event Study

Event studies are often used in Accounting and Finance (MacKinlay, 1997, p. 38). James Dolley's work about the effect of stock splits on returns in 1933 constitutes the first research using the event study methodology (Dolley, 1933, p. 513-529). These studies are commonly used to assess an event's information content by analyzing the behavior of a security price around the specific event. Event studies can also be con-ducted to test market efficiency (Bowman, 1983, p. 562).

Our paper mainly follows Mackinlay's event study approach and therefore breaks down the methodology into six steps: (MacKinlay, 1997, pp. 14–38):

1. Definition of the object of investigation (event)

The scope of this paper is to conduct an event study on the effect of orphan drug ap-provals by the EMA on the shareholder value of a pharmaceutical company. Hence, to mention the study does not include the FDA approval of the identical drug.

2. Definition of the database and sources of information

The general database originates from the web page of the vfa. The event study looks at all orphan drugs approved until the 6th of September 2022. The database contains differ-ent information such as indication, substance, brand name, month of approval, market-ing authorization date, orphan drug status, pharmaceutical company, number of people in the EU that suffer from disease, International Securities Identification Number (ISIN), and

confounding events/reasons for not including into the study. Apart from the marketing authorization date, the ISIN, and the overlapping events column, all the data originate from the vfa (vfa, n.d.).

To ensure data quality, the marketing authorization date is gathered from the web page of the EMA by using the information included in the EPAR (EMA, n.d.-a). According to the EMA, a medical product can only be offered in the EEA when a marketing au-thorization has been granted (EMA, 2019, p. 4). Possible confounding events were then adjusted in the sample to secure the expressive power of the study. Confounding events are, for example, changes in executives, announcements of mergers, or general financial events (McWilliams & Siegel, 1997, p. 637).

Table 2: Sample Filtering

Baseline study sample	269
• Insufficient market or finance data	161
• Insufficient event assignability on the EMA website	31
• Overlapping medicine or indication approvals	18
• Overlap with financial releases	11
• Overlap with Mergers & Acquisition (M&A) events	2
Remaining study sample	46

Own table

## 4.0 DETERMINATION OF THE ESTIMATION AND EVENT WINDOW

Following MacKinlays logic, an event window of two days, meaning the event day and the day after the event, is sufficient for conducting an event study (MacKinlay, 1997, p. 15). McWilliams and Siegel, who examined event studies in the context of management research, point out that the day before the event should also be considered since there is a possibility that information may become known before the official publication (McWilliams & Siegel, 1997, p. 634). Brown and Warner made an equally important finding for the duration of the event period. Their results indicate that testing powers increased when using fewer days within the event window (Brown & Warner, 1985, p. 14; Sturm, 2007, p. 109).

Based on the above findings, an event window of three days is observed for the event study. This approach ensures that the event itself, the possibility of information flow prior to the event, and investors reacting later to the event are covered by the event window without running the risk of weaker test statistics.

Regarding the estimation window, the work of MacKinlay and Sarkar is referenced as both use 120 days for the estimation window (MacKinlay, 1997, p. 15; Sarkar & de Jong, 2006, p. 590).

Especially the case of Sarkar is highly relevant to this paper as his study deals with FDA drug approvals representing scientific intersections to this work (Sarkar & de Jong, 2006). Consequently, the research of this thesis is based on an event window of three days and an estimation window of 120 days. The literature recom-mends defining a gap between the event and the estimation window to prevent estimat-ed parameters from impacting the event (Goerke, 2009, p. 475). For this reason, a gap of 20 days between the event and estimation window was chosen for the study.
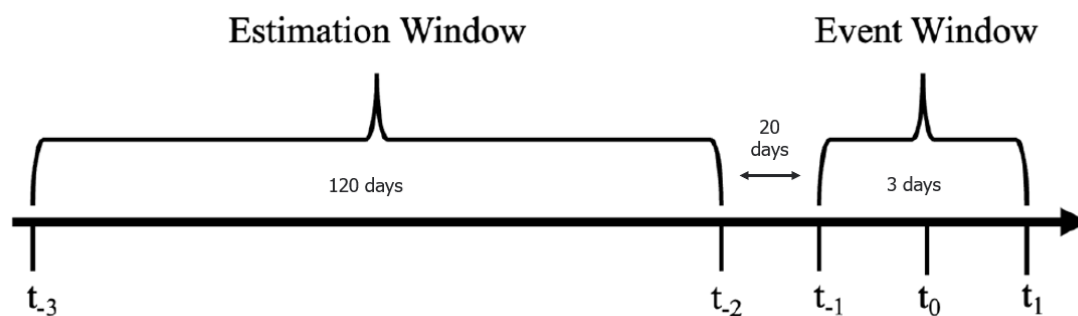
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5.0 SELECTION OF A MODEL TO CALCULATE ABNORMAL RETURNS

Often used when conducting event studies is the market model (MM) (MacKinlay, 1997, p. 19) which refers to a benchmark called market proxy to calculate expected re-turns (Gehrke, 2019, p. 271). For the MM, a linear relation is assumed between the stock and the market returns (MacKinlay, 1997, pp. 15–18).

Implementing the MM requires a certain amount of preparatory work. In the first step, the linear relationship between market returns and stock returns, by estimating alpha and beta, needs to be specified. The common method concerning the MM is the OLS regres-sion, which draws a line that minimizes the deviations between the observed values of the dependent and the independent variable (MacKinlay, 1997, pp. 15–20). For a more detailed explanation, we recommend the paper of Brown and Warner, which discusses possible effects when using an OLS estimation regarding the MM (Brown & Warner, 1985).

Since the MM assumes a linear relationship between the market and the stock return, a benchmark, which is used as a comparative index to the stock, must be selected. Here, selecting a broad index is recommended (MacKinlay, 1997, pp. 15–18). As this study includes pharmaceutical companies from different countries, the global stock indices MSCI World and S&P Global 1200 were set as pre-selection.

Both indices cover different countries and branches, whereby the American market is weighted most heavily, with approximately 69% and 65%. The healthcare sector in both indices is included with about 14% (MSCI World Factsheet, 2022, p. 2; S&P Global 1200 Factsheet, 2022, p. 5). The strong weighting of the American industry coincides with the study sample, as approximately 52% of the stocks included in the study have their country of origin in the United States.

Following the approach of another study, the indices are compared regarding the quality of the benchmark to choose the index that is more consistent with the study data (Sturm, 2007, pp. 187–190). To assess the quality of the indices, the R2 serves as an in-dicator to conduct the index comparison. The R2 also called the coefficient of determi-nation, can measure the fit of the dependent and independent variables in the regression and take values between 0 and 1, respectively, 0% and 100%. An R2 of 1 describes a perfect fit accordingly (Günther & Velten, 2015).

For the study, six orphan drug approvals from different pharmaceutical companies were picked to run a regression with the MSCI World on the one hand and the S&P Global 1200 on the other hand. The regression includes returns from the stock and the index in the event window and 140 trading days in advance. The average R2 and the average adjusted R2 were compared to allow a direct comparison. The adjusted R2 is often used as it includes the number of predictors and the sample size in the calculation and is less susceptible to overestimating the explained variance of the model (Leach & Henson, 2007, p. 2).

Table 3: R^2 Comparison of MSCI World and S&P Global 1200

	MSCI World	S&P Global	Δ%
Average R^2	2.96%	5.77%	~ 49%
Average Adjusted R^2	2.15%	4.99%	~ 56%

Own table

The average R2 of S&P Global is approximately 49% higher than the average R2 from the MSCI World. Looking at the average adjusted R2, it becomes clear that the S&P Global 1200 achieves a higher explanatory share, here about 5%, and thus 56% more than the MSCI World. These testing results conclude that the S&P Global 1200 represents the better fit based on the randomly selected sample. Accordingly, the S&P Global 1200 is used as a benchmark in the event study. The development of the indices is illustrated in the appendix.

6.0 CALCULATION OF ABNORMAL RETURNS

The AR of a stock is obtained from the difference between the realized returns and the expected returns. Researchers can choose between a continuous or discrete approach when calculating a stock's realized return (Rit). The discrete calculation methodology is the more frequently used approach and was also applied in this study (Hauser, 2003, pp. 145–146; Röder, 1999, pp. 13–15). As stated above, the market model (MM) is used in the framework of this paper for the calculation of expected returns.

Since not only one but several stocks are observed within the scope of the study, the literature recommends using the average abnormal returns (AAR). In doing so, one can aggregate the ARs for the whole sample each day in the event window.

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

The numerator includes the sum of the ARs of the stocks i on day t. The denominator divides the sum by the total number of the sample n to get the AAR (Suryanto, 2015, p. 13). When the event window includes more than one day, ARs are summed up to receive the cumulative abnormal return (CAR). Following the logic of the AARs, it may be helpful to aggregate the CARs for the whole study sample to obtain the cumulative average abnormal return (CAAR). The subsequent formula is based on MacKinlay but adjusted by the defined event window (see MacKinlay, 1997, p. 21). Here, t-1 represents the day before the event and t1 the day after the event resulting in a CAAR calculation of three days for the stock i.

$$CAAR = \frac{1}{n}\sum_{i=1}^{n} CAR_i$$

Decision for the methodology of the significance testing and the testing itself

The last step to finalize the event study is testing for significance. For this purpose, nonparametric and parametric tests can be used to test the empirical results on statistical significance (Brown & Warner, 1980, p. 217).

The following is the test statistic of abnormal returns for security i on day t.

$$t_{AR_{it}} = \frac{AR_{it}}{\sqrt{\frac{\sum_{-122}^{-2}(AR_{it} - \overline{AR})^2}{120}}}$$

The $\overline{AR}$ represents the average abnormal return in the estimation period, which amounts to 120 days as stated in the denominator. The CAR can be illustrated as follows:

$$t_{CAR_{it}} = \frac{CAR_{it}}{\sqrt{\frac{\sum_{-122}^{-2}(AR_{it} - \overline{AR})^2}{120}}}$$

The test results are then transformed into the p-value to assess the 1%, 5%, and 10% significance. In addition to the t-tests, correlations between different variables will be examined. The strength of a linear relationship of different variables can be determined using the correlation coefficient.

Hypotheses

In the following, the relevant hypotheses are summarized:

Hypothesis1:
a) The pharmaceutical companies generate positive ARs within the event window

b) The pharmaceutical companies generate positive CARs within the event window

After clinical trials have been conducted and active ingredients have been successfully approved, a rewarding period is anticipated for the respective pharmaceutical compa-nies. These hypotheses assume that the approval of a drug will positively affect the in-vestor perspective and thus increase the share price. The hypothesis is supported by the results of prior event studies investigating drug approvals' effect on pharmaceutical companies' share prices (see Sarkar & de Jong, 2006; Sharma & Lacey, 2004; Sturm, 2007).

In practice, the abnormal returns for every company, each day of the event window, and the cumulative abnormal returns are assessed with the t-test and the respective p-value.

> **Hypothesis2:**
> The larger the number of diseased individuals within the indication in the EU, the higher the CARs in the event window.

The second hypothesis builds on the assumption of the first hypothesis. In addition, it is assumed that more patients in the disease area led to higher ARs since more patients can be treated, and the company can generate more profits. The patient numbers of the dis-ease for which the respective drug is approved are taken from the vfa website (vfa, n.d.).

> **Hypothesis 3:**
> The more recent the approval date, the higher the CARs within the event window.

The third hypothesis assumes that orphan drugs and their relevance in treating rare dis-eases have become better known to the masses and that approval will be reflected more strongly in the security price of pharmaceutical companies.

7.0 RESULTS OF THE EVENT STUDY

7.1 Descriptive Statistics

First, the distribution of drug approvals in the sample over time is shown in the figure below. Most of the drug approvals included in the study occurred in 2021, with nine approvals, and the fewest number can be found in 2019, with only one approval. On average, the study includes 4.6 approvals per year.

Figure 11: Distribution of Event Study Sample from 2013 to 2022
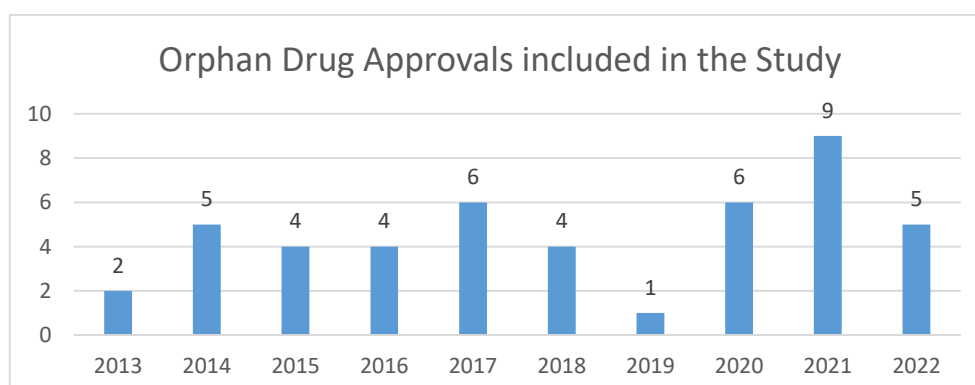
Own chart

Besides the study's approval distribution over time, readers might also be interested in the approval distribution by pharmaceutical companies. In total, 24 different pharmaceu-tical companies were included in the study. 52.17% of the approvals derive from com-panies having the US as their country of origin, 26.08% from Switzerland, 6.5% from Great Britain, and the remaining 15.25% from Sweden, Germany, Australia, Italy, and the Netherlands. With five approvals each within the study, BioMarin Europe, Novartis, and Pfizer are the most represented pharmaceutical companies, closely followed by Roche and Bristol Myers Squibb with four approvals each. Further details can be seen in the appendix.

The number of diseased people for the respective drug approval within the EU is weighted with the following proportions:

- $> 200,000$ diseased in the EU: 17.39% of the study approvals
- $< 200,000$ and > 100.000 diseased in the EU: 10.86% of the study approvals
- $< 100,000$ and > 10.000 diseased in the EU: 58.69% of the study approvals
- less than 10,000 diseased in the EU: 13.04% of the study approvals

7.2 Review of Abnormal Returns

To get a first impression of general trends, the AAR and CAAR were calculated.

Both AAR and CAAR appear to show a similar trend. The rationale for the similar trend is that the CAARs only represent the summed-up AARs within the event window [-1;1].

Figure 4: AAR and CAAR Development in Event Window
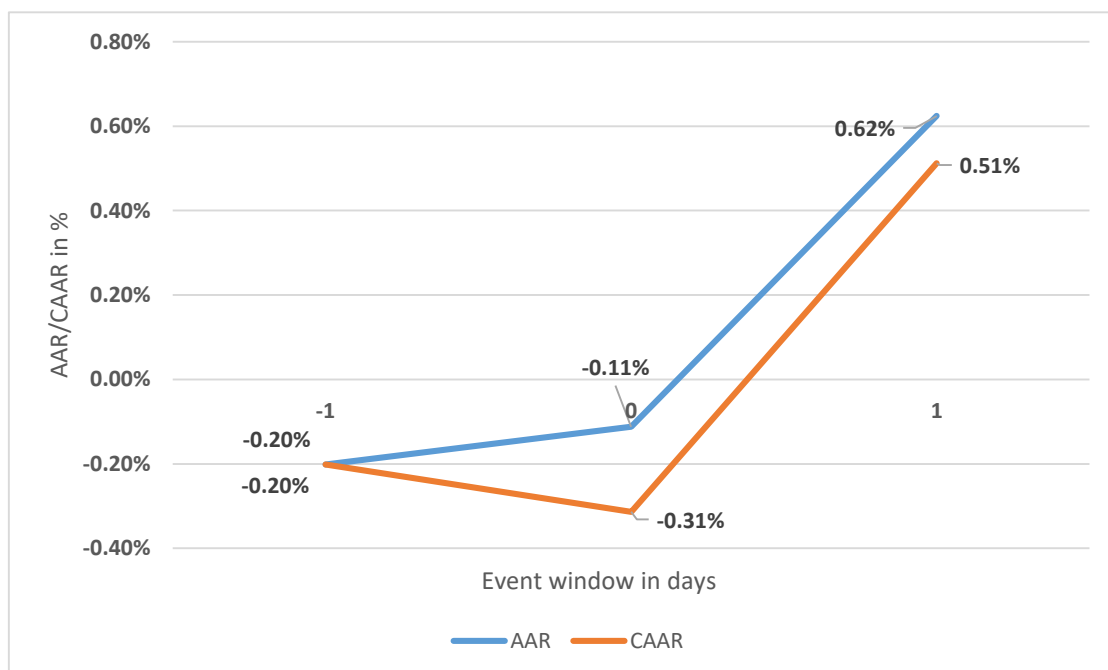
Own chart

The AARs increase slightly up to the event day and increase rapidly the day after. A similar pattern can be observed for the CAARs, although the CAARs on the event day decrease slightly compared to the AARs on the event day. Given the above, an assump-tion can be made that orphan drug approvals influence a pharmaceutical company's share price, mainly shown by an increase in AARs the day after the event. Although no signif-icance was tested, this visualization gives a first tendency.

Hypothesis 1 a) and 1b)

The following table gives an overview of the testing results of the ARs on the day prior to the event, the event date itself, and the post-event date testing at the significance levels of 10%, 5%, and 1.

Table 4: AR and CAR Results of the Event Study

Significance level	AR			CAR
	[-1]	[0]	[1]	[-1,1]
10%	0	0	3	2
5%	1	1	2	2
1%	2	1	2	4
Not Significant	43	44	39	38
Total	46	46	46	46

Own table

First, it can be stated that there are few significant ARs on each day of the event win-dow. Apart from two negative significant returns which occurred at a 1% significance level on the day AstraZeneca obtained approval for Olaparib and at a 10% level when Lilly received approval for Ramucirumab, all the significant ARs derive from positive share price developments.

The average of the significant positive ARs is 2.57% on t-1 and 4.44% and 4.36% on t0 and t1, respectively.

Table 5: AR Results of the Event Study

Day in Event Window	Company	Substance	AR	Significance Level	Average AR
-1	Novartis	Panobinostat	3,26%	1%	2,57%
-1	Lilly	Ramucirumab	1,89%	5%	
0	AbbVie	Venetoclax	2,93%	5%	4,44%
0	Lilly	Olaratumab	5,95%	1%	
1	Basilea	Isavuconazol	7,76%	1%	4,36%
1	Bayer	Riociguat	1,94%	10%	

1	BioMarin Europe	Vosoritid	5,91%	1%	
1	Roche	Polatuzumab Vedotin	2,02%	5%	
1	Santhera	Idebenon	5,39%	5%	
1	Vertex	Tezacaftor	3,16%	10%	

Accordingly, the null hypothesis under hypothesis 1a) that ARs on a given day are not significantly different from zero and appear positive can be rejected for two drug ap-provals on t-1, two on t0, and six on t1.

The data indicates that the drug approval information did not reach most investors until the day after the event. This underscores the plot of the AAR and CAAR, which showed the strongest positive fluctuations the day after the event. Nevertheless, two of the significant positive abnormal returns on the post-event day fall just short of the last significance threshold of 10% and represent weaker statements than the significant ap-provals at a 5% and 1% level.

Besides the AR, the CAR shows significant results for eight drug approvals. Here, two approvals significantly differ from zero at a 10% level, two at a 5% level, and four at a 1% level. The average CAR of the significant positive results within the data sample amounts to 5.43%. The two significant approvals at a 10% level derive from negative CARs, which means that these do not support the study assumptions. This means the null hypothesis for hypothesis 1b) can be rejected for six cases thus 13.04% of the whole study sample.

Concluding the AR and the CAR assessments, it can be stated that significantly positive ARs and significantly positive CARs can be observed during the event window, but most of the orphan drug approvals included in the study did not lead to ARs.

Hypothesis 2

The figure below illustrates the result of the correlation analysis to test the relation be-tween CARs and the diseased individuals in the EU.

**Figure 5: Correlation Analysis between CAR and Diseased in the EU**
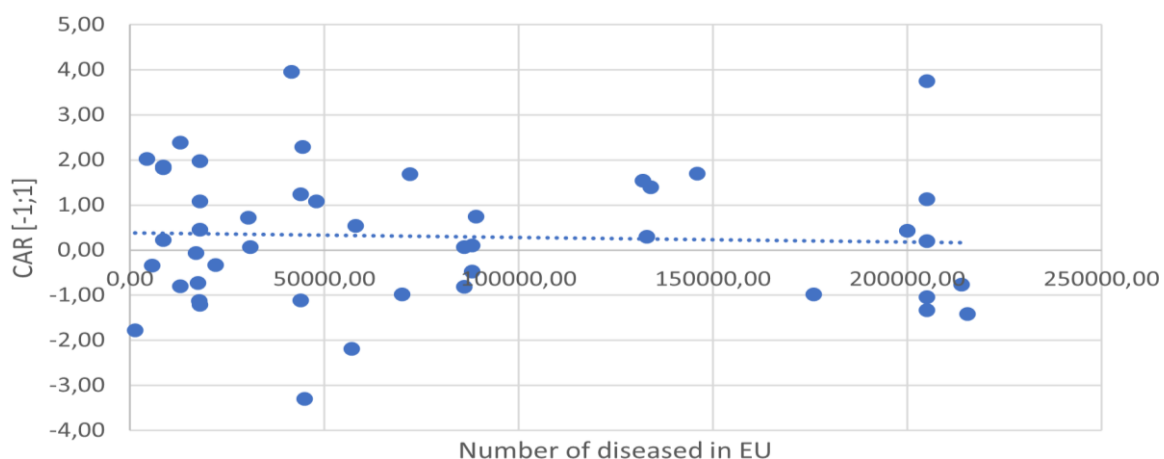
Own chart

On the y-axis, the CARs of the respective drug approval event window represent the variables to be explained, and on the x-axis, the diseased person in the EU represents the explanatory variables. A first look at the scatterplot distribution does not allow any early assumptions regarding a possible correlation. Contrary to the expectations, the data set shows a slightly negative relationship between the two variables, as seen from the trend line. Calculating the correlation coefficient according to Pearson results in a weak nega-tive correlation of -4.77%. The p-value deriving from this result and the respective test statistic is 75.271%, thus summarizing the results based on the study data as insignifi-cant.

Hypothesis 3

Next, the correlation between returns and approval years over time was tested.

Figure 6: Correlation Analysis between CAR and Approval Year
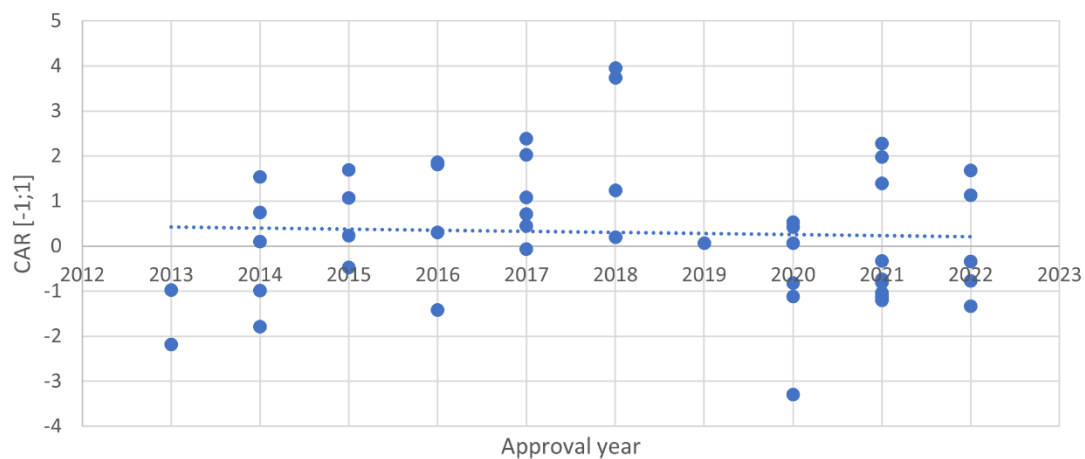
Own chart

The highest CARs can be detected in 2018, reaching CARs up to approximately 4%. The lowest CAR can be seen in 2020, with a negative CAR slightly less than -3%. Comparable to the previous analysis, the trendline shows a negative relation of -4.49% according to the Pearson correlation coefficient, indicating a weak negative correlation. The corresponding p-value is 76.688%, describing the result as statistically insignificant.

Reference to the EMH

To accurately test the EMH, the ARs five days after the event window was observed. From the ten orphan drug approvals that showed significantly positive abnormal returns on one of the days within the event window, five also showed significantly positive ARs five days after the event. The result of information processing on the event day and the day after the event is in line with other event study work, even though most of the significant ARs were observed on the event day itself (Schmidt, 2022a, pp. 135–136). Two out of 46 orphan drug approvals included in the study show significantly positive ARs on the day before the event. However,

the small number of significant results only allows us to make vague assumptions about market efficiency.

7.3 Directions for Further Research

In the following, limitations and ideas to further improve the design of this work are outlined.

Regarding the database, our study was filtered by different overlapping effects. Among other exclusion criteria, overlapping approvals, financial events, or M&A transactions were considered. Another potential exclusion criterium to prevent result distortions could be filtering extreme security price fluctuations. Extreme price reactions in or close to the event window indicate another influential event that may bias the research results. Hence, excluding these events from the data sample can be recommended.

Concerning the event window, we used three days. However, other event studies may use more than one CAR window to make further statements about event effects, such as [-1;0]. [0;1] or [-3;3] to investigate the events CARs more precisely with varying event days. Müller and Reuse 2022 recommend wider event windows of up to 11 days in total [-5;5].

Regarding the market model, we like to highlight that by implementing the model, vari-ous assumptions are made for the OLS regression, which were not discussed in detail. A violation of the assumptions can impact the efficiency of the study result and signifi-cantly distort our findings. To reduce the risk of distorted results, further comparisons against non-parametric models are required. Finally, our study revealed that S&P Global showed a stronger explanatory power than the MSCI World based on the sample test, we recommend assessing our results and future studies against more than one index to obtain more comprehensive and comparable results with the MM.

Since not only the approval itself but also the various steps in the development process of a drug influence the valuation of a company, we recommend analyzing the impact of all phases in earlier development phases in more detail. In addition, it will be interesting to learn how investors perceive the orphan designation process, as this represents the authorities' first recognition of orphan status.

8.0 CONCLUSION

Several papers have examined investors' perceptions of orphan drugs (see Gorry & Useche, 2017; Michaeli et al., 2022; Miller, 2017). We tried to complement prior ambi-tions by solely focusing on European orphan drug approvals, which represent a critical milestone within the life cycle of pharmaceutical companies. We specifically studied the effects of orphan drug approvals on the shareholder value of pharmaceutical companies.

We can summarize that the interest in orphan drugs is not only found among physicians, patients, and clinicians but also among investors. There is a correlation between orphan drugs and investor behavior. Our findings show that investors respond positively to pharmaceutical companies doing R&D in the orphan drug area. Abnormal returns were observed in the event windows, which, although not valid for the entire dataset, indi-cates a trend toward positive

influence. Significant positive CARs were identified for 13.04% of the observed drug approvals, which underlines the existence of an impact on orphan drug approvals.

For investors, it can be concluded that pharmaceutical companies that conduct orphan drug research offer positive abnormal returns. It can be argued that such companies of-fer a comparative appealing risk-return model given incentives such as special market exclusivity or cost reductions, which send positive signals to the investors. In addition, regulatory incentives for orphan drug development make the respective companies an attractive investment opportunity.

Overall, the healthcare sector is experiencing steady revenue growth in orphan drugs, which is expected to continue to increase. Additionally, new technologies, including artificial intelligence, will gain relevance regarding finding new treatment options for rare diseases, which can support and boost the R&D in this sector (Brasil et al., 2019, p. 17). It can be assumed that orphan drugs or therapies for unique and rare diseases will continue gaining more public attention.

Appendix

Figure 8: Index Development of MSCI World and S&P Global 1200 from 2012 to 2022
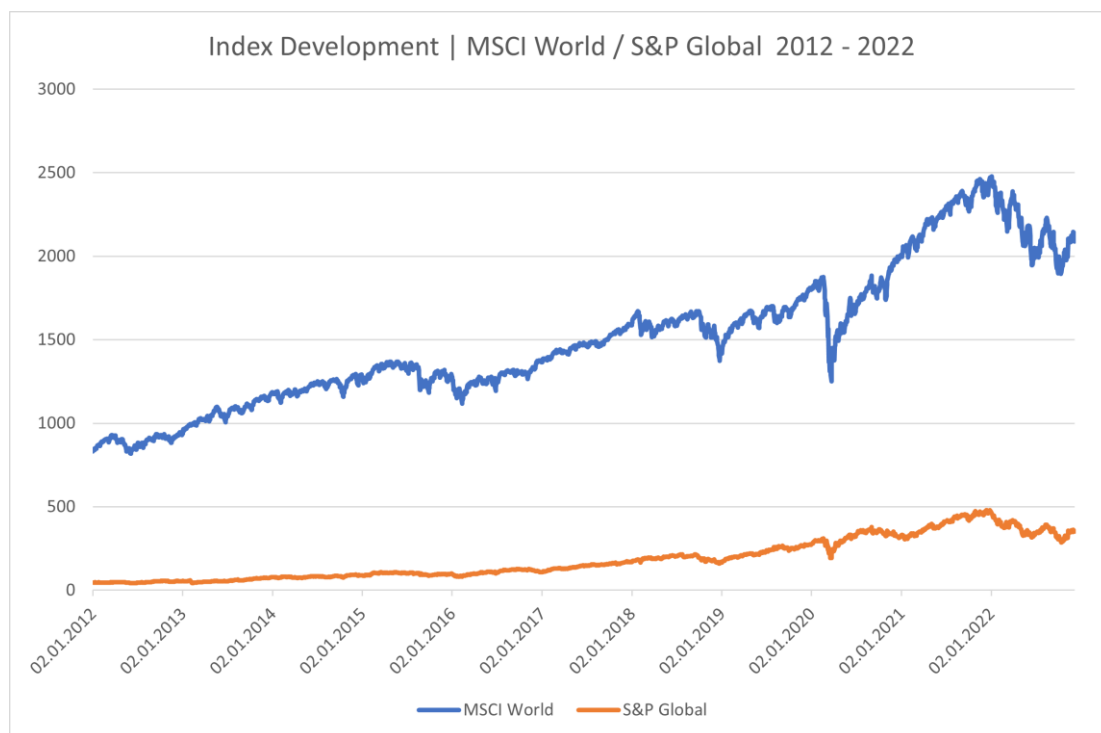
Own chart

The figure shows the value development of the indices according to the NDA_Last_Adjusted historical prices retrieved from Refinitiv between 2012 and 2022. It illustrates a constant positive trend for the two indices, albeit weak for S&P Global 1200.

Table 5: Distribution of Event Study Approvals by Company

Company	Approvals in Study	Company	Approvals in Study
AbbVie	1	Merck	1
AstraZeneca	3	Mylan	1
Basilea	1	Novartis	5
Bayer	1	Pfizer	5
Biogen	1	Recordati	1
BioMarin Europe	5	Roche	4
bluebird bio	1	Santhera	1
Bristol Myers Squibb	4	Swedish Orphan Biovitrum	2
CSL Behring	1	United Therapeutics	2
Gilead	1	Vertex	2
Johnson & Johnson	1	Vifor Pharma	2
Lilly	2		
Total	46		

Own table

Table 6: List of pharmaceutical companies in Study

AbbVie
AstraZeneca
Basilea
Bayer
Biogen
BioMarin Europe
bluebird bio
Bristol Myers Squibb
CSL Behring
Gilead
Johnson & Johnson
Lilly
Merck
Mylan
Novartis
Pfizer
Recordati
Roche
Santhera
Swedish Orphan Biovitrum

United Therapeutics
Vertex
Vifor Pharma

Own table

Figure 8: Correlation Analysis between CAR and Turnover
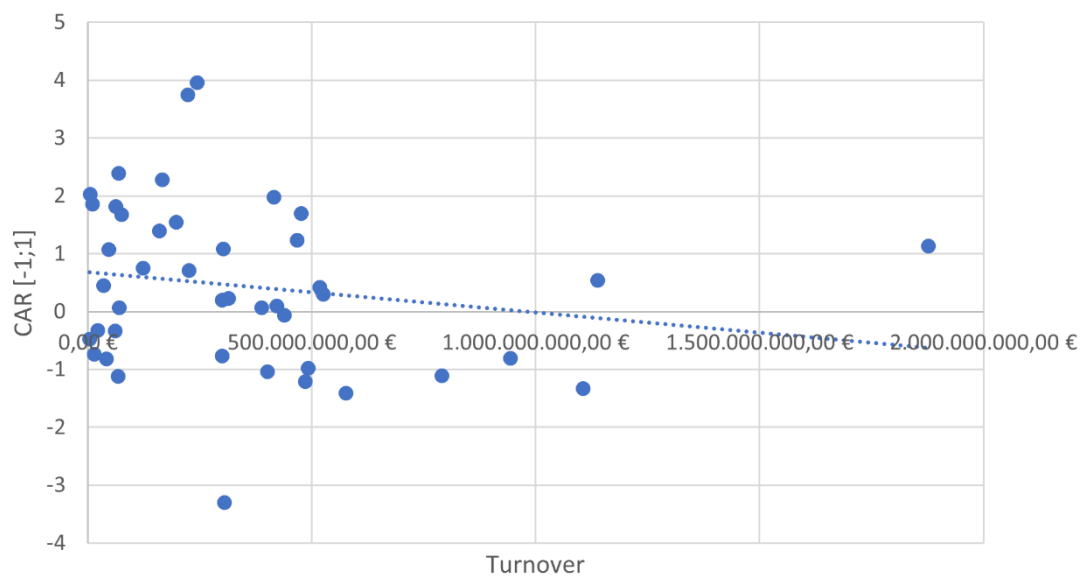
Own chart

As can be seen from the chart, most pharmaceutical companies are in the range of turno-ver values below 500 million. There are only a few outliners which have a turnover value on the event day of more than 1 billion or even 2 billion. The correlation analyses show a negative relation between the size of a company and its abnormal returns. The negative correlation amounts to -17.97%. The respective p-value amounts to 24.89% and indi-cates no significant results for the correlation.

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