BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018587
Article Type:	Research
Date Submitted by the Author:	12-Jul-2017
Complete List of Authors:	Zeitoun, Jean-David; Hôtel Dieu Hospital, Epidémiologie Clinique; Saint-Antoine Hospital, Gastroenterology and Nutrition Ross, Joseph; Yale University School of Medicine, Internal Medicine Atal, Ignacio; Hotel Dieu Hospital, Epidémiologie Clinique Vivot, Alexandre; Hotel Dieu Hospital, Epidémiologie Clinique Downing, Nicholas; Brigham and Women's Hospital and Harvard Medical School, Medicine Baron, Gabriel; INSERM U1153; Hôtel Dieu Hospital, Centre d'Epidémiologie Clinique Ravaud, Philippe; Université Paris Descartes, Centre d'épidémiologie clinique; INSERM U1153
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Research methods, Public health
Keywords:	THERAPEUTICS, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY

Post-marketing trials for novel drugs approved by both the FDA and EMA between 2005 and 2010: a cross-sectional study

Jean-David Zeitoun, MD, MHPM, PhD candidate [1, 2, 3], Joseph S. Ross, MD, MHS [4, 5, 6, 7], Ignacio Atal, MSc [1, 8], Alexandre Vivot [1,8], Nicholas S. Downing, MD [9], Gabriel Baron, PhD [1, 8, 10], Philippe Ravaud, MD, PhD [1, 8, 10, 11]

1. Centre d'Épidémiologie Clinique, Hôpital Hôtel Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France
2. Gastroenterology and Nutrition, Hôpital Saint-Antoine, Assistance Publiques-Hôpitaux de Paris, Paris, France
3. Proctology, Groupe Hospitalier Diaconesses-Croix Saint-Simon, Paris, France
4. Department of Internal Medicine, Robert Wood Johnson Foundation Clinical Scholars Program, Yale School of Medicine, New Haven, Connecticut, USA
5. Department of Internal Medicine, Section of General Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA
6. Department of Health Policy and Management, Yale School of Public Health, New Haven, Connecticut, USA
7. Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Connecticut, USA
8. INSERM UMR 1153, Centre de Recherche Épidémiologie et Statistique Paris Sorbonne Cité (CRESS), METHODS Team, Paris, France
9. Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts
10. Université Paris Descartes, Sorbonne Paris Cité, Paris, France
11. Department of Epidemiology, Columbia University Mailman School of Public Health, New York, New York, United States of America.

Corresponding author: Dr. Jean-David Zeitoun, MD, MHPM, PhD candidate, Centre d'Epidémiologie Clinique, Hôpital Hôtel Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France. E-mail: jdzeitoun@yahoo.fr

Word count: 3520

Abstract: 300

References: 25

Figures: 3

Tables: 2

ABSTRACT

Objectives: To characterize post-marketing trials for drugs that were newly approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Design and Setting: Cross-sectional analysis of post-marketing trials registered in ClinicalTrials.gov until September 2014 for all novel drugs approved by both regulators between 2005 and 2010. Regulatory documents from both agencies were also used.

Primary and secondary outcome measures: All identified post-marketing trials were classified according to the following features: planned enrolment, funding, status, geographical location. We also determined whether trials studied the originally-approved indication.

Results: There were 69 novel drugs approved between 2005 and 2010 that were eligible for inclusion. A total of 6679 relevant post-marketing trials were identified. Median values of the number of trials per drug was 55 (interquartile range [IQR]: 33-119) and of the number of patients to be enrolled per trial was 60 (IQR, 28-183). Industry was the primary sponsor of 2713 trials (40.6%) and involved as a primary or secondary sponsor in 4176 trials (62.5%). We found that 2901 trials (43.4%) were completed, 487 (7.3%) terminated, 1013 (15.2%) were active yet not recruiting, 1895 (28.4%) recruiting, and 319 (4.8%) not yet recruiting. Geographical data showed that 80% of post-marketing trials were conducted in only one country and 84.4% of trials took place in Europe and (or) North America. We found that 2561 post-marketing trials (38.3%) studied another indication than the originally-approved indication. Trials for which industry was a funder were less likely to assess the drug in another indication (54.6% vs. 68.6%; p<0.0001).

Conclusions: Post-marketing pharmaceutical research was found to be highly variable among drugs, predominantly located in North America and Europe. Post-marketing trials were frequently designed to study other indications than the originally-approved one. Although

some findings were reassuring, others question the lack of coordination of post-marketing research.

Strengths and limitations of this study

This is the first study to systematically assess clinical trials performed after marketing approval by the two leading regulators, namely the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

This approach allowed us to examine a substantial number of post-marketing trials over a long time period.

However and due to registration bias, we cannot exclude that some true post-marketing trials were missed and therefore unanalyzed.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: Dr. Zeitoun reports that he serves as an advisor for several consulting firms and communication companies linked with the pharmaceutical industry (Cepton, Oliver Wyman, Roland Berger, McCann Healthcare, Omnicom, Grey Healthcare, Saatchi and Saatchi Healthcare, Sudler& Hennessey, TBWA, inVentiv Health France, Havas). He also reports compensation for lectures given to manufacturer professional associations; collaboration with Mayoly-Spindler, Merck, Teva, Johnson & Johnson, and Menarini; unpaid consultancy for EY; conducting workshops funded by Amgen; and being invited to a French medical congress by AbbVie. Dr. Ross receives support through Yale University from

Johnson and Johnson to develop methods of clinical trial data-sharing; from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting; from Medtronic, Inc. and the US FDA to develop methods for post-market surveillance of medical devices; from the Blue Cross Blue Shield Association to better understand medical technology evaluation; and from the Laura and John Arnold Foundation to support the Collaboration on Research Integrity and Transparency (CRIT) at Yale.

Introduction

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are the two largest and most influential drug regulators worldwide. They tend to maintain similar premarket regulatory standards, and drug manufacturers likely submit the same evidence to both as part of the premarket application process. Drug evaluation continues after regulatory approval, in particular through post-authorization requirements and commitments. Yet these post-marketing clinical studies are limited in number and are not consistently completed. [1–3] This situation raises the question of whether other trials of these drugs after regulatory approval, including those conducted by industry and independent investigators, but not to fulfill regulatory requirements, should be considered part of ongoing, continuous evaluation efforts.

Post-marketing trials are designed with different intent than are premarket trials. Their designs are not systematically submitted to regulatory agencies before initiation because many post-marketing trials are conducted by independent investigators, and their conduct is less rigorously regulated. [4] Post-marketing trials seek to evaluate safety regarding rare events, to assess the real-life effectiveness of novel drugs and to measure their long-term effects. They also permit drug evaluation in different populations, other indications for the same disease, other diseases or with different delivery systems or dosage forms. Moreover, although premarket trials are nearly exclusively sponsored by the manufacturers, post-marketing trials can be funded by manufacturers but also academic or other types of non-profit institutions.

Nevertheless, post-marketing trials have considerable influence on all stakeholders, in particular researchers, practitioners and regulators or decision makers, because they provide cumulative evidence regarding marketed products. However, we lack an overall assessment of post-marketing trials regarding novel drugs. Post-marketing research has been studied for

high-risk devices [5] or even for drugs, but with a focused approach: safety [6,7] or given therapeutic areas. [8–11]Some of those studies produced reassuring results, yet others showed inconsistencies, with gaps in knowledge regarding some issues.

Our research objective was to provide a comprehensive description of post-marketing trials registered in ClinicalTrials.gov, a publicly-accessible clinical trial registry maintained by the US National Institutes of Health over almost a decade for a sample of drugs approved by both the FDA and EMA from 2005 to 2010. We aimed to characterize the total number of trials and patients studied, the geographical location of trials and their status (e.g., completed or ongoing). We also sought to examine differences between the initial label and the specific clinical condition studied in the post-marketing trials.

Methods

Data sources and study sample

We identified all novel drugs approved between January 1, 2005 and December 31, 2010 by both the FDA and EMA through its Centralized Authorization Procedure. For the FDA, Drugs@FDA is a publicly accessible database listing relevant regulatory actions for all approved drugs. [12] For the EMA, information was accessible in the European Public Assessment Reports, which provide a summary of scientific review and list notable regulatory events for all drug submissions.[13] Studies of generic drugs, reformulations, combination therapies and non-therapeutic agents such as radiographic dye were not included. This first search led to a sample of 71 novel drugs approved by both regulators between 2005 and 2010. Two drugs, everolimus and temsirolimus, were excluded because they were associated with an abnormally high number of post-marketing trials involving drug-eluting stents.

Drug and manufacturer characteristics

The following data were retrieved for each drug: agent type (small molecule or biologic), dates of regulatory submissions for both the FDA and EMA, orphan status according to the FDA, orphan designation from the EMA, therapeutic class according to the Anatomical Therapeutic Chemical code, [14] initial label from both regulators, degree of novelty (first-in-class, advance-in-class, addition-to-class) as previously described in a paper from FDA officials [15] and size of the marketing-authorization holder (i.e., manufacturer). This latter information was obtained by personal communication with EMA officials (Dr. Constantinos Ziogas, Small and Medium-sized Manufacturer Office, EMA), who classified manufacturers as large pharmaceutical companies, intermediated-size companies or small- and medium-size companies according to the European Union definition based on headcount and financial turnover or balance sheet total.

Preapproval FDA pivotal trial characteristics

We obtained data for the expected length of treatment and number of patients from pivotal efficacy trials supporting FDA approvals that had been collected for a previous work. [16]

Post-marketing trials

On September 24, 2014, we extracted all trials that were registered at ClinicalTrials.gov for each drug of our sample, regardless of dates and other details. We then excluded trials with the following characteristics: included in the FDA regulatory submission (by a manual review of Drugs@FDA), with inadequate registered status (expanded-access trials, withdrawn trials, suspended trials), and mistakenly extracted (i.e., trials actually not assessing the drug of interest). We decided that all trials whose starting date had preceded the first regulatory submission (to the FDA or EMA) by 1 year or less would be classified as post-marketing trials. Trials that pertained to more than one drug in our sample were manually reviewed so as

to assign them to only one drug for the sake of further statistical analysis. Clinical judgment was applied to choose the "leading" drug in each trial. When we could not determine the leading drug, we used the following rules. If the trial was funded by a marketing-authorization holder of one of the drugs, this drug was considered the leading drug. Otherwise, if the trial involved a drug that was assessed for another indication than the originally approved indication, this drug was considered the leading drug. Finally, when no leading drug could be determined, the drug for which the last regulatory approval had been granted was considered the drug tested and was classified as the leading drug.

For all remaining post-marketing trials, the following data were collected: condition studied, starting date, study sponsors (as a primary sponsor or a collaborator), status at the date of extraction (not yet recruiting, recruiting, active yet not recruiting, enrolling by invitation, completed, terminated), number and list of countries, number of centers, trial phase, study type (observational or interventional), randomization, and planned enrollment. In addition, trials were classified as assessing the drug for its originally approved indication or not, depending on the initial label. When the initial label differed between the FDA and EMA, we accepted both labels as defining the originally approved indication. One of us (JDZ) performed this classification after careful review of each primary label.

Supplemental indications

We also collected approvals of supplemental indications by the FDA during the study period (2005-2014) by manual review of Drugs@FDA. In the "Approval date(s) and History, Letters, Labels, Reviews" section, all events designated as "efficacy-new indication" or "efficacy" were reviewed and retained if deemed appropriate. Labeling revision (such as those related to a modified indication or an expanded patient population) and manufacturing change or addition were not included, nor were irrelevant supplemental indications. We also aimed to assess the average number of patients to be enrolled in post-marketing trials to gain approval

of a supplemental indication. For this purpose, we took into account all patients from all post-marketing trials from the start of our sample through 1 year before the issuance of the supplemental indication by the FDA.

Statistical analysis

Using descriptive statistics, we characterized the premarket characteristics of the novel drugs included in our sample (drugs approved by both the FDA and EMA between 2005 and 2010). Next, we used descriptive statistics to characterize features of all identified post-marketing trials registered at ClinicalTrials.gov for all novel drugs. We used a series of trend charts representing the annual number of post-marketing trials over the life-cycle of the drugs according to off- and on-condition trials. All statistical tests were two-tailed, with a type I error rate of 0.05. We used SAS 9.4 (SAS Institute; Cary, NC) for all statistical analyses.

Results

Drug sample

Our study sample included 69 novel drugs approved between 2005 and 2010 by both the FDA and EMA. In all, 51 drugs (73.9%) were small molecules and 18 (26.1%) were biologics (Table 1). The FDA had granted orphan status to 18 drugs (26.1%) and the EMA an orphan designation to 20 (29.0%). Among these 69 novel drugs, 24 (34.8%) were first-in-class, 24 (34.8%) advance-in-class and 21 (30.4%) addition-to-class. The most prevalent therapeutic category was antineoplastic and immunomodulating agents (29% of all novel drugs from the sample) and many drugs (68.1%) were for chronic treatment. The manufacturer was a large pharmaceutical company for 44 (63.8%) of the drugs. Other details are in Table 1.

Number of post-marketing trials, status and patients recruited

Sequential exclusions leading to our final study sample of 6679 relevant post-marketing trials related to all 69 novel drugs are in Supplemental Material (S1). Characteristics of all post-marketing trials are in Table 2. In all, 2901 trials (43.4%) were completed, 487 (7.3%) terminated, 1013 (15.2%) active yet not recruiting, 1895 (28.4%) recruiting, and 319 (4.8%) not yet recruiting. When comparing respective numbers of post-marketing trials and all clinical trials (preapproval trials and post-marketing trials), the median proportion of post-marketing trials per drug was 0.91 (interquartile range [IQR] 0.88-0.96). However, we found high variability in number of post-marketing trials per drug, with a median of 55 trials per drug (IQR, 33-119) and mean of 96.8 trials per drug (SD 110.3). Galsulfase, an orphan medication indicated for Mucopolysaccharidosis VI, was associated with the lowest number of post-marketing trials (n=3) and sorafenib, a tyrosine kinase inhibitor initially indicated for kidney cancer, with the highest number of post-marketing trials (n=530).

Planned enrollment was also highly variable, with trials only including one patient, and one trial intending to recruit 904 585 patients (actually a prospective population-based cohort study examining risk of congenital malformations after use of varenicline, a tobacco-use cessation drug, in pregnant women). However, the median number of patients to be enrolled per trial was 60 (IQR 28-183). Data on the total population to be enrolled in all post-marketing trials for a given drug was also highly varied, with a median total sample of 15 418 patients (IQR 4932-37 523). Velaglucerase alfa, an orphan medication indicated for Gaucher disease, was associated with the lowest population size to be included in trials (n=67), and varenicline was associated with the greatest population to be enrolled (>1 million patients overall). Supplemental Material (S2) shows the total number of patients to be included in post-marketing trials for each drug and proportions of industry and non-industry funders.

Supplemental Material (S3) presents for each drug the number of patients included in preapproval trials as compared with post-marketing trials. The median proportion for the population recruited in post-marketing trials to the total population (i.e., preapproval samples and post-marketing trials) was 0.92 (IQR 0.85-0.96). Again, alglucidase and velaglucerase alfa were associated with the lowest number of patients in preapproval trials. In contrast, for dabigatran, a drug initially indicated for preventing venous thromboembolism in the European Union and to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation in the United States, preapproval trials had recruited the highest number of patients. The same figure also shows the proportions of patients enrolled in post-marketing trials designed for the originally approved indication, another indication and both.

Trial characteristics

Data regarding study phases are shown in Table 2; only 18.6% of identified post-marketing trials were considered phase IV trials, whereas the most prevalent category was phase II trials (32.6%). Data regarding randomization were missing for 2452 post-marketing trials (36.7%). Among the remaining trials for which these data were available, 3067 were randomized (72.6%). Other data are in Table 2.

Sponsor

Industry funded or partially funded nearly two-thirds of post-marketing trials. Indeed, as shown in Table 2, industry was the primary sponsor of 2713 trials (40.6%), but when also considering manufacturers as minority funders, industry was involved in a total of 4176 trials (62.5%). Data regarding post-marketing trials stratified by sponsorship are in Table 2. Figure 1 presents the drug sample with respect to the number of post-marketing trials and the proportion of industry and non-industry funders for each drug. Supplemental Material (S4) provides the same information but with a 4-year follow-up for each drug.

Conditions addressed in trials

Review of indications showed that 2441 post-marketing trials (36.5%) were launched for another indication than the originally approved indication. Figure 2 displays the number of non-approved indications studied in post-marketing trials for each drug of our sample, with information regarding the more advanced phase for each newly targeted indication. When comparing those trials with the total number of clinical trials (preapproval trials and post-marketing trials), we found a median proportion of 0.24 (IQR, 0.09-0.42). The median proportion for the population recruited in post-marketing trials designed for another indication than the originally approved indication to the total population from all clinical trials (preapproval trials and post-marketing trials) was 0.11 (IQR 0.03-0.30).

When analyzing the relationship between the trial sponsor and the trial indication, we found that trials for which industry was a sole or partial funder were less likely to assess the drug for another indication than the originally approved indication (54.6% of trials with industry funding vs 68.6% without industry funding; $p<0.0001$). Findings regarding planned enrollment according to the indication and stratified on funding origin are in Supplemental Material (eTable). Regardless of the funder, post-marketing trials targeting originally approved indications planned to enroll more patients than those studying other indications.

Timing

The annual number of post-marketing trials over the life-cycle of drugs, stratified by indication, is shown in Figure 3, exhibiting an asymmetric bell pattern, with a rapid increase in number of post-marketing trials launched, a peak of activity within the third year after the first regulatory submission, then a progressive decline in number of launched trials. Detailed examination shows a greater proportion of trials designed for another indication than the originally approved indication at the beginning and end of drug life-cycles. Supplemental

Material (S5) is based on the same data but displays information regarding sponsors. Former post-marketing trials were predominantly funded by industry versus academic or not-for-profit entities and this proportion increased until the second year after the first regulatory submission. Afterwards, the proportion of non-industry funders tended to increase over time.

Location

Overall, 80% of post-marketing trials were conducted in only one country. For 66 drugs, at least one trial was conducted in at least two countries. Sorafenib was the most concerned drug in this regard, with 74 trials involving at least two countries. Data regarding locations of trials for each drug are in Supplemental Material (S6). In brief, post-marketing research was highly concentrated in North America (i.e., United States and/or Canada; 44.8% of all post-marketing trials of the sample) and Europe (25.0%). Post-marketing trials conducted in other areas represented 15.6% of all trials, and trials conducted in multiple continents were few. When examining the relation between trial location and study design with respect to the original label, we found that trials from North America (United States and/or Canada) were more frequently conducted for indications other than the originally approved indication versus those located in Europe (50.4% v. 36.9%).

Supplemental indications

During the study period, 18 novel drugs (26.1%) were associated with a least a supplemental indication by the FDA: one with 4 supplemental indications, one with 3 supplemental indications, 5 with two supplemental indications and 11 with one supplemental indication. The mean time between the first regulatory submission and subsequent supplemental indication was 4.4 years (SD 1.7; IQR 3.3-5.7). The mean number of patients to be enrolled in post-marketing trials before approval of a supplemental indication was 12763.1 (SD 12474.3; IQR 3891.0-15856.0).

Discussion

In our study of post-marketing clinical research studies conducted for novel drugs approved by both the FDA and EMA between 2005 and 2010, we found high variability in number of post-marketing trials per drug and planned enrollment per trial. Indeed, the median planned enrollment was low, 60 patients, with a median of 55 trials per drug, most of which had not yet been completed at a minimum of 4 years after approval. Locations were concentrated, with 72.3% of post-marketing trials conducted in North America and/or Europe and 80% conducted in only one country. Approximately 40% of post-marketing trials were designed for an indication other than the originally approved one, more frequently concerning trials not involving industry funding. Overall, those findings reflect the lack of global coordination of post-marketing research for novel drugs.

Our study has several strengths. First, we focused on a sample of drugs approved by the two leading medical product regulators, FDA and EMA, which suggests that these drugs are likely to be of the greatest interest and importance to clinicians worldwide. Most previous studies focused on the FDA or EMA but rarely both. [16,17] Second, few comprehensive studies have analyzed post-marketing research despite its undisputed public health impact. Most research focused on safety or was limited to a given therapeutic area, or even only one drug. In addition, we chose a large study period, with a 6-year span for drug approvals, and nearly 10 years for the trial sample. Moreover, we followed a rigorous method for selecting post-marketing trials, excluding clinical trials included in the FDA submission, trials that had not been launched, trials mistakenly classified as involving the drug in ClinicalTrials.gov and trials whose starting date was too early as compared to regulatory submission. Third, we provide unique insights into the clinical research programs examining non-approved drug uses. Many studies have investigated off-label prescriptions, [18,19] but we used a slightly different approach. In effect, most drug labels are stringently phrased so as to be rigorously

aligned to pivotal trial criteria. [20] Therefore, categorizing trials according to the actual off- or on-label status of the drug investigated would have led to classifying most as involving off-label drug use. Put another way, the label was judged too narrow, and our method offers a more significant picture for clinicians and epidemiologists. We believe that our classification better reflects substantial evolution regarding the initially authorized use of novel drugs.

Our findings raise several issues worthy of consideration about post-marketing research. First, we showed that post-marketing research is both a heterogeneous and concentrated landscape, probably linked to its loose regulation [4] and to market forces. Therefore, most initiatives are at the discretion of funders, either industry or academic institutions, and driven by various factors not necessarily linked to medical need or relevancy. The number of post-marketing trials per novel drug and planned enrollment were highly variable, but most trials were conducted in only one country and North America and Europe were by far the most frequent locations. Median planned enrollment was low and many trials were still not completed at the time of data acquisition. These findings question the absence of steering or the lack of effectiveness or incentive policies for post-marketing research. Second, almost 40% of post-marketing trials were designed for an indication other than the originally approved indication, with non-industry trials more likely concerned. Although industry has been blamed for testing their products in a too-liberal manner, [21] our findings suggest that academics and other non-industry bodies might be more prone to assess authorized drugs in innovative ways to evaluate novel indications. Third, we found that post-marketing trials designed for the originally approved indication planned to enroll a greater number of patients on average than those targeting novel indications. This latter finding is somewhat reassuring because post-marketing trials for an already approved indication aim to refine knowledge regarding the long-term effect and/or safety and should therefore include more patients than preapproval trials.

Our study has limitations. The first may be a registration bias at ClinicalTrials.gov, which would alter the exhaustiveness of our assessment. Some trials are not registered by researchers [22,23] and were therefore not included in our study. Others are imperfectly registered, with some information missing. However, ClinicalTrials.gov is widely recognized as a benchmark registry, and recent reports showed that compliance might have improved over time. [24] Another limitation is the definition of post-marketing trials, in that clinical trials are designed and launched according to a continuous timing and a single threshold might be lacking for distinguishing pre- and post-marketing trials. Therefore, we decided to consider trials starting at most 1 year before the first regulatory submission as post-marketing trials even though we could have made another choice. A third limitation is related to data sources. For some data, we relied on only one of the two selected regulators. We used such an approach for the sake of convenience and recognize that this could be interpreted as a bias, yet to our knowledge, there are very few if any differences in data between the two studied regulators. Therefore, this latter limitation in the methods seems unlikely to affect our findings.

In conclusion, our research shows that post-marketing research is highly variable and concentrated, with on one hand, great differences in the number of post-marketing trials per drug and in planned enrollment and on the other, most trials being conducted in only one country, with North America and Europe the most represented locations. Approximately 40% of post-marketing trials assessed the drug for an indication other than the originally approved indication, more frequently non-industry trials. Even though some of our findings can be seen as reassuring, others underline the lack of global coordination of post-marketing research for novel drugs despite the undisputed influence of such research.

Contributors: Dr. Zeitoun and Pr. Ravaud were responsible for the conception and design of this work. Dr. Zeitoun drafted the manuscript and was responsible for most of the data acquisition. M. Ignacio Atal was responsible for data exportation and structuration. Dr. Nicholas Downing was responsible for some of the data acquisition. Dr. Gabriel Baron conducted the statistical analysis. Drs. Ross and Ravaud provided supervision. All authors participated in the analysis and interpretation of the data and critically revised the manuscript for important intellectual content.

Data sharing statement: Data files are available from the corresponding author on reasonable request.

Acknowledgements: The authors are grateful to EMA officials who graciously helped them classify drug manufacturers. They also thank Geoffroy Beraud-Chaulet for his useful work on Drugs@FDA and Elise Diard for her invaluable help on figures.

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Legends

Figure 1: Number of post-marketing trials and respective proportion of industry and non-industry funders.

Figure 2: Number of non-approved indications targeted in post-marketing trials for each drug of our study sample. Indications are rank-ordered on the basis of the number of post-marketing trials launched (from the greatest number of post-marketing trials on the left side of the figure to the lowest number on the right side). Color of boxes varies according to the advanced phase of the targeted indication. Indications are classified according to the Global Burden of Diseases classification. [25] Indications belonging to residual categories or health conditions not relevant to the Global Burden of Diseases were excluded and therefore are not represented in the Figure.

Figure 3: Annual number of post-marketing trials over the life-cycle of drugs, stratified by indication.

Supplemental File S1: Flow chart leading to the final study sample of 6679 relevant post-marketing trials.

Supplemental File S2: Total number of patients to be included in post-marketing trials for each drug.

Supplemental File S3: Population in preapproval trials and post-marketing trials.

Supplemental File S4: Number of post-marketing trials and respective proportion of industry and non-industry funders, with a 4-year follow-up for each drug.

Supplemental File S5: Annual number of post-marketing trials over the life-cycle of drugs, stratified by sponsor.

Supplemental File S6: Locations of post-marketing trials.

Table 1. Characteristics of 69 novel drugs approved by both the FDA and EMA between 2005 and 2010 (excluding everolimus and temsirolimus).

Characteristics	**n (%)**
Agent type	
Small molecule	51 (73.9%)
Biologic	18 (26.1%)
Orphan status (FDA)	18 (26.1%)
Orphan designation (EMA)	20 (29.0%)
Therapeutic class according to the ATC code	
Alimentary tract and metabolism	10 (14.5%)
Anti-infectives for systemic use	12 (17.4%)
Antineoplastic and immunomodulating agents	20 (29.0%)
Blood and blood forming organs	5 (7.2%)
Cardiovascular system	5 (7.2%)
Nervous system	6 (8.7%)
Other*	11 (15.9%)
Degree of novelty (according to Lanthier *et al*)	
First-in-class	24 (34.8%)
Advance-in-class	24 (34.8%)
Addition-to-class	21 (30.4%)
Size of the marketing-authorization holder	
Large pharmaceutical company	44 (63.8%)
Intermediated-size company	23 (33.3%)
Small- and medium-size company	2 (2.9%)
Premarket evidence	
At least one pivotal trial using an active comparator	28 (40.6%)

Placebo only	34 (49.3%)
No comparator	7 (10.1%)
Total no. of included patients	
Min/max	18/18040
Median [Q1-Q3]	923 [324-1996]
Mean (SD)	1806 (2897)
Expected length of treatment	
Acute	8 (11.6%)
Intermediate	14 (20.3%)
Chronic	47 (68.1%)

ATC, Anatomical Therapeutic Chemical

*includes dermatological, genitourinary system and sex hormones, musculoskeletal system, sensory organs, systemic hormonal preparations, excluding sex hormones, and others

Table 2. Characteristics of industry and non-industry post-marketing trials registered at ClinicalTrials.gov before September 24, 2014 for the 69 novel drugs in the study sample.

Characteristics			Industry trials	Non-industry trials
Primary sponsor	Industry NIH US Fed Other	2713 (40.6%) 286 (4.3%) 15 (0.2%) 3665 (54.9%)		
Industry involved either as a primary sponsor or a collaborator		4176 (62.5%)		
No. of post-marketing trials per drug	Min/max Median [Q1-Q3] Mean (SD)	3/530 55 [30-119] 96.8 (110.3)		
Population size per drug	Min/max Median [Q1-Q3] Mean (SD)	67/1.05E6 15418 [4932-37523] 62748 (166644)		

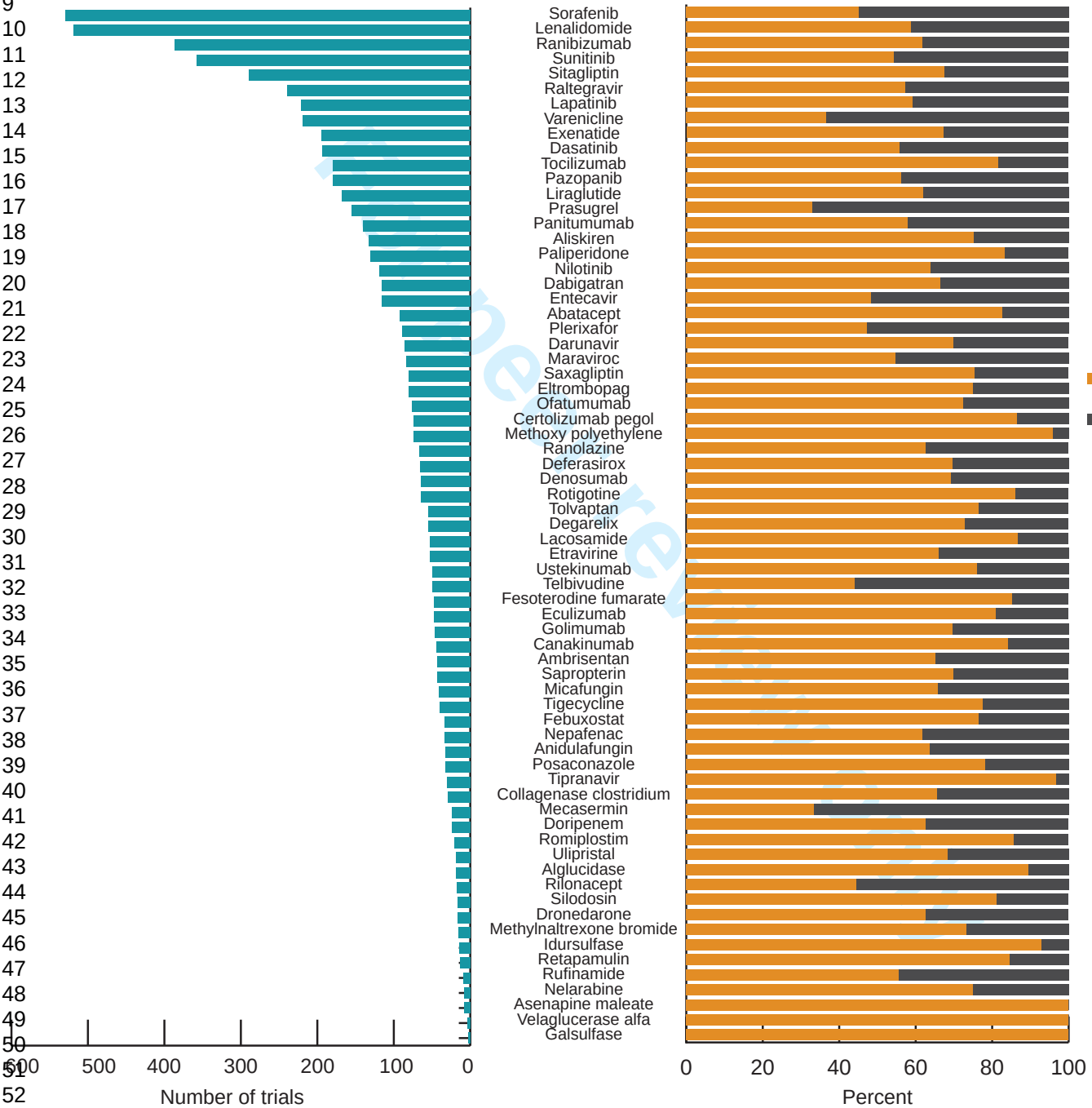
Therapeutic class according to the ATC code				
Alimentary tract and metabolism		832 (12.5%)	570 (68.5%)	262 (31.5%)
Anti-infectives for systemic use		828 (12.4%)	504 (60.9%)	324 (39.1%)
Antineoplastic and immunomodulating agents		3040 (45.5%)	1818 (59.8%)	1222 (40.2%)
Blood and blood forming organs		446 (6.7%)	277 (62.1%)	169 (37.9%)
Nervous system		485 (7.3%)	304 (62.7%)	181 (37.3%)
Other*		1048 (15.7%)	703 (67.1%)	345 (32.9%)
Trial design with respect to primary label	Another indication than the originally approved indication	2561 (38.3%)	1397 (54.5%)	1164 (45.5%)
	Originally approved indication	3889 (58.2%)	2666 (68.6%)	1223 (31.4%)
	Both the originally approved indication and another indication	229 (3.4%)	113 (49.3%)	116 (50.7%)
Study type	Observational	707 (10.6%)	468 (66.2%)	239 (33.8%)
	Interventional	5972 (89.4%)	3708 (62.1%)	2264 (37.9%)

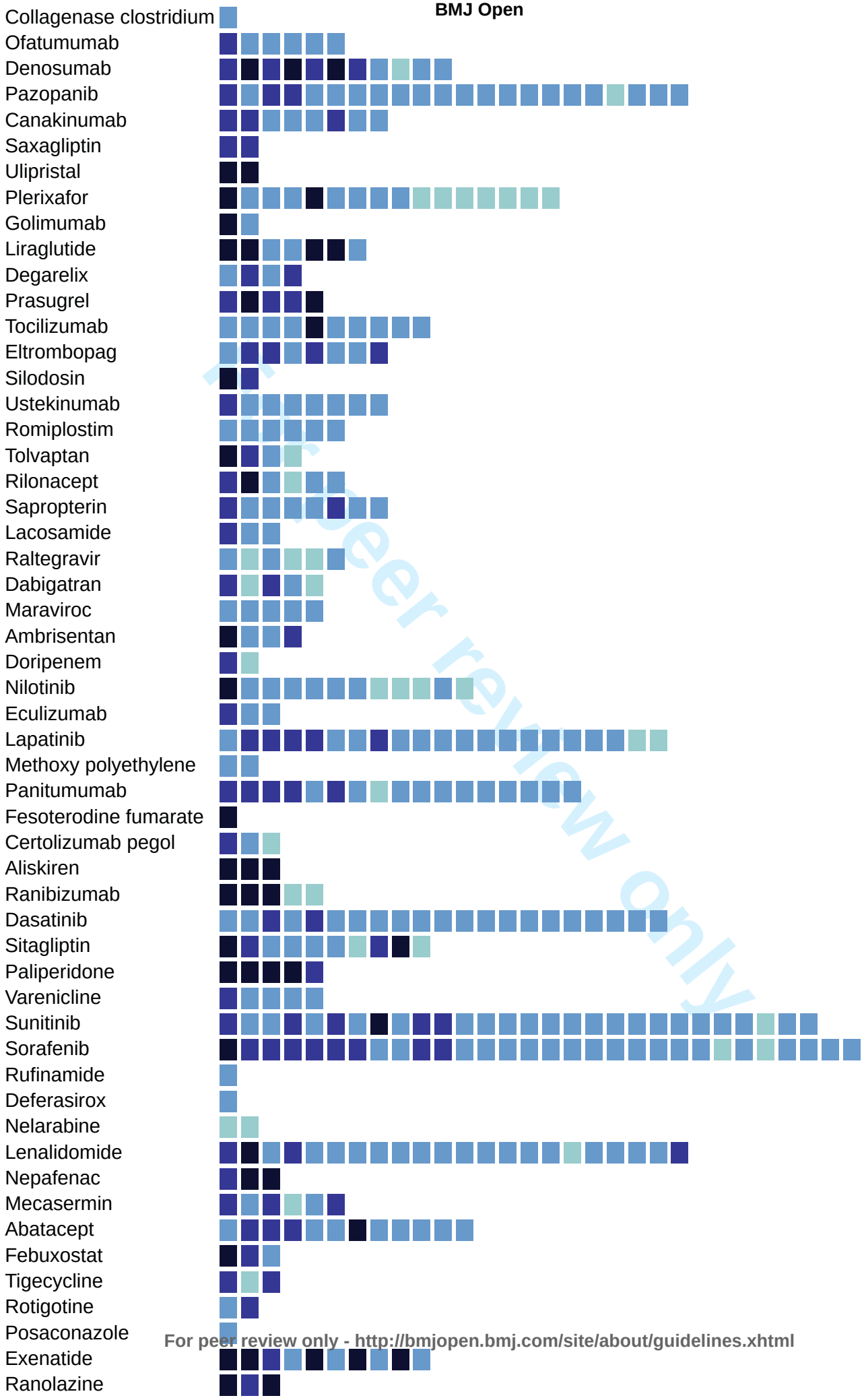
Randomization	Missing data	2452		
	Yes	3067 (72.6%)	1979 (64.5%)	1088 (35.5%)
	No	1160 (27.4%)	769 (66.3%)	391 (33.7%)
Study phase	0	34 (0.6%)	13 (38.2%)	21 (61.8%)
	I	933 (16.6%)	651 (69.8%)	282 (30.2%)
	I/II	423 (7.5%)	245 (58.0%)	178 (42.0%)
	II	1837 (32.6%)	1047 (57.0%)	790 (43.0%)
	II/III	109 (1.9%)	52 (47.7%)	57 (52.3%)
	III	1246 (22.1%)	1018 (81.7%)	228 (18.3%)
	IV	1045 (18.6%)	596 (57.0%)	449 (43.0%)
Centers	Missing data	503	428	75
	Min/max	1/1616	1/1616	1/922
	Median [Q1-Q3]	2 [1-12]	4 [1-23]	1 [1-2]
	Mean (SD)	19.9 (62.1)	26.4 (70.5)	9.8 (44.7)
Countries	Min/max	1/46	1/46	1/15
	Median [Q1-Q3]	1 [1-1]	1 [1-2]	1 [1-1]
	Mean (SD)	2.6 (4.7)	3.6 (5.8)	1.1 (0.7)

Planned enrollment	Min/max	1/904585	1/904585	1/61050
	Median [Q1-Q3]	60 [28-183]	72 [30-248]	48 [24-100]
	Mean (SD)	649.6 (12812)	943.8 (16167)	158.9 (1274.7)
Status at the time of data exportation	Not yet recruiting	319 (4.8%)	136 (42.6%)	183 (57.4%)
	Recruiting	1895 (28.4%)	886 (46.8%)	1009 (53.2%)
	Active, not recruiting	1013 (15.2%)	627 (61.9%)	386 (38.1%)
	Enrolling by invitation	64 (1.0%)	42 (65.6%)	22 (34.4%)
	Completed	2901 (43.4%)	2147 (74.0%)	754 (26.0%)
	Terminated	487 (7.3%)	338 (69.4%)	149 (30.6%)

NIH, US National Institutes of Health

*includes cardiovascular system, dermatological, genitourinary system and sex hormones, musculoskeletal system, sensory organs, systemic hormonal preparations, excluding sex hormones, and other





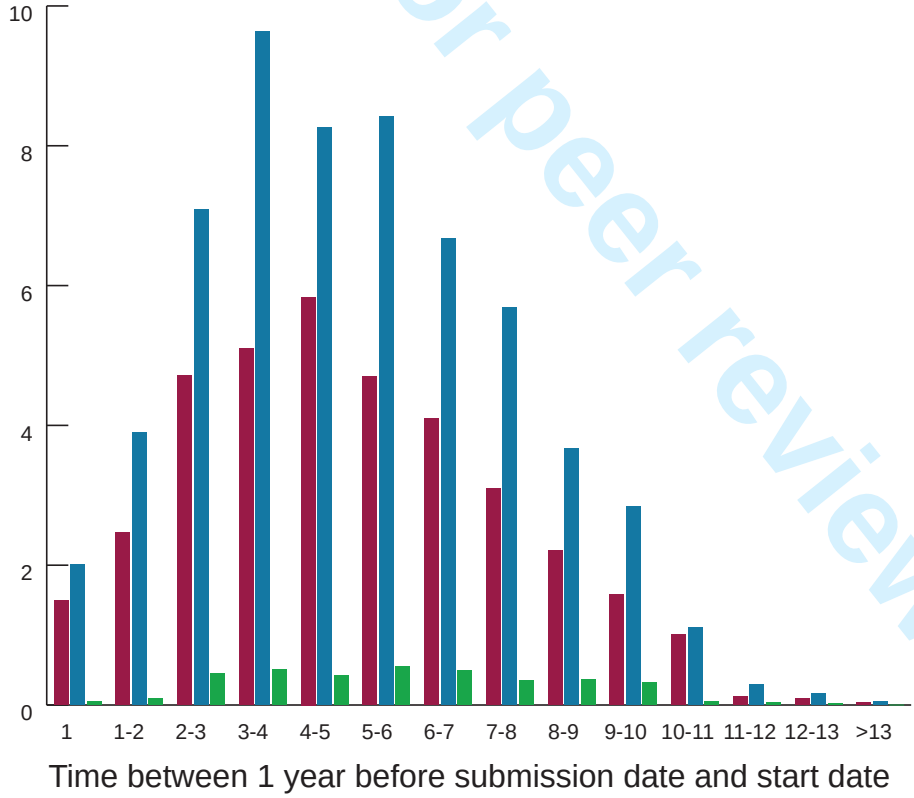
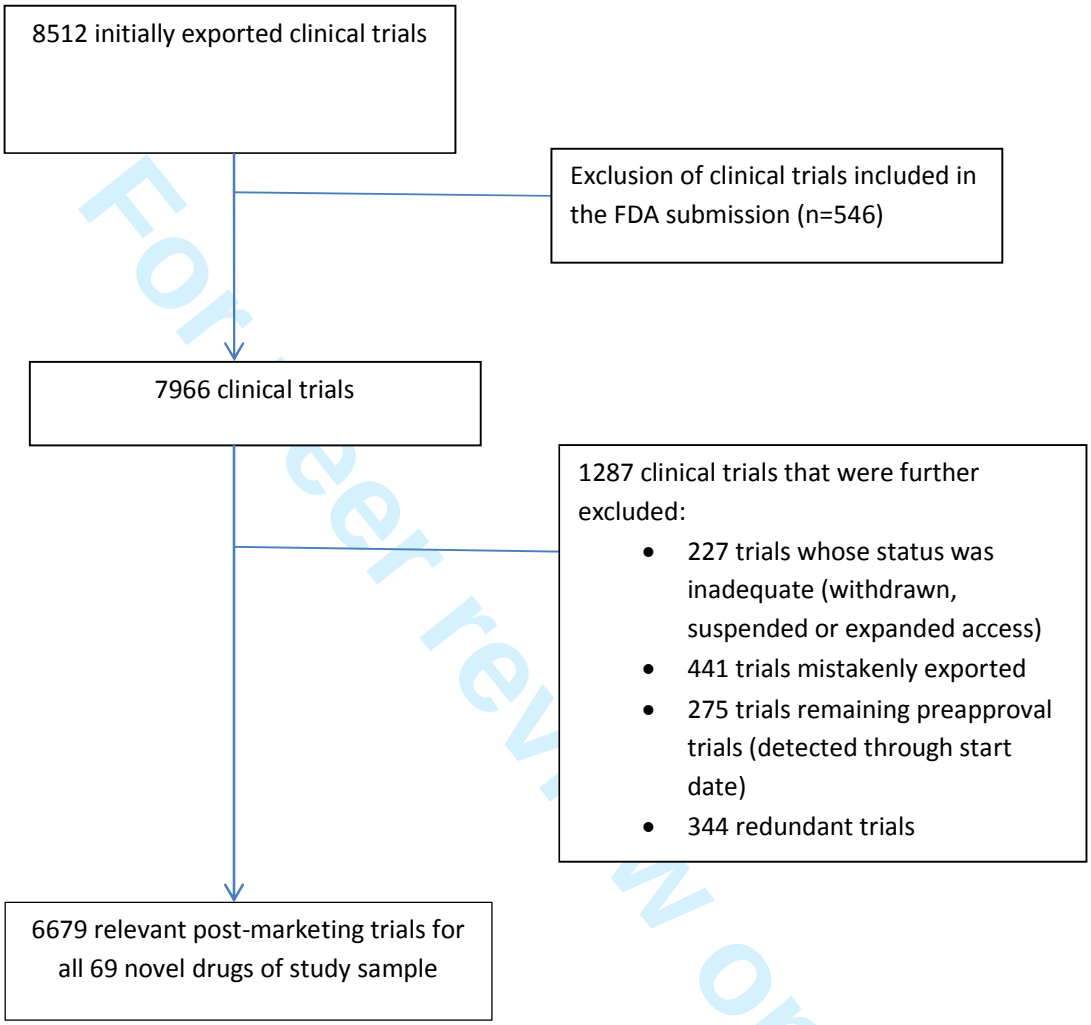
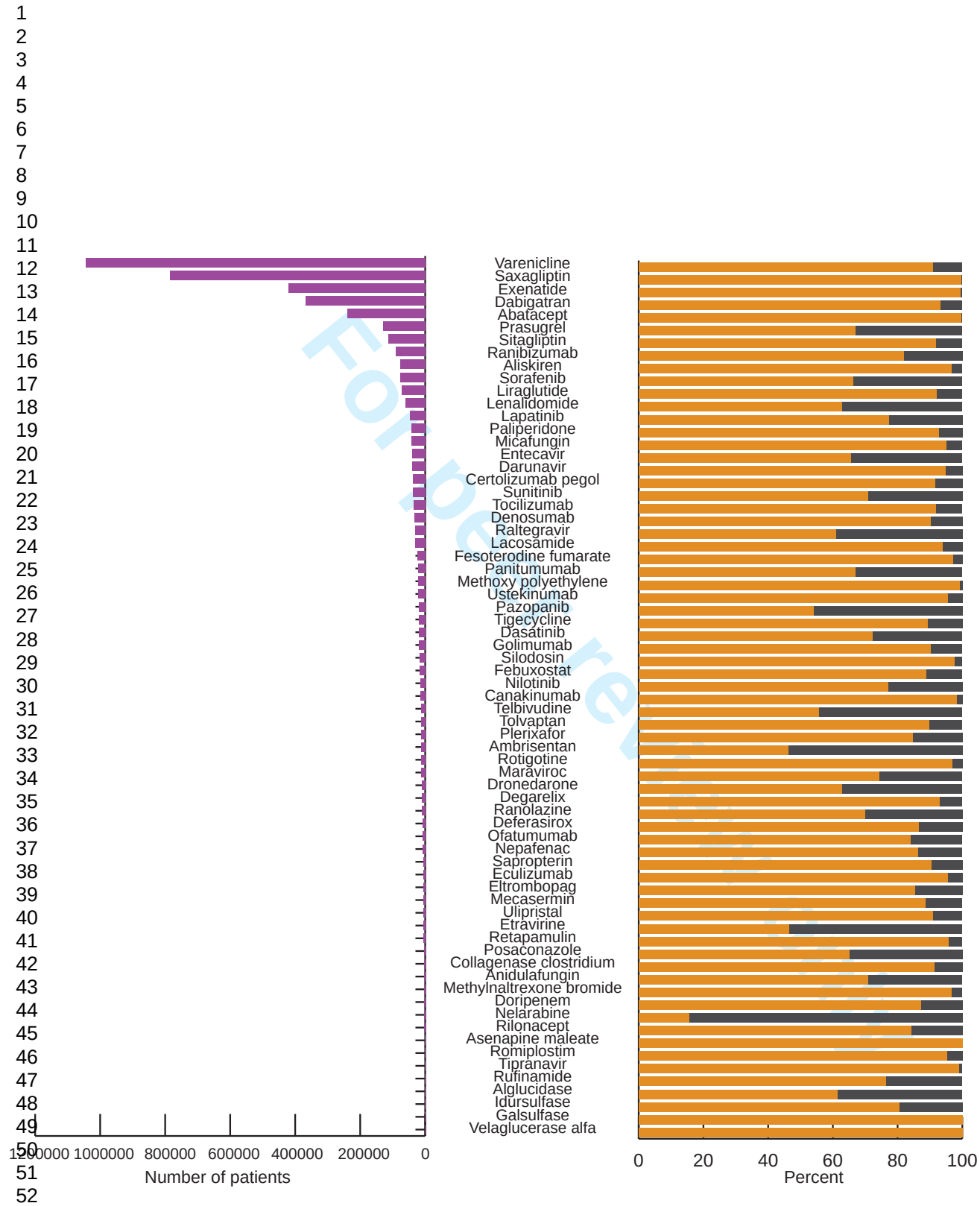
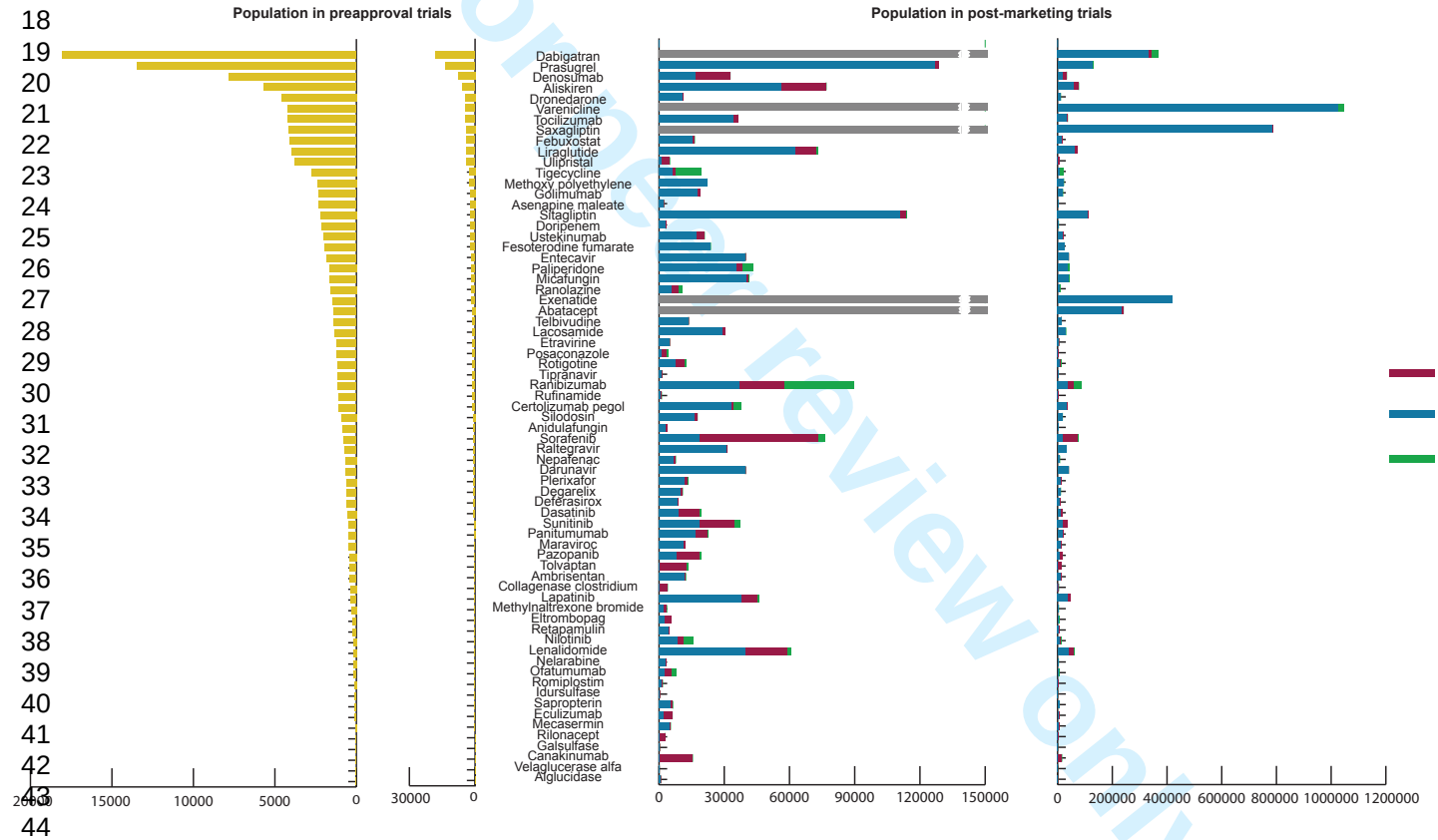
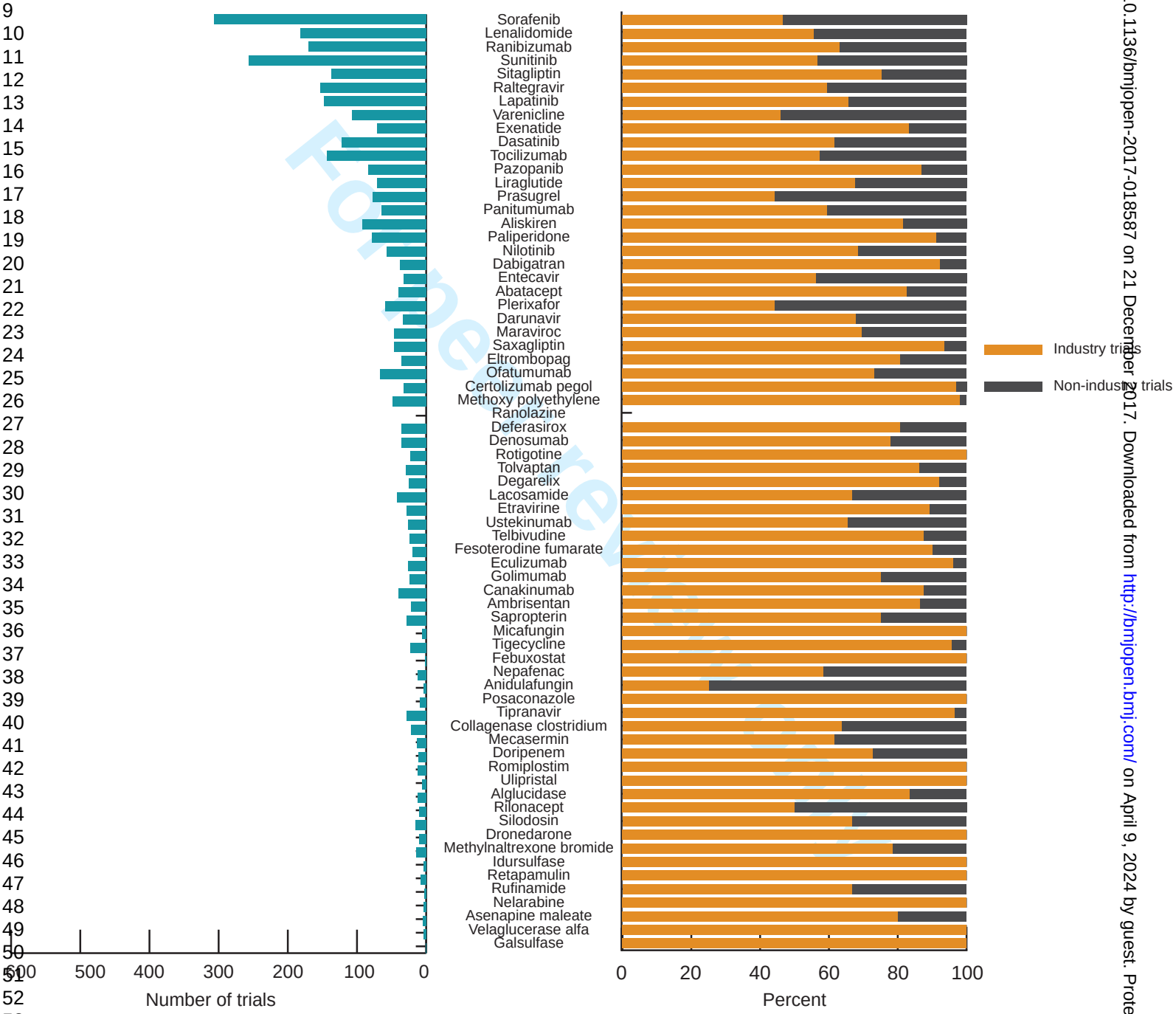


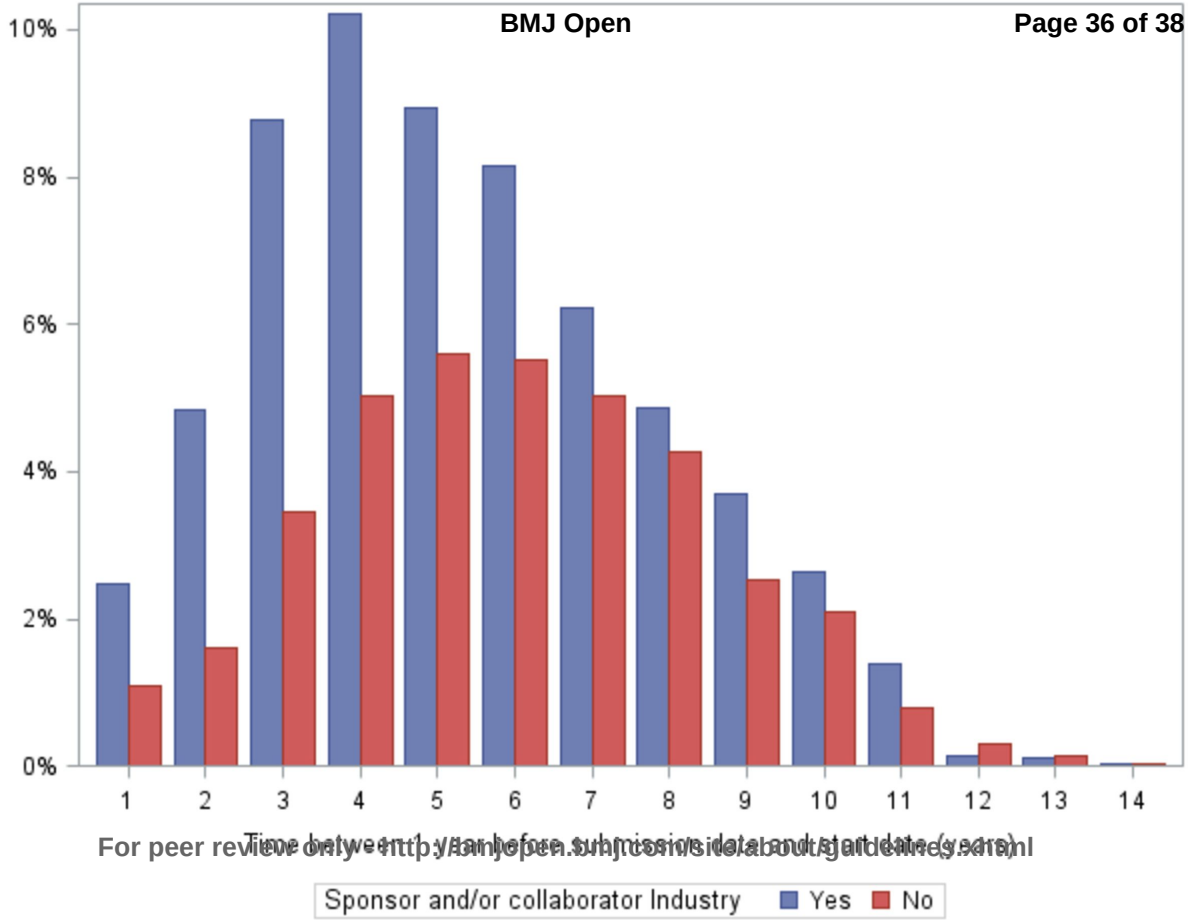
Figure 1. Sample construction of relevant post-marketing trials related to all 69 novel drugs both approved by the FDA and the EMA between 2005 and 2010, after exclusion of everolimus and temsirolimus

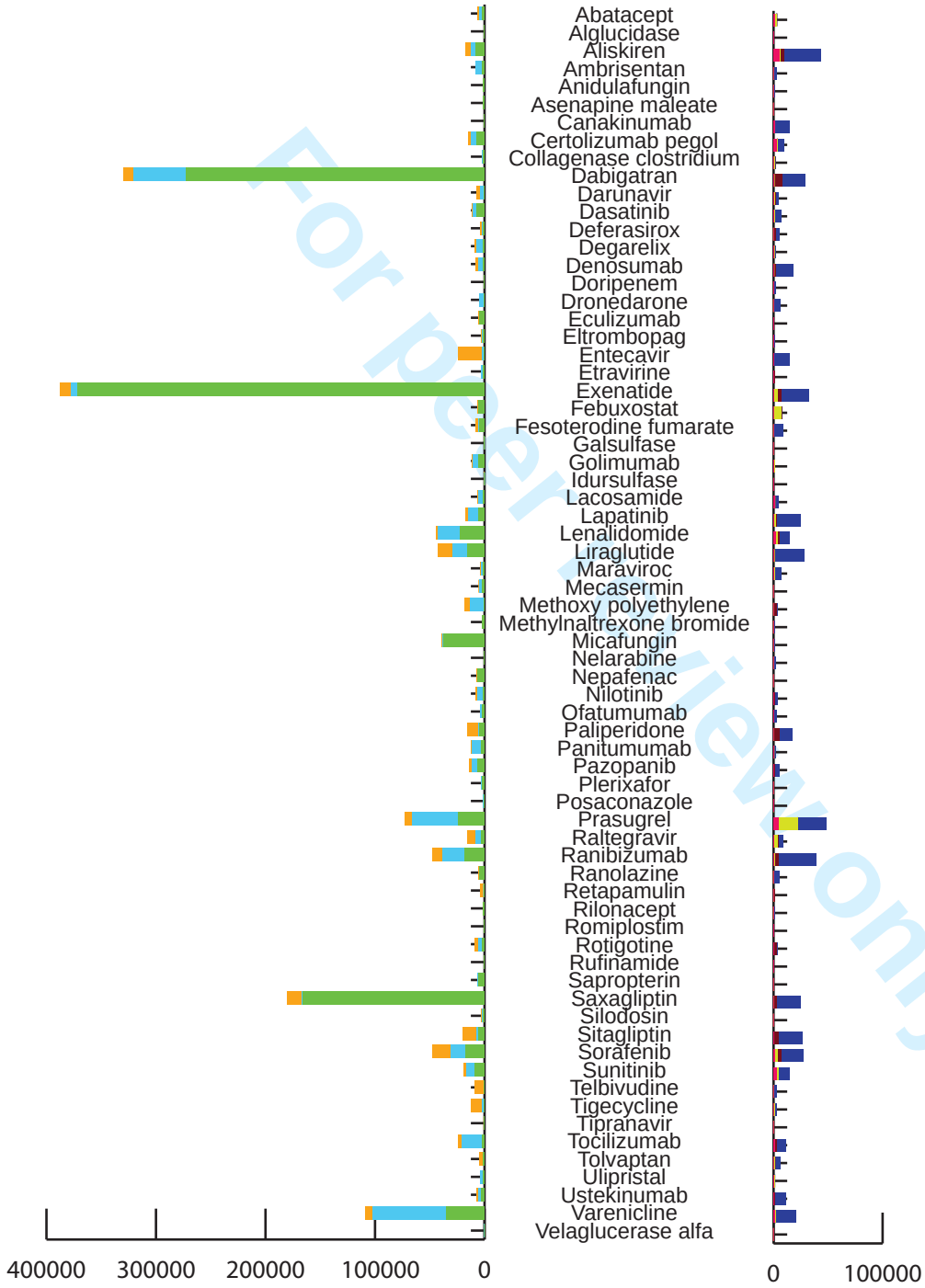












eTable. Planned enrollment of post-marketing trials by industry and non-industry funding for indications targeted in trials.

Indication	Industry funding		Non-industry funding	
	No. of trials	Planned enrollment	No. of trials	Planned enrollment
Originally approved indication	2742	Median [Q1-Q3]: 100 [33-323] Mean (SD): 1322.0 (19921.8)	1251	Median [Q1-Q3]: 60 [29.5-150] Mean (SD): 230.9 (1771.2)
Other indication(s)	1310	Median [Q1-Q3]: 45 [24-128] Mean (SD): 167.7 (SD: 544.1)	1131	Median [Q1-Q3]: 40 [21-70] Mean (SD): 72.9 (148.0)
Both the originally approved indication and another indication	124	Median [Q1-Q3]: 60 [30-224] Mean (SD): 765.2 (2961.8)	121	Median [Q1-Q3]: 50 [30-120] Mean (SD): 218.1 (934.9)

Data were missing for 9 industry-funded trials and 5 other trials.

BMJ Open

Post-marketing studies for novel drugs approved by both the FDA and EMA between 2005 and 2010: a cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018587.R1
Article Type:	Research
Date Submitted by the Author:	13-Sep-2017
Complete List of Authors:	Zeitoun, Jean-David; Hôtel Dieu Hospital, Epidémiologie Clinique; Saint-Antoine Hospital, Gastroenterology and Nutrition Ross, Joseph; Yale University School of Medicine, Internal Medicine Atal, Ignacio; Hotel Dieu Hospital, Epidémiologie Clinique Vivot, Alexandre; Hotel Dieu Hospital, Epidémiologie Clinique Downing, Nicholas; Brigham and Women's Hospital and Harvard Medical School, Medicine Baron, Gabriel; INSERM U1153; Hôtel Dieu Hospital, Centre d'Epidémiologie Clinique Ravaud, Philippe; Université Paris Descartes, Centre d'épidémiologie clinique; INSERM U1153
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Research methods, Public health
Keywords:	THERAPEUTICS, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY

Post-marketing studies for novel drugs approved by both the FDA and EMA between 2005 and 2010: a cross-sectional study

Jean-David Zeitoun, MD, MHPM, PhD candidate [1, 2, 3], Joseph S. Ross, MD, MHS [4, 5, 6, 7], Ignacio Atal, MSc [1, 8], Alexandre Vivot, MD, MPH, [1,8], Nicholas S. Downing, MD [9], Gabriel Baron, PhD [1, 8, 10], Philippe Ravaud, MD, PhD [1, 8, 10, 11]

1. Centre d'Épidémiologie Clinique, Hôpital Hôtel Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France
2. Gastroenterology and Nutrition, Hôpital Saint-Antoine, Assistance Publiques-Hôpitaux de Paris, Paris, France
3. Proctology, Groupe Hospitalier Diaconesses-Croix Saint-Simon, Paris, France
4. Department of Internal Medicine, Robert Wood Johnson Foundation Clinical Scholars Program, Yale School of Medicine, New Haven, Connecticut, USA
5. Department of Internal Medicine, Section of General Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA
6. Department of Health Policy and Management, Yale School of Public Health, New Haven, Connecticut, USA
7. Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Connecticut, USA
8. INSERM UMR 1153, Centre de Recherche Épidémiologie et Statistique Paris Sorbonne Cité (CRESS), METHODS Team, Paris, France
9. Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts
10. Université Paris Descartes, Sorbonne Paris Cité, Paris, France
11. Department of Epidemiology, Columbia University Mailman School of Public Health, New York, New York, United States of America.

Corresponding author: Dr. Jean-David Zeitoun, MD, MHPM, PhD candidate, Centre d'Epidémiologie Clinique, Hôpital Hôtel Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France. E-mail: jdzeitoun@yahoo.fr

Word count: 3736

Abstract: 282

References: 29

Figures: 3

Tables: 2

ABSTRACT

Objectives: To characterize post-marketing studies for drugs that were newly approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Design and Setting: Cross-sectional analysis of post-marketing studies registered in ClinicalTrials.gov until September 2014 for all novel drugs approved by both regulators between 2005 and 2010. Regulatory documents from both agencies were used.

Primary and secondary outcome measures: All identified post-marketing studies were classified according to planned enrolment, funding, status, and geographical location, and we determined whether studies studied the originally approved indication.

Results: Overall, 69 novel drugs approved between 2005 and 2010 were eligible for inclusion. A total of 6679 relevant post-marketing studies were identified; 5972 were interventional (89.4%). The median number of studies per drug was 55 (interquartile range [IQR]: 33-119) and median number of patients to be enrolled per study was 60 (IQR, 28-183). Industry was the primary sponsor of 2713 studies (40.6%) and was a primary or secondary sponsor in 4176 studies (62.5%). In all, 2901 studies (43.4%) were completed, 487 (7.3%) terminated, 1013 (15.2%) active yet not recruiting, 1895 (28.4%) recruiting, and 319 (4.8%) not yet recruiting. A total of 80% of studies were conducted in only one country and 84.4% took place in Europe and/or North America; 2561 (38.3%) studied another indication than the originally approved indication. Studies for which industry was a funder were less likely to assess the drug in another indication (54.6% vs. 68.6%; p<0.0001).

Conclusions: Post-marketing pharmaceutical research was highly variable and predominantly located in North America and Europe. Post-marketing studies were frequently designed to study indications other than the originally approved one. Although some findings were reassuring, others question the lack of coordination of post-marketing research.

Strengths and limitations of this study

This is the first study to systematically assess clinical studies performed after marketing approval by the two leading regulators, namely the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

This approach allowed us to examine a substantial number of post-marketing studies over a long time period.

However and due to registration bias, we cannot exclude that some true post-marketing studies were missed and therefore unanalyzed.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: Dr. Zeitoun reports that he serves as an advisor for several consulting firms and communication companies linked with the pharmaceutical industry (Cepton, Oliver Wyman, Roland Berger, McCann Healthcare, Omnicom, Grey Healthcare, Saatchi and Saatchi Healthcare, Sudler & Hennessey, TBWA, inVentiv Health France, Havas). He also reports compensation for lectures given to manufacturer professional associations; collaboration with Mayoly-Spindler, Merck, Teva, Johnson & Johnson, and Menarini; unpaid consultancy for EY; conducting workshops funded by Amgen; and being invited to a French medical congress by AbbVie. Dr. Ross receives support through Yale University from Johnson and Johnson to develop methods of clinical trial data-sharing; from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting; from Medtronic, Inc. and the US FDA to develop methods for

post-market surveillance of medical devices; from the Blue Cross Blue Shield Association to better understand medical technology evaluation; and from the Laura and John Arnold Foundation to support the Collaboration on Research Integrity and Transparency (CRIT) at Yale.

Introduction

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are the two largest and most influential drug regulators worldwide. They tend to maintain similar premarket regulatory standards, and drug manufacturers probably tend to submit the same evidence to both as part of the premarket application process, even though we lack comparative data. Drug evaluation continues after regulatory approval, in particular through post-authorization requirements and commitments. The US FDA can use several regulatory instruments and harness various sources for post-marketing evaluation of approved drugs. Among them are the FDA Adverse Reporting System and the Sentinel System. [1] The EMA also has a set of post-authorization measures, from direct request by its dedicated committee, to specific obligations for certain drugs, all aiming at retrieving data for post-marketing assessment.[2] Yet these post-marketing clinical studies required by regulators are limited in number and are not consistently completed. [3–5] This situation raises the question of whether other studies of these drugs after regulatory approval, including those conducted by industry and independent investigators, but not to fulfill regulatory requirements, should be considered part of ongoing, continuous evaluation efforts.

Post-marketing studies are designed with different intent than are premarket trials. Their designs are not systematically submitted to regulatory agencies before initiation because many post-marketing studies are conducted by independent investigators, and their conduct is less rigorously regulated. [6] Post-marketing studies seek to evaluate safety regarding rare events, to assess the real-life effectiveness of novel drugs and to measure their long-term effects. They also permit drug evaluation in different populations, other indications for the same disease, other diseases or with different delivery systems or dosage forms. Moreover, although premarket trials are nearly exclusively sponsored by the manufacturers, post-marketing studies can be funded by manufacturers but also academic or other types of non-

profit institutions. Some research also suggested that a substantial proportion of post-marketing trials, even those with results eventually published in high-impact-factor journals, were designed for marketing purposes rather than medical interest. [7,8]

Nevertheless, post-marketing studies have considerable influence on all stakeholders, in particular researchers, practitioners and regulators or decision makers, because they provide cumulative evidence regarding marketed products. However, we lack an overall assessment of post-marketing studies regarding novel drugs. Post-marketing research has been studied for high-risk devices [9] or even for drugs, but with a focused approach: safety [10,11] or given therapeutic areas. [12–15]Some of those studies produced reassuring results, yet others showed inconsistencies, with gaps in knowledge regarding some issues.

Our research objective was to provide a comprehensive description of post-marketing studies registered in ClinicalTrials.gov, a publicly-accessible clinical trial registry maintained by the US National Institutes of Health over almost a decade for a sample of drugs approved by both the FDA and EMA from 2005 to 2010. We aimed to characterize the total number of studies and patients studied, targeted indications, funding origin, geographical location of studies and status (e.g., completed or ongoing). We also sought to examine differences between the condition of the initial label and the specific clinical condition studied in the post-marketing studies, to assess the influence of the sponsor on the targeted indication, and to describe supplemental indications.

Methods

Data sources and study sample

We identified all novel drugs approved between January 1, 2005 and December 31, 2010 by both the FDA and EMA through its Centralized Authorization Procedure. For the FDA, Drugs@FDA is a publicly accessible database listing relevant regulatory actions for all approved drugs. [16] For the EMA, information was accessible in the European Public Assessment Reports, which provide a summary of scientific review and list notable regulatory events for all drug submissions.[17] Generic drugs, reformulations, combination therapies and non-therapeutic agents such as radiographic dye were not included. This first search led to a sample of 71 novel drugs approved by both regulators between 2005 and 2010. Two drugs, everolimus and temsirolimus, were excluded because they were associated with an abnormally high number of post-marketing studies involving drug-eluting stents.

Drug and manufacturer characteristics

The following data were retrieved for each drug: agent type (small molecule or biologic), dates of regulatory submissions for both the FDA and EMA, orphan status according to the FDA, orphan designation from the EMA, therapeutic class according to the Anatomical Therapeutic Chemical classification, [18] initial label from both regulators, degree of novelty (first-in-class, advance-in-class, addition-to-class) as previously described in a paper from FDA officials [19] and size of the marketing-authorization holder (i.e., manufacturer). This latter information was obtained by personal communication with EMA officials (Dr. Constantinos Ziogas, Small and Medium-sized Manufacturer Office, EMA), who classified manufacturers as large pharmaceutical companies, intermediated-size companies or small- and medium-size companies according to the European Union definition based on headcount and financial turnover or balance sheet total.

Preapproval FDA pivotal trial characteristics

We obtained data for the expected length of treatment and number of patients from pivotal efficacy trials supporting FDA approvals that had been collected for a previous work. [20] In brief, acute treatment was defined as expected use < 1 month, intermediate treatment as expected use from 1 month to 2 years, and chronic treatment as expected use > 2 years.

Post-marketing trials

On September 24, 2014, we extracted all studies that were registered at ClinicalTrials.gov for each drug of our sample, regardless of dates and other details. We then excluded studies with the following characteristics: included in the FDA regulatory submission (by a manual review of Drugs@FDA), with inadequate registered status (expanded-access studies, withdrawn studies, suspended studies), and mistakenly extracted (i.e., studies actually not assessing the drug of interest). We decided that all studies whose starting date had preceded the first regulatory submission (to the FDA or EMA) by 1 year or less would be classified as post-marketing studies. Trials that pertained to more than one drug in our sample were manually reviewed so as to assign them to only one drug for the sake of further statistical analysis. Clinical judgment was applied to choose the "leading" drug in each study. When we could not determine the leading drug, we used the following rules. If the study was funded by a marketing-authorization holder of one of the drugs, this drug was considered the leading drug. Otherwise, if the study involved a drug that was assessed for another indication than the originally approved indication, this drug was considered the leading drug. Finally, when no leading drug could be determined, the drug for which the last regulatory approval had been granted was considered the drug tested and was classified as the leading drug.

For all remaining post-marketing studies, the following data were collected: condition studied, starting date, study sponsors (as a primary sponsor or a collaborator), status at the

date of extraction (not yet recruiting, recruiting, active yet not recruiting, enrolling by invitation, completed, terminated), number and list of countries, number of centers, study phase, study type (observational or interventional), randomization, and planned enrollment. In addition, studies were classified as assessing the drug for its originally approved indication or not, depending on the initial label. When the initial label differed between the FDA and EMA, we accepted both labels as defining the originally approved indication. One of us (JDZ) performed this classification after careful review of each primary label.

Supplemental indications

We also collected approvals of supplemental indications by the FDA during the study period (2005-2014) by manual review of Drugs@FDA. In the "Approval date(s) and History, Letters, Labels, Reviews" section, all events designated as "efficacy-new indication" or "efficacy" were reviewed and retained if deemed appropriate. Labeling revision (such as those related to a modified indication or an expanded patient population) and manufacturing change or addition were not included, nor were irrelevant supplemental indications. We also aimed to assess the average number of patients to be enrolled in post-marketing studies to gain approval of a supplemental indication. For this purpose, we took into account all patients from all post-marketing studies from the start of our sample through 1 year before the issuance of the supplemental indication by the FDA.

Statistical analysis

Using descriptive statistics, we characterized the premarket characteristics of the novel drugs included in our sample (drugs approved by both the FDA and EMA between 2005 and 2010). Next, we used descriptive statistics to characterize features of all identified post-marketing studies registered at ClinicalTrials.gov for all novel drugs. We used a series of trend charts representing the annual number of post-marketing studies over the life-cycle of the drugs

according to off- and on-condition studies. All statistical tests were two-tailed, with a type I error rate of 0.05. We used SAS 9.4 (SAS Institute; Cary, NC) for all statistical analyses.

Results

Drug sample

Our study sample included 69 novel drugs approved between 2005 and 2010 by both the FDA and EMA. In all, 51 drugs (73.9%) were small molecules and 18 (26.1%) were biologics (Table 1). The FDA had granted orphan status to 18 drugs (26.1%) and the EMA an orphan designation to 20 (29.0%). Among these 69 novel drugs, 24 (34.8%) were first-in-class, 24 (34.8%) advance-in-class and 21 (30.4%) addition-to-class. The most prevalent therapeutic category was antineoplastic and immunomodulating agents (29% of all novel drugs from the sample) and many drugs (68.1%) were for chronic treatment. The manufacturer was a large pharmaceutical company for 44 (63.8%) of the drugs. Other details are in Table 1.

Number of post-marketing trials, status and patients recruited

Sequential exclusions leading to our final study sample of 6679 relevant post-marketing studies related to all 69 novel drugs are in Supplemental Material (S1). Characteristics of all post-marketing studies are in Table 2. In all, 2901 studies (43.4%) were completed, 487 (7.3%) terminated, 1013 (15.2%) active yet not recruiting, 1895 (28.4%) recruiting, and 319 (4.8%) not yet recruiting. When comparing respective numbers of post-marketing studies and all clinical studies (preapproval pivotal trials and post-marketing studies), the median proportion of post-marketing studies per drug was 0.91 (interquartile range [IQR] 0.88-0.96). However, we found high variability in number of post-marketing studies per drug, with a median of 55 studies per drug (IQR, 33-119) and mean of 96.8 studies per drug (SD 110.3). Galsulfase, an orphan medication indicated for Mucopolysaccharidosis VI, was associated with the lowest number of post-marketing studies (n=3) and sorafenib, a tyrosine kinase

inhibitor initially indicated for kidney cancer, with the highest number of post-marketing studies (n=530).

Planned enrollment was also highly variable, with studies only including one patient, and one study intending to recruit 904 585 patients (actually a prospective population-based cohort study examining risk of congenital malformations after use of varenicline, a tobacco-use cessation drug, in pregnant women). However, the median number of patients to be enrolled per study was 60 (IQR 28-183). Data on the total population to be enrolled in all post-marketing studies for a given drug was also highly varied, with a median total sample of 15 418 patients (IQR 4932-37 523). Velaglucerase alfa, an orphan medication indicated for Gaucher disease, was associated with the lowest population size to be included in studies (n=67), and varenicline was associated with the greatest population to be enrolled (>1 million patients overall). Supplemental Material (S2) shows the total number of patients to be included in post-marketing studies for each drug and proportions of industry and non-industry funders.

Supplemental Material (S3) presents for each drug the number of patients included in preapproval pivotal trials as compared with post-marketing studies. The median proportion for the population recruited in post-marketing studies to the total population (i.e., preapproval samples and post-marketing studies) was 0.92 (IQR 0.85-0.96). Again, alglucidase and velaglucerase alfa were associated with the lowest number of patients in preapproval pivotal trials. In contrast, for dabigatran, a drug initially indicated for preventing venous thromboembolism in the European Union and to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation in the United States, preapproval pivotal trials had recruited the highest number of patients. The same figure also shows the proportions of patients enrolled in post-marketing studies designed for the originally approved indication, another indication and both.

Trial characteristics

Data regarding study phases are shown in Table 2; only 18.6% of identified post-marketing studies were considered phase IV studies, whereas the most prevalent category was phase II studies (32.6%). Data regarding randomization were missing for 2452 post-marketing studies (36.7%). Among the remaining studies for which these data were available, 3067 were randomized (72.6%). Other data are in Table 2.

Sponsor

Industry funded or partially funded nearly two-thirds of post-marketing studies. Indeed, as shown in Table 2, industry was the primary sponsor of 2713 studies (40.6%), but when also considering manufacturers as minority funders, industry was involved in a total of 4176 studies (62.5%). Data regarding post-marketing studies stratified by sponsorship are in Table 2. Figure 1 presents the drug sample with respect to the number of post-marketing studies and the proportion of industry and non-industry funders for each drug. Supplemental Material (S4) provides the same information but with a 4-year follow-up for each drug.

Conditions addressed in trials

Review of indications showed that 2441 post-marketing studies (36.5%) were launched for another indication than the originally approved indication. Figure 2 displays the number of non-approved indications studied in post-marketing studies for each drug of our sample, with information regarding the more advanced phase for each newly targeted indication. When comparing those studies with the total number of clinical studies (preapproval pivotal trials and post-marketing studies), we found a median proportion of 0.24 (IQR, 0.09-0.42). The median proportion for the population recruited in post-marketing studies designed for another indication than the originally approved indication to the total population from all clinical studies (preapproval pivotal trials and post-marketing studies) was 0.11 (IQR 0.03-0.30).

When analyzing the relationship between the study sponsor and the study indication, we found that studies for which industry was a sole or partial funder were less likely to assess the drug for another indication than the originally approved indication (54.6% of studies with industry funding vs 68.6% without industry funding; $p<0.0001$). Findings regarding planned enrollment according to the indication and stratified on funding origin are in Supplemental Material (eTable). Regardless of the funder, post-marketing studies targeting originally approved indications planned to enroll more patients than those studying other indications.

Timing

The annual number of post-marketing studies over the life-cycle of drugs, stratified by indication, is shown in Figure 3, exhibiting an asymmetric bell pattern, with a rapid increase in number of post-marketing studies launched, a peak of activity within the third year after the first regulatory submission, then a progressive decline in number of launched studies. Detailed examination shows a greater proportion of studies designed for another indication than the originally approved indication at the beginning and end of drug life-cycles. Supplemental Material (S5) is based on the same data but displays information regarding sponsors. Former post-marketing studies were predominantly funded by industry versus academic or not-for-profit entities and this proportion increased until the second year after the first regulatory submission. Afterwards, the proportion of non-industry funders tended to increase over time.

Location

Overall, 80% of post-marketing studies were conducted in only one country. For 66 drugs, at least one study was conducted in at least two countries. Sorafenib was the most concerned drug in this regard, with 74 studies involving at least two countries. Data regarding locations of studies for each drug are in Supplemental Material (S6). In brief, post-marketing research

was highly concentrated in North America (i.e., United States and/or Canada; 44.8% of all post-marketing studies of the sample) and Europe (25.0%). Post-marketing studies conducted in other areas represented 15.6% of all studies, and studies conducted in multiple continents were few. When examining the relation between study location and study design with respect to the original label, we found that studies from North America (United States and/or Canada) were more frequently conducted for indications other than the originally approved indication versus those located in Europe (50.4% v. 36.9%).

Supplemental indications

During the study period, 18 novel drugs (26.1%) were associated with a least a supplemental indication by the FDA: one with 4 supplemental indications, one with 3 supplemental indications, 5 with two supplemental indications and 11 with one supplemental indication. The mean time between the first regulatory submission and subsequent supplemental indication was 4.4 years (SD 1.7; IQR 3.3-5.7). The mean number of patients to be enrolled in post-marketing studies before approval of a supplemental indication was 12763.1 (SD 12474.3; IQR 3891.0-15856.0).

Discussion

In our study of post-marketing clinical research studies conducted for novel drugs approved by both the FDA and EMA between 2005 and 2010, we found high variability in number of post-marketing studies per drug and planned enrollment per study. Indeed, the median planned enrollment was low, 60 patients, with a median of 55 studies per drug, most of which had not yet been completed at a minimum of 4 years after approval. Locations were concentrated, with 72.3% of post-marketing studies conducted in North America and/or Europe and 80% conducted in only one country. Approximately 40% of post-marketing studies were designed for an indication other than the originally approved one, more

frequently concerning studies not involving industry funding. Overall, those findings reflect the lack of global coordination of post-marketing research for novel drugs.

Our study has several strengths. First, we focused on a sample of drugs approved by the two leading medical product regulators, FDA and EMA, which suggests that these drugs are likely to be of the greatest interest and importance to clinicians worldwide. Most previous studies focused on the FDA or EMA but rarely both. [20,21] Second, few comprehensive studies have analyzed post-marketing research despite its undisputed public health impact. [9–14] Most research focused on safety or was limited to a given therapeutic area, or even only one drug. In addition, we chose a large study period, with a 6-year span for drug approvals, and more than 10 years for the trial sample. Moreover, we followed a rigorous method for selecting post-marketing studies, excluding clinical trials included in the FDA submission, studies that had not been launched, studies mistakenly classified as involving the drug in ClinicalTrials.gov and studies whose starting date was too early as compared to regulatory submission. Third, we provide unique insights into the clinical research programs examining non-approved drug uses. Many studies have investigated off-label prescriptions, [22,23] but we used a slightly different approach. In effect, most drug labels are stringently phrased so as to be rigorously aligned to pivotal trial criteria. [24] Therefore, categorizing studies according to the actual off- or on-label status of the drug investigated would have led to classifying most as involving off-label drug use. Put another way, the label was judged too narrow, and our method offers a more significant picture for clinicians and epidemiologists. We believe that our classification better reflects substantial evolution regarding the initially authorized use of novel drugs.

Our findings raise several issues worthy of consideration about post-marketing research. First, we showed that post-marketing research is both a heterogeneous and concentrated landscape, probably linked to its loose regulation [6] and to market forces.

Therefore, most initiatives are at the discretion of funders, either industry or academic institutions, and driven by various factors not necessarily linked to medical need or relevancy. For instance, prior research has shown that many post-marketing trials were "seeding trials", designed for marketing purposes rather than scientific relevancy. [7,8] The number of post-marketing studies per novel drug and planned enrollment were highly variable, but most studies were conducted in only one country and North America and Europe were by far the most frequent locations. Median planned enrollment was low and many studies were still not completed at the time of data acquisition. These findings question the absence of steering or the lack of effectiveness or incentive policies for post-marketing research. Second, almost 40% of post-marketing studies were designed for an indication other than the originally approved indication, with non-industry trials more likely concerned. Although industry has been blamed for testing their products in a too-liberal manner, [25] our findings suggest that academics and other non-industry bodies might be more prone to assess authorized drugs in innovative ways to evaluate novel indications. Third, we found that post-marketing studies designed for the originally approved indication planned to enroll a greater number of patients on average than those targeting novel indications. This latter finding is somewhat reassuring because post-marketing studies for an already approved indication aim to refine knowledge regarding the long-term effect and/or safety and should therefore include more patients than preapproval pivotal trials.

Our study has limitations. The first may be a registration bias at ClinicalTrials.gov, which would alter the exhaustiveness of our assessment. Some studies are not registered by researchers [26,27] and were therefore not included in our study. Others are imperfectly registered, with some information missing. However, ClinicalTrials.gov is widely recognized as a benchmark registry, and recent reports showed that compliance might have improved over time. [28] Another limitation is the definition of post-marketing studies, in that clinical

studies are designed and launched according to a continuous timing and a single threshold might be lacking for distinguishing pre- and post-marketing trials. Therefore, we decided to consider studies starting at most 1 year before the first regulatory submission as post-marketing studies even though we could have made another choice. A third limitation is related to data sources. For some data, we relied on only one of the two selected regulators. We used such an approach for the sake of convenience and recognize that this could be interpreted as a bias, yet to our knowledge, there are very few if any differences in data between the two studied regulators. Therefore, this latter limitation in the methods seems unlikely to affect our findings. Finally, we could not identify whether post-marketing trials were relevant or useful because we did not analyze their design, endpoints, or comparators, among other factors.

In conclusion, our research shows that post-marketing research is highly variable and concentrated, with on one hand, great differences in the number of post-marketing studies per drug and in planned enrollment and on the other, most studies being conducted in only one country, with North America and Europe the most represented locations. Approximately 40% of post-marketing studies assessed the drug for an indication other than the originally approved indication, more frequently non-industry studies. Even though some of our findings can be seen as reassuring, others underline the lack of global coordination of post-marketing research for novel drugs despite the undisputed influence of such research.

Contributors: Dr. Zeitoun and Pr. Ravaud were responsible for the conception and design of this work. Dr. Zeitoun drafted the manuscript and was responsible for most of the data acquisition. M. Ignacio Atal was responsible for data exportation and structuration. Dr. Nicholas Downing was responsible for some of the data acquisition. Dr. Gabriel Baron

conducted the statistical analysis. Drs. Ross and Ravaud provided supervision. All authors participated in the analysis and interpretation of the data and critically revised the manuscript for important intellectual content.

Data sharing statement: Data files are available from the corresponding author on reasonable request.

Acknowledgements: The authors are grateful to EMA officials who graciously helped them classify drug manufacturers. They also thank Geoffroy Beraud-Chaulet for his useful work on Drugs@FDA and Elise Diard for her invaluable help on figures.

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Legends

Figure 1: Number of post-marketing studies and respective proportion of industry and non-industry funders.

Figure 2: Number of non-approved indications targeted in post-marketing studies for each drug of our study sample. Indications are rank-ordered on the basis of the number of post-marketing studies launched (from the greatest number of post-marketing studies on the left side of the figure to the lowest number on the right side). Color of boxes varies according to the advanced phase of the targeted indication. Indications are classified according to the Global Burden of Diseases classification. [29] Indications belonging to residual categories or health conditions not relevant to the Global Burden of Diseases were excluded and therefore are not represented in the Figure.

Figure 3: Annual number of post-marketing studies over the life-cycle of drugs, stratified by indication.

Supplemental File S1: Flow chart leading to the final study sample of 6679 relevant post-marketing studies.

Supplemental File S2: Total number of patients to be included in post-marketing studies for each drug.

Supplemental File S3: Population in preapproval pivotal trials and post-marketing studies.

Supplemental File S4: Number of post-marketing studies and respective proportion of industry and non-industry funders, with a 4-year follow-up for each drug.

Supplemental File S5: Annual number of post-marketing studies over the life-cycle of drugs, stratified by sponsor.

Supplemental File S6: Locations of post-marketing studies.

Supplemental File S7: Data from S2, S3 and S6, presented as tables.

Table 1. Characteristics of 69 novel drugs approved by both the FDA and EMA between 2005 and 2010 (excluding everolimus and temsirolimus).

Characteristics	**n (%)**
Agent type	
Small molecule	51 (73.9%)
Biologic	18 (26.1%)
Orphan status (FDA)	18 (26.1%)
Orphan designation (EMA)	20 (29.0%)
Accelerated approval (FDA)	14 (20.3%)
Therapeutic class according to the ATC classification	
Alimentary tract and metabolism	10 (14.5%)
Anti-infectives for systemic use	12 (17.4%)
Antineoplastic and immunomodulating agents	20 (29.0%)
Blood and blood forming organs	5 (7.2%)
Cardiovascular system	5 (7.2%)
Nervous system	6 (8.7%)
Other*	11 (15.9%)
Degree of novelty (according to Lanthier *et al*)	
First-in-class	24 (34.8%)
Advance-in-class	24 (34.8%)
Addition-to-class	21 (30.4%)
Size of the marketing-authorization holder	
Large pharmaceutical company	44 (63.8%)
Intermediated-size company	23 (33.3%)
Small- and medium-size company	2 (2.9%)
Premarket evidence	

Total no. of included patients	
Min/max	18/18040
Median [Q1-Q3]	923 [324-1996]
Mean (SD)	1806 (2897)
Expected length of treatment	
Acute	8 (11.6%)
Intermediate	14 (20.3%)
Chronic	47 (68.1%)

ATC, Anatomical Therapeutic Chemical

*includes dermatological, genitourinary system and sex hormones, musculoskeletal system, sensory organs, systemic hormonal preparations, excluding sex hormones, and others

Table 2. Characteristics of industry and non-industry post-marketing studies registered at ClinicalTrials.gov before September 24, 2014 for the 69 novel drugs in the study sample.

Characteristics			Industry studies	Non-industry studies
Primary sponsor	Industry NIH US Fed Other	2713 (40.6%) 286 (4.3%) 15 (0.2%) 3665 (54.9%)		
Industry involved either as a primary sponsor or a collaborator		4176 (62.5%)		
No. of post-marketing studies per drug	Min/max Median [Q1-Q3] Mean (SD)	3/530 55 [30-119] 96.8 (110.3)		
Population size per drug	Min/max Median [Q1-Q3] Mean (SD)	67/1.05E6 15418 [4932-37523] 62748 (166644)		

Therapeutic class according to the ATC				
Alimentary tract and metabolism		832 (12.5%)	570 (68.5%)	262 (31.5%)
Anti-infectives for systemic use		828 (12.4%)	504 (60.9%)	324 (39.1%)
Antineoplastic and immunomodulating agents		3040 (45.5%)	1818 (59.8%)	1222 (40.2%)
Blood and blood forming organs		446 (6.7%)	277 (62.1%)	169 (37.9%)
Nervous system		485 (7.3%)	304 (62.7%)	181 (37.3%)
Other*		1048 (15.7%)	703 (67.1%)	345 (32.9%)
Study design with respect to primary label	Another indication than the originally approved indication	2561 (38.3%)	1397 (54.5%)	1164 (45.5%)
	Originally approved indication	3889 (58.2%)	2666 (68.6%)	1223 (31.4%)
	Both the originally approved indication and another indication	229 (3.4%)	113 (49.3%)	116 (50.7%)
Study type	Observational	707 (10.6%)	468 (66.2%)	239 (33.8%)
	Interventional	5972 (89.4%)	3708 (62.1%)	2264 (37.9%)

Randomization	Missing data	2452		
	Yes	3067 (72.6%)	1979 (64.5%)	1088 (35.5%)
	No	1160 (27.4%)	769 (66.3%)	391 (33.7%)
Study phase	0	34 (0.6%)	13 (38.2%)	21 (61.8%)
	I	933 (16.6%)	651 (69.8%)	282 (30.2%)
	I/II	423 (7.5%)	245 (58.0%)	178 (42.0%)
	II	1837 (32.6%)	1047 (57.0%)	790 (43.0%)
	II/III	109 (1.9%)	52 (47.7%)	57 (52.3%)
	III	1246 (22.1%)	1018 (81.7%)	228 (18.3%)
	IV	1045 (18.6%)	596 (57.0%)	449 (43.0%)
Centers	Missing data	503	428	75
	Min/max	1/1616	1/1616	1/922
	Median [Q1-Q3]	2 [1-12]	4 [1-23]	1 [1-2]
	Mean (SD)	19.9 (62.1)	26.4 (70.5)	9.8 (44.7)
Countries	Min/max	1/46	1/46	1/15
	Median [Q1-Q3]	1 [1-1]	1 [1-2]	1 [1-1]
	Mean (SD)	2.6 (4.7)	3.6 (5.8)	1.1 (0.7)

Planned enrollment	Min/max	1/904585	1/904585	1/61050
	Median [Q1-Q3]	60 [28-183]	72 [30-248]	48 [24-100]
	Mean (SD)	649.6 (12812)	943.8 (16167)	158.9 (1274.7)
Status at the time of data exportation	Not yet recruiting	319 (4.8%)	136 (42.6%)	183 (57.4%)
	Recruiting	1895 (28.4%)	886 (46.8%)	1009 (53.2%)
	Active, not recruiting	1013 (15.2%)	627 (61.9%)	386 (38.1%)
	Enrolling by invitation	64 (1.0%)	42 (65.6%)	22 (34.4%)
	Completed	2901 (43.4%)	2147 (74.0%)	754 (26.0%)
	Terminated	487 (7.3%)	338 (69.4%)	149 (30.6%)

NIH, US National Institutes of Health

*includes cardiovascular system, dermatological, genitourinary system and sex hormones, musculoskeletal system, sensory organs, systemic hormonal preparations, excluding sex hormones, and other

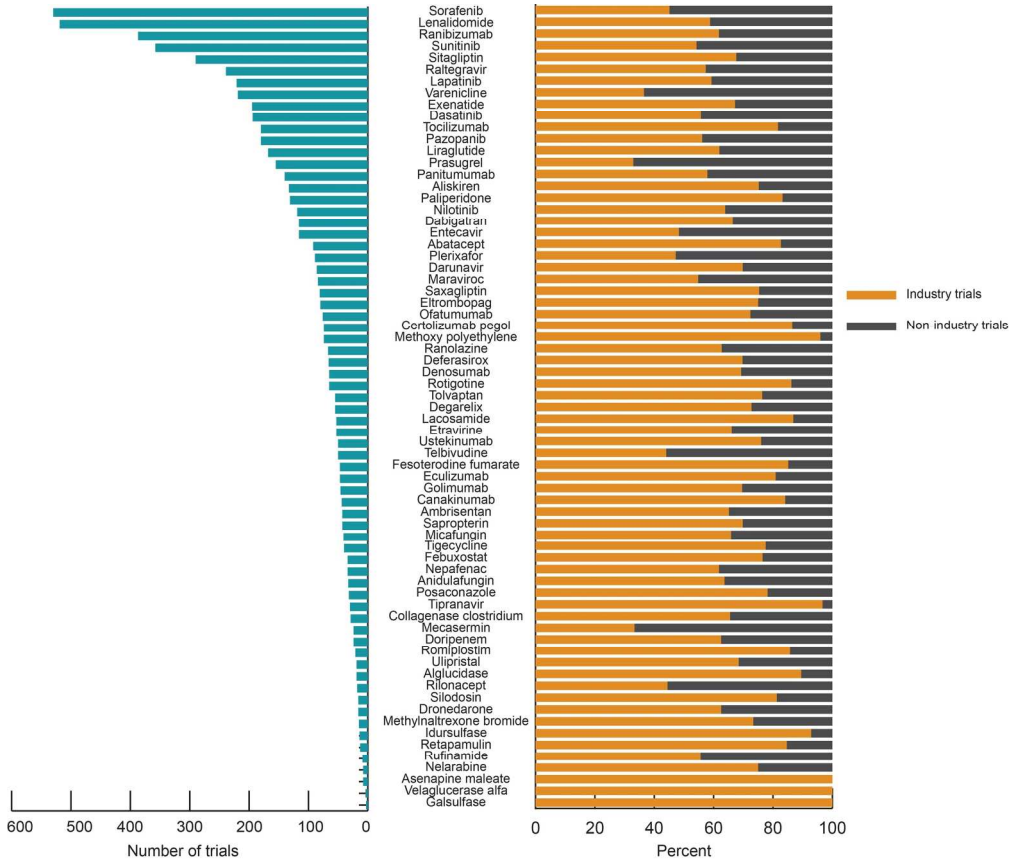

Figure 1

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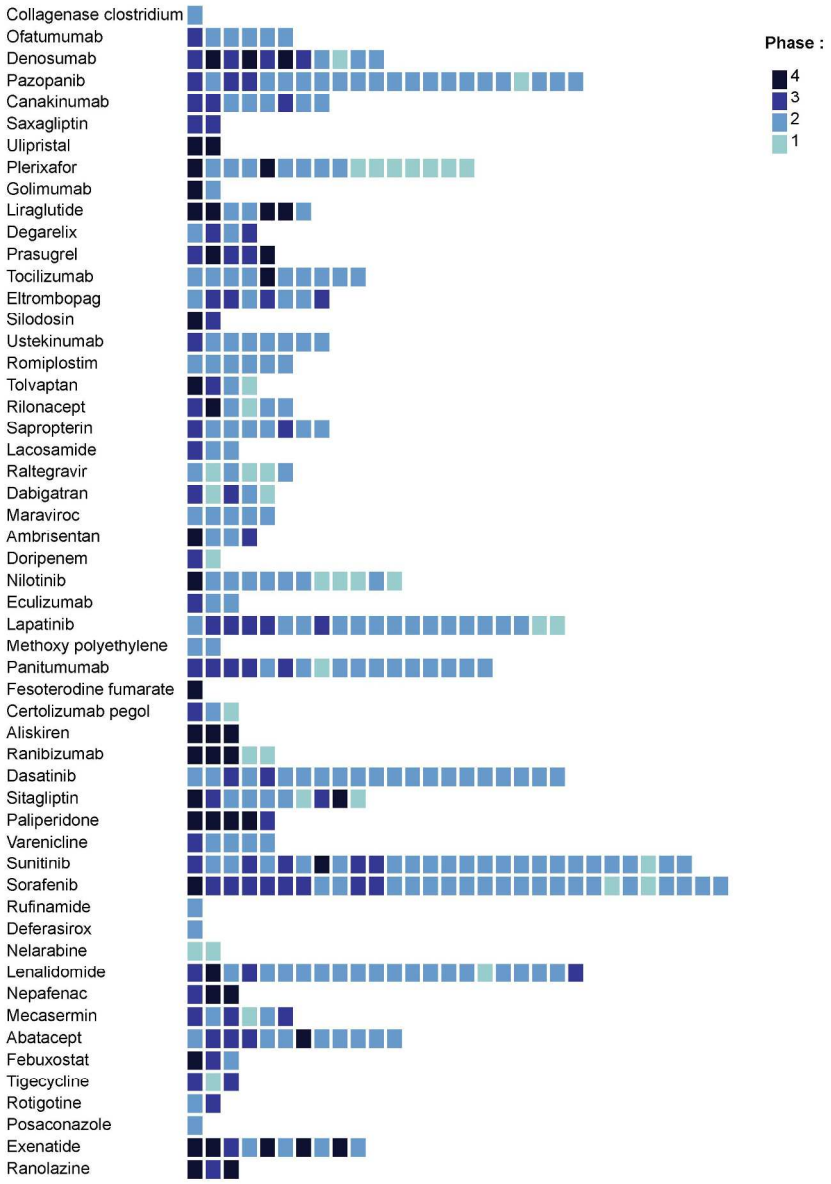

Figure 2

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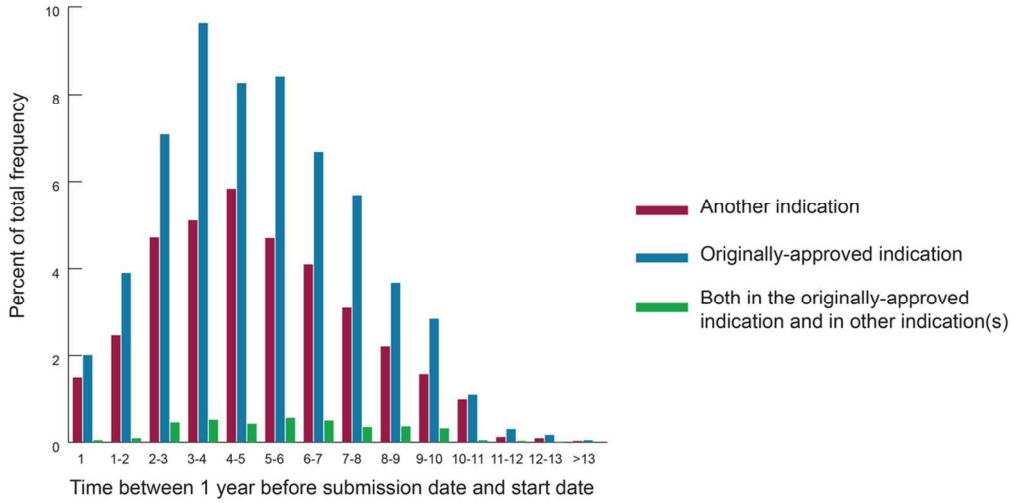

Figure 3

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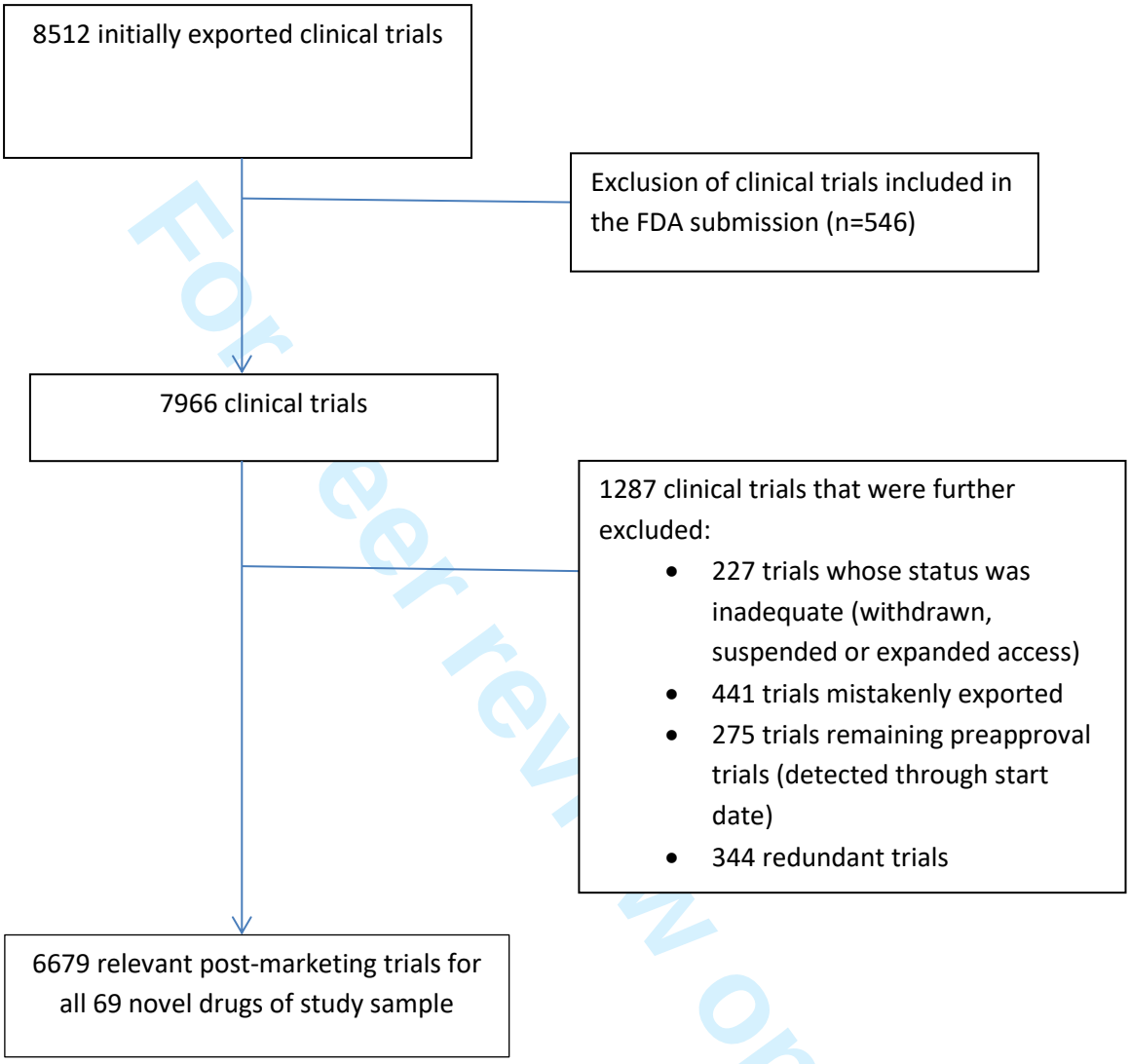
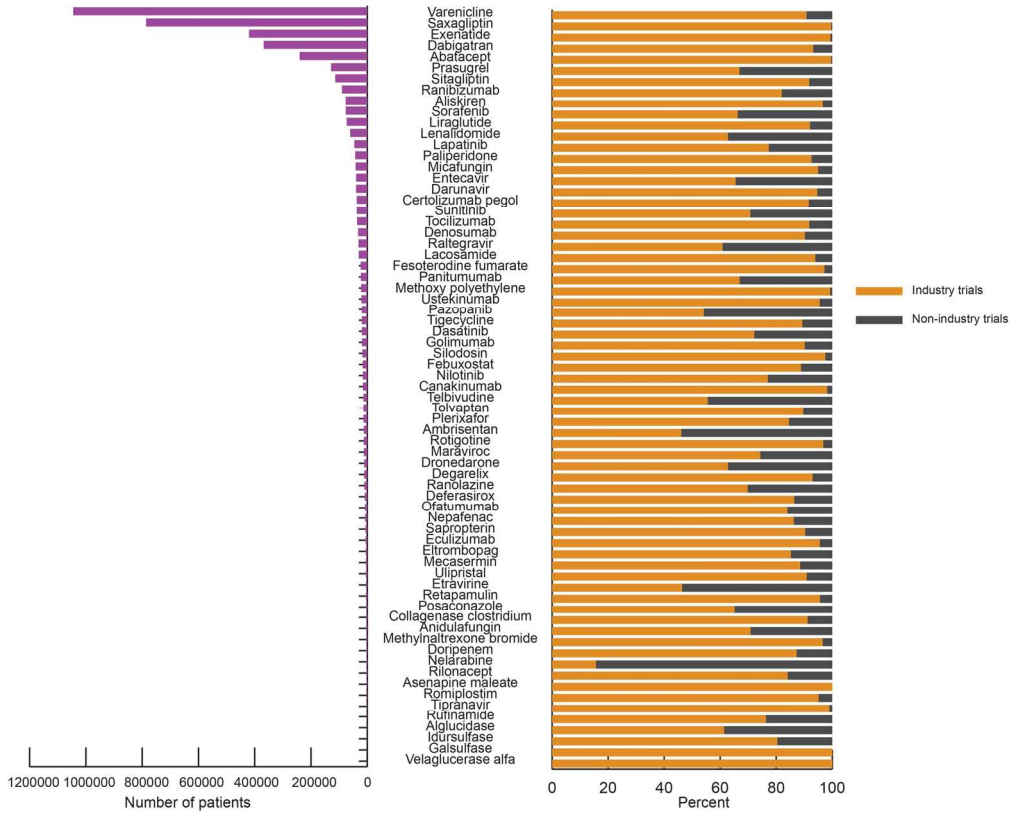
Supplemental Material 1. Sample construction of relevant post-marketing trials related to all 69 novel drugs both approved by the FDA and the EMA between 2005 and 2010, after exclusion of everolimus and temsirolimus





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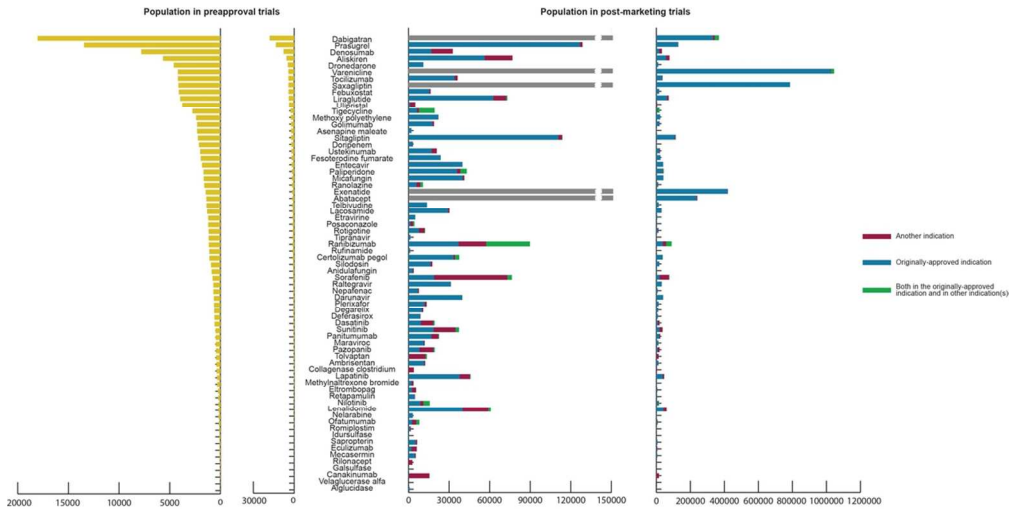

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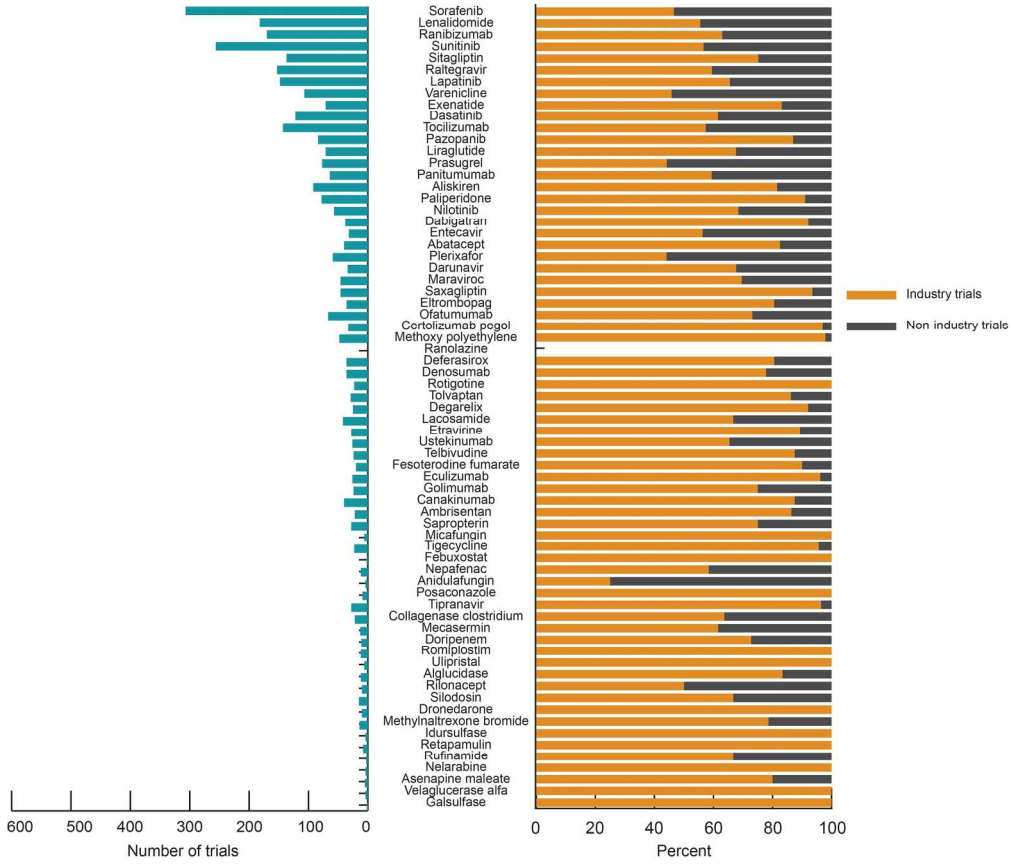

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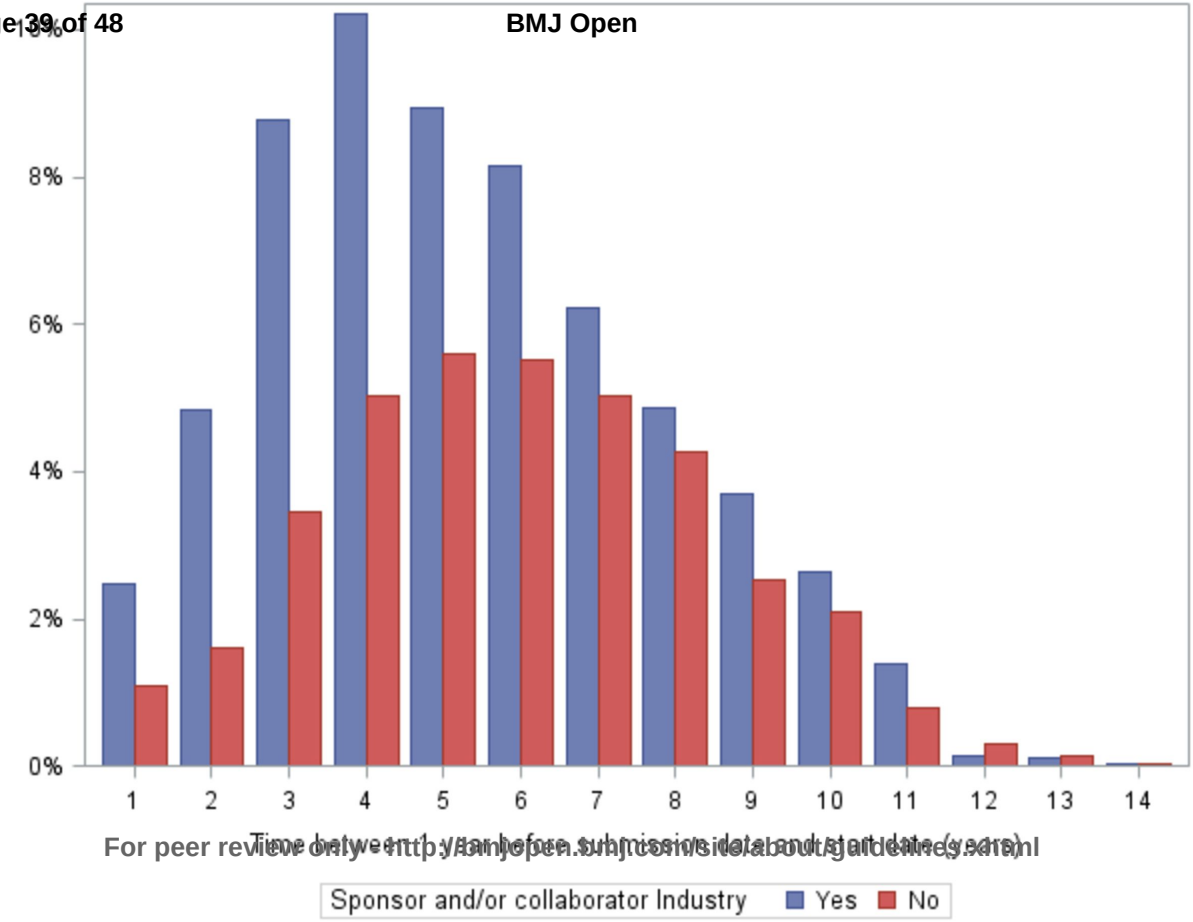

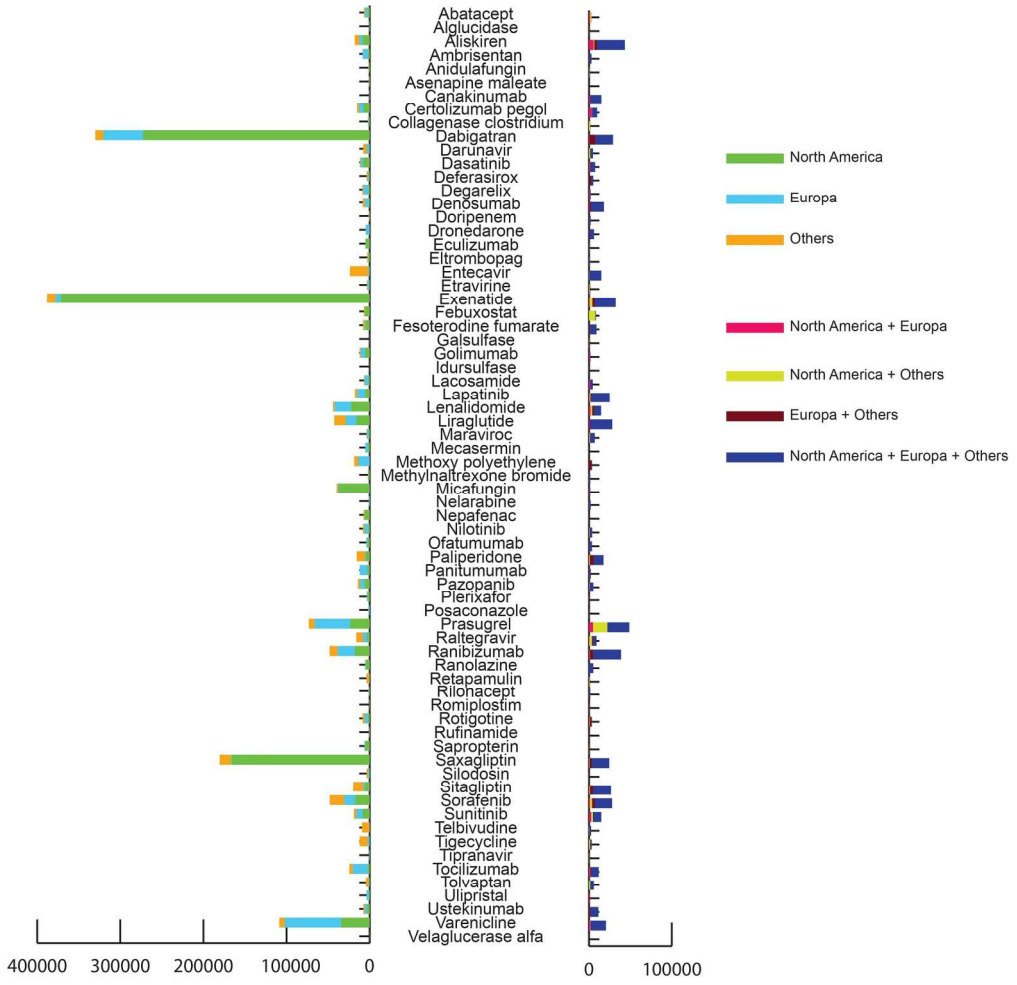

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Supplemental file S2 **bis**: Total number of patients to be included in post-marketing studies for each drug

Drug	Total number of patients to be included in post-marketing studies	Percentage of industry funders	Percentage of non-industry funders
Varenicline	1045002	90.8	9.2
Saxagliptin	785853	99.6	0.4
Exenatide	420256	99.3	0.7
Dabigatran	368063	93.1	6.9
Abatacept	240227	99.6	0.4
Prasugrel	128744	66.9	33.1
Sitagliptin	113824	91.8	8.2
Ranibizumab	89765	81.9	18.1
Aliskiren	76864	96.6	3.4
Sorafenib	76434	66.2	33.8
Liraglutide	73106	92.0	8.0
Lenalidomide	60805	62.8	37.2
Lapatinib	45881	77.4	22.6
Paliperidone	43024	92.6	7.4
Micafungin	41363	95.0	5.0
Entecavir	39787	65.5	34.5
Darunavir	39773	94.7	5.3
Certolizumab pegol	37523	91.6	8.4
Sunitinib	37320	70.7	29.3
Tocilizumab	36262	91.8	8.2
Denosumab	32688	90.2	9.8
Raltegravir	31285	60.8	39.2
Lacosamide	30236	93.9	6.1
Fesoterodine fumarate	23699	97.2	2.8
Panitumumab	22585	66.9	33.1
Methoxy polyethylene	22102	99.2	0.8
Ustekinumab	20873	95.5	4.5
Pazopanib	19332	54.1	45.9
Tigecycline	19322	89.3	10.7
Dasatinib	19320	72.2	27.8
Golimumab	18801	90.1	9.9
Silodosin	17591	97.5	2.5
Febuxostat	16330	88.8	11.2
Nilotinib	15657	77.0	23.0
Canakinumab	15418	98.2	1.8
Telbivudine	13590	55.6	44.4
Tolvaptan	13552	89.7	10.3
Plerixafor	13450	84.6	15.4
Ambrisentan	12300	46.1	53.9

Drug	Total number of patients to be included in post-marketing studies	Percentage of industry funders	Percentage of non-industry funders
Rotigotine	12258	96.8	3.2
Maraviroc	11957	74.3	25.7
Dronedarone	10947	62.7	37.3
Degarelix	10811	93.0	7.0
Ranolazine	10614	69.8	30.2
Deferasirox	8812	86.4	13.6
Ofatumumab	7988	84.0	16.0
Nepafenac	7627	86.2	13.8
Sapropterin	6328	90.3	9.7
Eculizumab	6065	95.5	4.5
Eltrombopag	5590	85.2	14.8
Mecasermin	5291	88.5	11.5
Ulipristal	4932	90.9	9.1
Etravirine	4881	46.4	53.6
Retapamulin	4819	95.6	4.4
Posaconazole	4391	65.1	34.9
Collagenase clostridium	3897	91.2	8.8
Anidulafungin	3819	70.8	29.2
Methylnaltrexone bromide	3581	96.6	3.4
Doripenem	3204	87.3	12.7
Nelarabine	3104	15.6	84.4
Rilonacept	2790	84.1	15.9
Asenapine maleate	2179	100.0	0.0
Romiplostim	1627	95.1	4.9
Tipranavir	1401	98.9	1.1
Rufinamide	1174	76.3	23.7
Alglucidase	803	61.4	38.6
Idursulfase	408	80.4	19.6
Galsulfase	269	100.0	0.0
Velaglucerase alfa	67	100.0	0.0

Supplemental file S3 **bis**: Population in preapproval pivotal trials and post-marketing studies

Drug	Population in preapproval pivotal trials	Population in post-marketing studies			
		Another indication	Originally-approved indication	Both in originally approved indication and in other(s) indication	Total
Dabigatran	18040	10896	332151	25016	368063
Prasugrel	13457	1960	126669	115	128744
Denosumab	7808	15825	16863	0	32688
Aliskiren	5663	20625	56239	0	76864
Dronedarone	4604	20	10927	0	10947
Varenicline	4198	1847	1024229	18926	1045002
Tocilizumab	4190	2201	34061	0	36262
Saxagliptin	4148	396	785457	0	785853
Febuxostat	4101	854	15476	0	16330
Liraglutide	3978	9509	62587	1010	73106
Ulipristal	3754	4012	920	0	4932
Tigecycline	2758	1339	6291	11692	19322
Methoxy polyethylene	2398	8	22094	0	22102
Golimumab	2297	1222	17579	0	18801
Asenapine maleate	2294	0	2179	0	2179
Sitagliptin	2220	2794	110745	285	113824
Doripenem	2117	267	2937	0	3204
Ustekinumab	1996	3793	17080	0	20873
Fesoterodine fumarate	1935	182	23517	0	23699
Entecavir	1814	0	39787	0	39787
Paliperidone	1665	2548	35755	4721	43024
Micafungin	1643	1105	39983	275	41363
Ranolazine	1593	2945	5773	1896	10614
Exenatide	1446	2810	417301	145	420256
Abatacept	1382	5622	234605	0	240227
Telbivudine	1367	0	13590	0	13590
Lacosamide	1308	1133	29103	0	30236
Etravirine	1203	0	4881	0	4881
Posaconazole	1202	1949	1282	1160	4391
Rotigotine	1163	4067	7671	520	12258
Tipranavir	1159	0	1365	36	1401
Ranibizumab	1139	20541	36906	32318	89765
Rufinamide	1097	288	886	0	1174
Certolizumab pegol	1088	1200	33077	3246	37523
Silodosin	923	1339	16252	0	17591
Anidulafungin	857	792	2993	34	3819
Sorafenib	769	54317	18809	3308	76434
Raltegravir	699	83	31202	0	31285
Nepafenac	688	815	6812	0	7627
Darunavir	637	0	39773	0	39773

Drug	Population in preapproval pivotal trials	Population in post-marketing studies			
		Another indication	Originally-approved indication	Both in originally approved indication and in other(s) indication	Total
Plerixafor	623	1467	11644	339	13450
Degarelix	610	791	10020	0	10811
Deferasirox	586	153	8609	50	8812
Dasatinib	565	9267	9090	963	19320
Sunitinib	481	16462	18362	2496	37320
Panitumumab	461	5197	16874	514	22585
Maraviroc	448	560	11397	0	11957
Pazopanib	435	10363	8060	909	19332
Tolvaptan	418	12221	356	975	13552
Ambrisentan	393	715	11585	0	12300
Collagenase clostridium	374	3897	0	0	3897
Lapatinib	324	7678	37714	489	45881
Methylnaltrexone bromide	321	1359	2222	0	3581
Eltrombopag	232	2957	2533	100	5590
Retapamulin	210	267	4417	135	4819
Nilotinib	196	2431	8531	4695	15657
Lenalidomide	193	19105	39873	1827	60805
Nelarabine	190	35	3069	0	3104
Ofatumumab	154	3076	2595	2317	7988
Romiplostim	125	543	1084	0	1627
Idursulfase	96	0	408	0	408
Sapropterin	88	1133	5195	0	6328
Eculizumab	87	3861	2204	0	6065
Mecasermin	70	623	4668	0	5291
Rilonacept	47	2765	25	0	2790
Galsulfase	39	0	269	0	269
Canakinumab	31	15157	261	0	15418
Velaglucerase alfa	25	0	67	0	67
Alglucidase	18	0	803	0	803

Supplemental file S6 **bis**: Location of post-marketing studies (sample size by location)

	Location						
	North America	Europa	Others	North America + Europa	North America + Others	Europa + Others	North America + Europa + Others
Abatacept	2267	2801	1575	1255	1715	0	9390
Alglucidase	633	5	0	83	22	20	40
Aliskiren	8269	3870	5760	5467	975	3097	33667
Ambrisentan	2128	6116	196	64	524	0	2330
Anidulafungin	1115	225	214	0	282	21	776
Asenapine maleate	950	0	0	0	0		0
Canakinumab	164	320	34	1037	0	274	13569
Certolizumab pegol	7278	5383	2401	3225	271	0	6265
Collagenase clostridium	1402	541	79	0	1286	0	400
Dabigatran	272415	47930	9639	636	0	7096	21220
Darunavir	755	2880	4076	12	1213	576	2940
Dasatinib	7476	2941	1139	768	195	484	5866
Deferasirox	1473	1023	1148	0	0	2506	2575
Degarelix	1613	5646	1522	783	0	0	1147
Denosumab	1168	4547	2692	427	0	1439	16134
Doripenem	82	195	818	52	0	0	1911
Dronedarone	480	4143	279	0	0	556	5436
Eculizumab	4683	447	52	60	92	80	463
Eltrombopag	1486	458	992	82	0	100	1059
Entecavir	807	1096	21848	4	200	184	14460
Etravirine	857	1730	570	30	671	279	536
Exenatide	371779	5876	10283	736	3323	2963	25151
Febuxostat	5473	0	1424	0	7500	0	744
Fesoterodine fumarate	4555	1231	2245	0	0	794	8210

	Location						
	North America	Europa	Others	North America + Europa	North America + Others	Europa + Others	North America + Europa + Others
Galsulfase	10	0	0	0	200	0	59
Golimumab	5459	5031	1361	706	11	120	811
Idursulfase	0	0	81	79	0	108	118
Lacosamide	1597	4167	946	1210	0	0	3281
Lapatinib	5446	9359	2989	502	1106	876	22398
Lenalidomide	22422	19825	1874	1804	1916	1972	8846
Liraglutide	15787	12960	13865	717	0	415	26892
Maraviroc	1268	1849	561	129	876	186	5698
Mecasermin	2073	3198	0	0	0	0	0
Methoxy polyethylene	340	13375	4841	0	0	2828	718
Methylnaltrexone bromide	1968	31	0	0	0	0	1462
Micafungin	37521	664	1518	0	84	619	836
Nelarabine	95	720	13	0	36	40	1900
Nepafenac	5927	227	1021	0	0	0	0
Nilotinib	1660	4393	1964	175	512	218	2882
Ofatumumab	2401	1549	20	60	14	122	3294
Paliperidone	4400	1064	10125	0	838	4753	11816
Panitumumab	2888	8858	164	375	0	0	1700
Pazopanib	5947	5436	2684	374	207	102	4518
Plerixafor	2374	850	164	0	61	46	0
Posaconazole	154	1370	126	96	0	0	600
Prasugrel	23597	42550	7015	4760	17372	0	26550
Raltegravir	3106	4949	8048	366	3156	1173	4308
Ranibizumab	17679	20576	9883	694	232	3832	33851
Ranolazine	4524	551	310	0	0	0	5102

	Location						
	North America	Europa	Others	North America + Europa	North America + Others	Europa + Others	North America + Europa + Others
Retapamulin	784	0	3000	0	508	465	60
Rilonacept	1242	30	0	0	0	244	1274
Romiplostim	280	119	76	63	62	0	175
Rotigotine	2229	3696	2553	220	601	2197	371
Rufinamide	230	278	366	75	0	0	0
Sapropterin	5120	1018	0	0	190	0	0
Saxagliptin	166072	594	13757	0	501	2670	21205
Silodosin	885	1196	1559	0	0	0	0
Sitagliptin	5577	2079	12049	164	804	3770	21728
Sorafenib	17405	13223	17312	973	2681	3230	20954
Sunitinib	8448	7676	2806	2557	2006	167	10074
Telbivudine	159	132	8934	0	308	367	1790
Tigecycline	473	1987	9632	0	1175	473	1588
Tipranavir	71	504	0	0	246	0	84
Tocilizumab	2511	17868	4033	1054	228	1270	9070
Tolvaptan	1227	304	3131	0	1300	0	4500
Ulipristal	855	2845	51	579	60	542	0
Ustekinumab	2823	2649	2004	166	0	1290	9859
Varenicline	34574	67592	6523	1307	360	0	18706
Velaglucerase alfa	0	50	17	0	0	0	0

eTable. Planned enrollment of post-marketing trials by industry and non-industry funding for indications targeted in trials.

Indication	Industry funding		Non-industry funding	
	No. of trials	Planned enrollment	No. of trials	Planned enrollment
Originally approved indication	2742	Median [Q1-Q3]: 100 [33-323] Mean (SD): 1322.0 (19921.8)	1251	Median [Q1-Q3]: 60 [29.5-150] Mean (SD): 230.9 (1771.2)
Other indication(s)	1310	Median [Q1-Q3]: 45 [24-128] Mean (SD): 167.7 (SD: 544.1)	1131	Median [Q1-Q3]: 40 [21-70] Mean (SD): 72.9 (148.0)
Both the originally approved indication and another indication	124	Median [Q1-Q3]: 60 [30-224] Mean (SD): 765.2 (2961.8)	121	Median [Q1-Q3]: 50 [30-120] Mean (SD): 218.1 (934.9)

Data were missing for 9 industry-funded trials and 5 other trials.

BMJ Open

Post-marketing studies for novel drugs approved by both the FDA and EMA between 2005 and 2010: a cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018587.R2
Article Type:	Research
Date Submitted by the Author:	03-Nov-2017
Complete List of Authors:	Zeitoun, Jean-David; Hôtel Dieu Hospital, Epidémiologie Clinique; Saint-Antoine Hospital, Gastroenterology and Nutrition Ross, Joseph; Yale University School of Medicine, Internal Medicine Atal, Ignacio; Hotel Dieu Hospital, Epidémiologie Clinique Vivot, Alexandre; Hotel Dieu Hospital, Epidémiologie Clinique Downing, Nicholas; Brigham and Women's Hospital and Harvard Medical School, Medicine Baron, Gabriel; INSERM U1153; Hôtel Dieu Hospital, Centre d'Epidémiologie Clinique Ravaud, Philippe; Université Paris Descartes, Centre d'épidémiologie clinique; INSERM U1153
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Research methods, Public health
Keywords:	THERAPEUTICS, STATISTICS & RESEARCH METHODS, EPIDEMIOLOGY

Post-marketing studies for novel drugs approved by both the FDA and EMA between 2005 and 2010: a cross-sectional study

Jean-David Zeitoun, MD, MHPM, PhD candidate [1, 2, 3], Joseph S. Ross, MD, MHS [4, 5, 6, 7], Ignacio Atal, MSc [1, 8], Alexandre Vivot, MD, MPH, [1,8], Nicholas S. Downing, MD [9], Gabriel Baron, PhD [1, 8, 10], Philippe Ravaud, MD, PhD [1, 8, 10, 11]

1. Centre d'Épidémiologie Clinique, Hôpital Hôtel Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France
2. Gastroenterology and Nutrition, Hôpital Saint-Antoine, Assistance Publiques-Hôpitaux de Paris, Paris, France
3. Proctology, Groupe Hospitalier Diaconesses-Croix Saint-Simon, Paris, France
4. Department of Internal Medicine, Robert Wood Johnson Foundation Clinical Scholars Program, Yale School of Medicine, New Haven, Connecticut, USA
5. Department of Internal Medicine, Section of General Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA
6. Department of Health Policy and Management, Yale School of Public Health, New Haven, Connecticut, USA
7. Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Connecticut, USA
8. INSERM UMR 1153, Centre de Recherche Épidémiologie et Statistique Paris Sorbonne Cité (CRESS), METHODS Team, Paris, France
9. Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts
10. Université Paris Descartes, Sorbonne Paris Cité, Paris, France
11. Department of Epidemiology, Columbia University Mailman School of Public Health, New York, New York, United States of America.

Corresponding author: Dr. Jean-David Zeitoun, MD, MHPM, PhD candidate, Centre d'Epidémiologie Clinique, Hôpital Hôtel Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France. E-mail: jdzeitoun@yahoo.fr

Word count: 3867

Abstract: 279

References: 29

Figures: 3

Tables: 2

ABSTRACT

Objectives: To characterize post-marketing studies for drugs that were newly approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Design and Setting: Cross-sectional analysis of post-marketing studies registered in ClinicalTrials.gov until September 2014 for all novel drugs approved by both regulators between 2005 and 2010. Regulatory documents from both agencies were used.

Primary and secondary outcome measures: All identified post-marketing studies were classified according to planned enrolment, funding, status, and geographical location, and we determined whether studies studied the originally approved indication.

Results: Overall, 69 novel drugs approved between 2005 and 2010 were eligible for inclusion. A total of 6679 relevant post-marketing studies were identified; 5972 were interventional (89.4%). The median number of studies per drug was 55 (interquartile range [IQR]: 33-119) and median number of patients to be enrolled per study was 60 (IQR, 28-183). Industry was the primary sponsor of 2713 studies (40.6%) and was a primary or secondary sponsor in 4176 studies (62.5%). In all, 2901 studies (43.4%) were completed, 487 (7.3%) terminated, 1013 (15.2%) active yet not recruiting, 1895 (28.4%) recruiting, and 319 (4.8%) not yet recruiting. A total of 80% of studies were conducted in only one country and 84.4% took place in Europe and/or North America; 2441 (36.5%) studied another indication than the originally approved indication. Studies designed in the originally-approved indication were found to be more industry-sponsored than others 68.7% vs. 53.7%; p<0.0001).

Conclusions: Post-marketing pharmaceutical research was highly variable and predominantly located in North America and Europe. Post-marketing studies were frequently designed to study indications other than the originally approved one. Although some findings were reassuring, others question the lack of coordination of post-marketing research.

Strengths and limitations of this study

This is the first study to systematically assess clinical studies performed after marketing approval by the two leading regulators, namely the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

This approach allowed us to examine a substantial number of post-marketing studies over a long time period.

However and due to registration bias, we cannot exclude that some true post-marketing studies were missed and therefore unanalyzed.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: Dr. Zeitoun reports that he serves as an advisor for several consulting firms and communication companies linked with the pharmaceutical industry (Cepton, Oliver Wyman, Roland Berger, McCann Healthcare, Omnicom, Grey Healthcare, Saatchi and Saatchi Healthcare, Sudler & Hennessey, TBWA, inVentiv Health France, Havas). He also reports compensation for lectures given to manufacturer professional associations; collaboration with Mayoly-Spindler, Merck, Teva, Johnson & Johnson, and Menarini; unpaid consultancy for EY; conducting workshops funded by Amgen; and being invited to a French medical congress by AbbVie. Dr. Ross receives support through Yale University from Johnson and Johnson to develop methods of clinical trial data-sharing; from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting; from Medtronic, Inc. and the US FDA to develop methods for

post-market surveillance of medical devices; from the Blue Cross Blue Shield Association to better understand medical technology evaluation; and from the Laura and John Arnold Foundation to support the Collaboration on Research Integrity and Transparency (CRIT) at Yale.

Introduction

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are the two largest and most influential drug regulators worldwide. They tend to maintain similar premarket regulatory standards, and drug manufacturers probably tend to submit the same evidence to both as part of the premarket application process, even though we lack comparative data. Drug evaluation continues after regulatory approval, in particular through post-authorization requirements and commitments. The US FDA can use several regulatory instruments and harness various sources for post-marketing evaluation of approved drugs. Among them are the FDA Adverse Reporting System and the Sentinel System. [1] The EMA also has a set of post-authorization measures, from direct request by its dedicated committee, to specific obligations for certain drugs, all aiming at retrieving data for post-marketing assessment.[2] Yet these post-marketing clinical studies required by regulators are limited in number and are not consistently completed. [3–5] This situation raises the question of whether other studies of these drugs after regulatory approval, including those conducted by industry and independent investigators, but not to fulfill regulatory requirements, should be considered part of ongoing, continuous evaluation efforts.

Post-marketing studies are designed with different intent than are premarket trials. Their designs are not systematically submitted to regulatory agencies before initiation because many post-marketing studies are conducted by independent investigators, and their conduct is less rigorously regulated. [6] Post-marketing studies seek to evaluate safety regarding rare events, to assess the real-life effectiveness of novel drugs and to measure their long-term effects. They also permit drug evaluation in different populations, other indications for the same disease, other diseases or with different delivery systems or dosage forms. Moreover, although premarket trials are nearly exclusively sponsored by the manufacturers, post-marketing studies can be funded by manufacturers but also academic or other types of non-

profit institutions. Some research also suggested that a substantial proportion of post-marketing trials, even those with results eventually published in high-impact-factor journals, were designed for marketing purposes rather than medical interest. [7,8]

Nevertheless, post-marketing studies have considerable influence on all stakeholders, in particular researchers, practitioners and regulators or decision makers, because they provide cumulative evidence regarding marketed products. However, we lack an overall assessment of post-marketing studies regarding novel drugs. Post-marketing research has been studied for high-risk devices [9] or even for drugs, but with a focused approach: safety [10,11] or given therapeutic areas. [12–15]Some of those studies produced reassuring results, yet others showed inconsistencies, with gaps in knowledge regarding some issues.

Our research objective was to provide a comprehensive description of post-marketing studies registered in ClinicalTrials.gov, a publicly-accessible clinical trial registry maintained by the US National Institutes of Health over almost a decade for a sample of drugs approved by both the FDA and EMA from 2005 to 2010. We aimed to characterize the total number of studies and patients studied, targeted indications, funding origin, geographical location of studies and status (e.g., completed or ongoing). We also sought to examine differences between the condition of the initial label and the specific clinical condition studied in the post-marketing studies, to assess the influence of the sponsor on the targeted indication, and to describe supplemental indications.

Methods

Data sources and study sample

We identified all novel drugs approved between January 1, 2005 and December 31, 2010 by both the FDA and EMA through its Centralized Authorization Procedure. For the FDA, Drugs@FDA is a publicly accessible database listing relevant regulatory actions for all approved drugs. [16] For the EMA, information was accessible in the European Public Assessment Reports, which provide a summary of scientific review and list notable regulatory events for all drug submissions.[17] Generic drugs, reformulations, combination therapies and non-therapeutic agents such as radiographic dye were not included. This first search led to a sample of 71 novel drugs approved by both regulators between 2005 and 2010. Two drugs, everolimus and temsirolimus, were excluded because they were associated with an abnormally high number of post-marketing studies involving drug-eluting stents.

Drug and manufacturer characteristics

The following data were retrieved for each drug: agent type (small molecule or biologic), dates of regulatory submissions for both the FDA and EMA, orphan status according to the FDA, orphan designation from the EMA, therapeutic class according to the Anatomical Therapeutic Chemical classification, [18] initial label from both regulators, degree of novelty (first-in-class, advance-in-class, addition-to-class) as previously described in a paper from FDA officials [19] and size of the marketing-authorization holder (i.e., manufacturer). This latter information was obtained by personal communication with EMA officials (Dr. Constantinos Ziogas, Small and Medium-sized Manufacturer Office, EMA), who classified manufacturers as large pharmaceutical companies, intermediated-size companies or small- and medium-size companies according to the European Union definition based on headcount and financial turnover or balance sheet total.

Preapproval FDA pivotal trial characteristics

We obtained data for the expected length of treatment and number of patients from pivotal efficacy trials supporting FDA approvals that had been collected for a previous work. [20] In brief, acute treatment was defined as expected use < 1 month, intermediate treatment as expected use from 1 month to 2 years, and chronic treatment as expected use > 2 years.

Post-marketing studies

On September 24, 2014, we extracted all studies that were registered at ClinicalTrials.gov for each drug of our sample, regardless of dates and other details. We then excluded studies with the following characteristics: included in the FDA regulatory submission (by a manual review of Drugs@FDA), with inadequate registered status (expanded-access studies, withdrawn studies, suspended studies), and mistakenly extracted (i.e., studies actually not assessing the drug of interest). For our main analysis, we decided that all studies whose starting date had preceded the first regulatory submission (to the FDA or EMA) by 1 year or less would be classified as post-marketing studies. However, we also performed most calculations with a slightly different set of studies, namely only those whose launch started after the first regulatory approval of any agency. Trials that pertained to more than one drug in our sample were manually reviewed so as to assign them to only one drug for the sake of further statistical analysis. Clinical judgment was applied to choose the "leading" drug in each study. When we could not determine the leading drug, we used the following rules. If the study was funded by a marketing-authorization holder of one of the drugs, this drug was considered the leading drug. Otherwise, if the study involved a drug that was assessed for another indication than the originally approved indication, this drug was considered the leading drug. Finally, when no leading drug could be determined, the drug for which the last regulatory approval had been granted was considered the drug tested and was classified as the leading drug.

For all remaining post-marketing studies, the following data were collected: condition studied, starting date, study sponsors (as a primary sponsor or a collaborator), status at the date of extraction (not yet recruiting, recruiting, active yet not recruiting, enrolling by invitation, completed, terminated), number and list of countries, number of centers, study phase, study type (observational or interventional), randomization, and planned enrollment. In addition, studies were classified as assessing the drug for its originally approved indication or not, depending on the initial label. When the initial label differed between the FDA and EMA, we accepted both labels as defining the originally approved indication. One of us (JDZ) performed this classification after careful review of each primary label. Indications were classified according to the Global Burden of Diseases classification. [21] Details of the classification of post-marketing studies are provided in the Appendix.

Supplemental indications

We also collected approvals of supplemental indications by the FDA during the study period (2005-2014) by manual review of Drugs@FDA. In the "Approval date(s) and History, Letters, Labels, Reviews" section, all events designated as "efficacy-new indication" or "efficacy" were reviewed and retained if deemed appropriate. Labeling revision (such as those related to a modified indication or an expanded patient population) and manufacturing change or addition were not included, nor were irrelevant supplemental indications. We also aimed to assess the average number of patients to be enrolled in post-marketing studies to gain approval of a supplemental indication. For this purpose, we took into account all patients from all post-marketing studies from the start of our sample through 1 year before the issuance of the supplemental indication by the FDA.

Statistical analysis

Using descriptive statistics, we characterized the premarket characteristics of the novel drugs included in our sample (drugs approved by both the FDA and EMA between 2005 and 2010).

Next, we used descriptive statistics to characterize features of all identified post-marketing studies registered at ClinicalTrials.gov for all novel drugs. We used a series of trend charts representing the annual number of post-marketing studies over the life-cycle of the drugs according to off- and on-condition studies. All statistical tests were two-tailed, with a type I error rate of 0.05. We used SAS 9.4 (SAS Institute; Cary, NC) for all statistical analyses.

Results

Drug sample

Our study sample included 69 novel drugs approved between 2005 and 2010 by both the FDA and EMA. In all, 51 drugs (73.9%) were small molecules and 18 (26.1%) were biologics (Table 1). The FDA had granted orphan status to 18 drugs (26.1%) and the EMA an orphan designation to 20 (29.0%). Among these 69 novel drugs, 24 (34.8%) were first-in-class, 24 (34.8%) advance-in-class and 21 (30.4%) addition-to-class. The most prevalent therapeutic category was antineoplastic and immunomodulating agents (29% of all novel drugs from the sample) and many drugs (68.1%) were for chronic treatment. The manufacturer was a large pharmaceutical company for 44 (63.8%) of the drugs. Other details are in Table 1.

Number of post-marketing trials, status and patients recruited

Sequential exclusions leading to our final study sample of 6679 relevant post-marketing studies related to all 69 novel drugs are in Supplemental Material (S1). Characteristics of all post-marketing studies are in Table 2. In all, 2901 studies (43.4%) were completed, 487 (7.3%) terminated, 1013 (15.2%) active yet not recruiting, 1895 (28.4%) recruiting, and 319 (4.8%) not yet recruiting. When comparing respective numbers of post-marketing studies and all clinical studies (preapproval pivotal trials and post-marketing studies), the median proportion of post-marketing studies per drug was 0.96 (interquartile range [IQR] 0.93-0.98). However, we found high variability in number of post-marketing studies per drug, with a

median of 55 studies per drug (IQR, 33-119) and mean of 96.8 studies per drug (SD 110.3). Galsulfase, an orphan medication indicated for Mucopolysaccharidosis VI, was associated with the lowest number of post-marketing studies (n=3) and sorafenib, a tyrosine kinase inhibitor initially indicated for kidney cancer, with the highest number of post-marketing studies (n=530).

Planned enrollment was also highly variable, with studies only including one patient, and one study intending to recruit 904 585 patients (actually a prospective population-based cohort study examining risk of congenital malformations after use of varenicline, a tobacco-use cessation drug, in pregnant women). However, the median number of patients to be enrolled per study was 60 (IQR 28-183). Data on the total population to be enrolled in all post-marketing studies for a given drug was also highly varied, with a median total sample of 15 418 patients (IQR 4932-37 523). Velaglucerase alfa, an orphan medication indicated for Gaucher disease, was associated with the lowest population size to be included in studies (n=67), and varenicline was associated with the greatest population to be enrolled (>1 million patients overall). Supplemental Material (S2) shows the total number of patients to be included in post-marketing studies for each drug and proportions of industry and non-industry funders.

Supplemental Material (S3) presents for each drug the number of patients included in preapproval pivotal trials as compared with post-marketing studies. The median proportion for the population recruited in post-marketing studies to the total population (i.e., preapproval samples and post-marketing studies) was 0.95 (IQR 0.90-0.98). Again, alglucidase and velaglucerase alfa were associated with the lowest number of patients in preapproval pivotal trials. In contrast, for dabigatran, a drug initially indicated for preventing venous thromboembolism in the European Union and to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation in the United States, preapproval

pivotal trials had recruited the highest number of patients. The same figure also shows the proportions of patients enrolled in post-marketing studies designed for the originally approved indication, another indication and both.

Trial characteristics

Data regarding study phases are shown in Table 2; only 18.6% of identified post-marketing studies were considered phase IV studies, whereas the most prevalent category was phase II studies (32.6%). Data regarding randomization were missing for 2452 post-marketing studies (36.7%). Among the remaining studies for which these data were available, 3067 were randomized (72.6%). Other data are in Table 2.

Sponsor

Industry funded or partially funded nearly two-thirds of post-marketing studies. Indeed, as shown in Table 2, industry was the primary sponsor of 2713 studies (40.6%), but when also considering manufacturers as minority funders, industry was involved in a total of 4176 studies (62.5%). Data regarding post-marketing studies stratified by sponsorship are in Table 2. Figure 1 presents the drug sample with respect to the number of post-marketing studies and the proportion of industry and non-industry funders for each drug. Supplemental Material (S4) provides the same information but with a 4-year follow-up for each drug.

Conditions addressed in trials

Review of indications showed that 2441 post-marketing studies (36.5%) were launched for another indication than the originally approved indication. Figure 2 displays the number of non-approved indications studied in post-marketing studies for each drug of our sample, with information regarding the more advanced phase for each newly targeted indication. When comparing those studies with the total number of clinical studies (preapproval pivotal trials

and post-marketing studies), we found a median proportion of 0.24 (IQR, 0.09-0.4). The median proportion for the population recruited in post-marketing studies designed for another indication than the originally approved indication to the total population from all clinical studies (preapproval pivotal trials and post-marketing studies) was 0.12 (IQR 0.03-0.33).

When analyzing the relationship between the study sponsor and the study indication, we found that 68.7% of studies designed in the originally-approved indication were sponsored by industry, as compared to 53.7% of studies designed in another indication ($p<0.0001$). Findings regarding planned enrollment according to the indication and stratified on funding origin are in Supplemental Material (eTable). Regardless of the funder, post-marketing studies targeting originally approved indications planned to enroll more patients than those studying other indications.

Timing

The annual number of post-marketing studies over the life-cycle of drugs, stratified by indication, is shown in Figure 3, exhibiting an asymmetric bell pattern, with a rapid increase in number of post-marketing studies launched, a peak of activity within the third year after the first regulatory submission, then a progressive decline in number of launched studies. Detailed examination shows a greater proportion of studies designed for another indication than the originally approved indication at the beginning and end of drug life-cycles. Supplemental Material (S5) is based on the same data but displays information regarding sponsors. Former post-marketing studies were predominantly funded by industry versus academic or not-for-profit entities and this proportion increased until the second year after the first regulatory submission. Afterwards, the proportion of non-industry funders tended to increase over time.

Location

Overall, 80% of post-marketing studies were conducted in only one country. For 66 drugs, at least one study was conducted in at least two countries. Sorafenib was the most concerned drug in this regard, with 74 studies involving at least two countries. Data regarding locations of studies for each drug are in Supplemental Material (S6). In brief, post-marketing research was highly concentrated in North America (i.e., United States and/or Canada; 44.8% of all post-marketing studies of the sample) and Europe (25.0%). Post-marketing studies conducted in other areas represented 15.6% of all studies, and studies conducted in multiple continents were few. When examining the relation between study location and study design with respect to the original label, we found that studies from North America (United States and/or Canada) were more frequently conducted for indications other than the originally approved indication versus those located in Europe (50.4% v. 36.9%). Data from Supplemental Materials S2, S3, and S6 are summarized as Tables in Supplemental Material S7.

Supplemental indications

During the study period, 18 novel drugs (26.1%) were associated with a least a supplemental indication by the FDA: one with 4 supplemental indications, one with 3 supplemental indications, 5 with two supplemental indications and 11 with one supplemental indication. The mean time between the first regulatory submission and subsequent supplemental indication was 4.4 years (SD 1.7; IQR 3.3-5.7). The mean number of patients to be enrolled in post-marketing studies before approval of a supplemental indication was 12763.1 (SD 12474.3; IQR 3891.0-15856.0).

Supplemental analysis

Analyses of post-marketing studies shown in Table 2 were also performed when only taking into account those whose launch started after the first regulatory approval. Put another way, this supplemental set of analysis led us to exclude the 275 studies (see flow chart in

Supplemental Material S1) whose starting date had preceded the first regulatory submission by 1 year or less. Results are displayed in Supplemental Material S8, showing no obvious difference with the main set of analysis.

Discussion

In our study of post-marketing clinical research studies conducted for novel drugs approved by both the FDA and EMA between 2005 and 2010, we found high variability in number of post-marketing studies per drug and planned enrollment per study. Indeed, the median planned enrollment was low, 60 patients, with a median of 55 studies per drug, most of which had not yet been completed at a minimum of 4 years after approval. Locations were concentrated, with 72.3% of post-marketing studies conducted in North America and/or Europe and 80% conducted in only one country. Approximately 40% of post-marketing studies were designed for an indication other than the originally approved one, more frequently concerning studies not involving industry funding. Overall, those findings reflect the lack of global coordination of post-marketing research for novel drugs.

Our study has several strengths. First, we focused on a sample of drugs approved by the two leading medical product regulators, FDA and EMA, which suggests that these drugs are likely to be of the greatest interest and importance to clinicians worldwide. Most previous studies focused on the FDA or EMA but rarely both. [20,22] Second, few comprehensive studies have analyzed post-marketing research despite its undisputed public health impact. [9–14] Most research focused on safety or was limited to a given therapeutic area, or even only one drug. In addition, we chose a large study period, with a 6-year span for drug approvals, and more than 10 years for the trial sample. Moreover, we followed a rigorous method for selecting post-marketing studies, excluding clinical trials included in the FDA submission, studies that had not been launched, studies mistakenly classified as involving the drug in

ClinicalTrials.gov and studies whose starting date was too early as compared to regulatory submission. Third, we provide unique insights into the clinical research programs examining non-approved drug uses. Many studies have investigated off-label prescriptions, [23,24] but we used a slightly different approach. In effect, most drug labels are stringently phrased so as to be rigorously aligned to pivotal trial criteria. [25] Therefore, categorizing studies according to the actual off- or on-label status of the drug investigated would have led to classifying most as involving off-label drug use. Put another way, the label was judged too narrow, and our method offers a more significant picture for clinicians and epidemiologists. We believe that our classification better reflects substantial evolution regarding the initially authorized use of novel drugs.

Our findings raise several issues worthy of consideration about post-marketing research. First, we showed that post-marketing research is both a heterogeneous and concentrated landscape, probably linked to its loose regulation [6] and to market forces. Therefore, most initiatives are at the discretion of funders, either industry or academic institutions, and driven by various factors not necessarily linked to medical need or relevancy. For instance, prior research has shown that many post-marketing trials were “seeding trials”, designed for marketing purposes rather than scientific relevancy. [7,8] The number of post-marketing studies per novel drug and planned enrollment were highly variable, but most studies were conducted in only one country and North America and Europe were by far the most frequent locations. Median planned enrollment was low and many studies were still not completed at the time of data acquisition. These findings question the absence of steering or the lack of effectiveness or incentive policies for post-marketing research. Second, almost 40% of post-marketing studies were designed for an indication other than the originally approved indication, with non-industry trials more likely concerned. Although industry has been blamed for testing their products in a too-liberal manner, [26] our findings suggest that

academics and other non-industry bodies might be more prone to assess authorized drugs in innovative ways to evaluate novel indications. Third, we found that post-marketing studies designed for the originally approved indication planned to enroll a greater number of patients on average than those targeting novel indications. This latter finding is somewhat reassuring because post-marketing studies for an already approved indication aim to refine knowledge regarding the long-term effect and/or safety and should therefore include more patients than preapproval pivotal trials.

Our study has limitations. The first may be a registration bias at ClinicalTrials.gov, which would alter the exhaustiveness of our assessment. Some studies are not registered by researchers [27,28] and were therefore not included in our study. Others are imperfectly registered, with some information missing. However, ClinicalTrials.gov is widely recognized as a benchmark registry, and recent reports showed that compliance might have improved over time. [29] Another limitation is the definition of post-marketing studies, in that clinical studies are designed and launched according to a continuous timing and a single threshold might be lacking for distinguishing pre- and post-marketing trials. Therefore, we decided to consider studies starting at most 1 year before the first regulatory submission as post-marketing studies even though we could have made another choice. A third limitation is related to data sources. For some data, we relied on only one of the two selected regulators. We used such an approach for the sake of convenience and recognize that this could be interpreted as a bias, yet to our knowledge, there are very few if any differences in data between the two studied regulators. Therefore, this latter limitation in the methods seems unlikely to affect our findings. Finally, we could not identify whether post-marketing trials were relevant or useful because we did not analyze their design, endpoints, or comparators, among other factors.

In conclusion, our research shows that post-marketing research is highly variable and concentrated, with on one hand, great differences in the number of post-marketing studies per drug and in planned enrollment and on the other, most studies being conducted in only one country, with North America and Europe the most represented locations. Approximately 40% of post-marketing studies assessed the drug for an indication other than the originally approved indication, more frequently non-industry studies. Even though some of our findings can be seen as reassuring, others underline the lack of global coordination of post-marketing research for novel drugs despite the undisputed influence of such research.

Contributors: Dr. Zeitoun and Pr. Ravaud were responsible for the conception and design of this work. Dr. Zeitoun drafted the manuscript and was responsible for most of the data acquisition. M. Ignacio Atal was responsible for data exportation and structuration. Dr. Alexandre Vivot was responsible for collection of some data and contributed to categorization of studies. Dr. Nicholas Downing was responsible for some of the data acquisition. Dr. Gabriel Baron conducted the statistical analysis. Drs. Ross and Ravaud provided supervision. All authors participated in the analysis and interpretation of the data and critically revised the manuscript for important intellectual content.

Data sharing statement: Data files are available from the corresponding author on reasonable request.

Acknowledgements: The authors are grateful to EMA officials who graciously helped them classify drug manufacturers. They also thank Geoffroy Beraud-Chaulet for his useful work on Drugs@FDA and Elise Diard for her invaluable help on figures.

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Legends

Figure 1: Number of post-marketing studies and respective proportion of industry and non-industry funders.

Figure 2: Number of non-approved indications targeted in post-marketing studies for each drug of our study sample. Indications are rank-ordered on the basis of the number of post-marketing studies launched (from the greatest number of post-marketing studies on the left side of the figure to the lowest number on the right side). Color of boxes varies according to the advanced phase of the targeted indication. Indications are classified according to the Global Burden of Diseases classification. [21] Indications belonging to residual categories or health conditions not relevant to the Global Burden of Diseases were excluded and therefore are not represented in the Figure.

Figure 3: Annual number of post-marketing studies over the life-cycle of drugs, stratified by indication.

Supplemental File S1: Flow chart leading to the final study sample of 6679 relevant post-marketing studies.

Supplemental File S2: Total number of patients to be included in post-marketing studies for each drug.

Supplemental File S3: Population in preapproval pivotal trials and post-marketing studies.

Supplemental File S4: Number of post-marketing studies and respective proportion of industry and non-industry funders, with a 4-year follow-up for each drug.

Supplemental File S5: Annual number of post-marketing studies over the life-cycle of drugs, stratified by sponsor.

Supplemental File S6: Locations of post-marketing studies.

Supplemental File S7: Data from S2, S3 and S6, presented as tables.

Supplemental File S8: Characteristics of industry and non-industry post-marketing studies when solely taking into account those whose launch started after the first regulatory approval.

Table 1. Characteristics of 69 novel drugs approved by both the FDA and EMA between 2005 and 2010 (excluding everolimus and temsirolimus).

Characteristics	**n (%)**
Agent type	
Small molecule	51 (73.9%)
Biologic	18 (26.1%)
Orphan status (FDA)	18 (26.1%)
Orphan designation (EMA)	20 (29.0%)
Accelerated approval (FDA)	14 (20.3%)
Therapeutic class according to the ATC classification	
Alimentary tract and metabolism	10 (14.5%)
Anti-infectives for systemic use	12 (17.4%)
Antineoplastic and immunomodulating agents	20 (29.0%)
Blood and blood forming organs	5 (7.2%)
Cardiovascular system	5 (7.2%)
Nervous system	6 (8.7%)
Other*	11 (15.9%)
Degree of novelty (according to Lanthier *et al*)	
First-in-class	24 (34.8%)
Advance-in-class	24 (34.8%)
Addition-to-class	21 (30.4%)
Size of the marketing-authorization holder	
Large pharmaceutical company	44 (63.8%)
Intermediated-size company	23 (33.3%)
Small- and medium-size company	2 (2.9%)
Premarket evidence	

Total no. of included patients	
Min/max	18/18040
Median [Q1-Q3]	923 [324-1996]
Mean (SD)	1806 (2897)
Expected length of treatment	
Acute	8 (11.6%)
Intermediate	14 (20.3%)
Chronic	47 (68.1%)

ATC, Anatomical Therapeutic Chemical

*includes dermatological, genitourinary system and sex hormones, musculoskeletal system, sensory organs, systemic hormonal preparations, excluding sex hormones, and others

Table 2. Characteristics of industry and non-industry post-marketing studies registered at ClinicalTrials.gov before September 24, 2014 for the 69 novel drugs in the study sample.

Characteristics		All (n=6679)	Industry studies (n=4176)	Non-industry studies (n=2503)
Primary sponsor	Industry NIH US Fed Other	2713 (40.6%) 286 (4.3%) 15 (0.2%) 3665 (54.9%)		
Industry involved either as a primary sponsor or a collaborator		4176 (62.5%)		
No. of post-marketing studies per drug	Min/max Median [Q1-Q3] Mean (SD)	3/530 55 [30-119] 96.8 (110.3)		
Population size per drug	Min/max Median [Q1-Q3] Mean (SD)	67/1.05E6 15418 [4932-37523] 62748 (166644)		

Therapeutic class according to the ATC				
Alimentary tract and metabolism		832 (12.5%)	570 (68.5%)	262 (31.5%)
Anti-infectives for systemic use		828 (12.4%)	504 (60.9%)	324 (39.1%)
Antineoplastic and immunomodulating agents		3040 (45.5%)	1818 (59.8%)	1222 (40.2%)
Blood and blood forming organs		446 (6.7%)	277 (62.1%)	169 (37.9%)
Nervous system		485 (7.3%)	304 (62.7%)	181 (37.3%)
Other*		1048 (15.7%)	703 (67.1%)	345 (32.9%)
Study design with respect to primary label	Another indication than the originally approved indication	2441 (36.5%)	1310 (53.6%)	1131 (46.4%)
	Originally approved indication	3993 (59.8%)	2742 (68.7%)	1251 (31.3%)
	Both the originally approved indication and another indication	245 (3.7%)	124 (50.6%)	121 (49.3%)
Study type	Observational	707 (10.6%)	468 (66.2%)	239 (33.8%)
	Interventional	5972 (89.4%)	3708 (62.1%)	2264 (37.9%)

Randomization	Missing data	2452	1428	1024
	Yes	3067 (72.6%)	1979 (64.5%)	1088 (35.5%)
	No	1160 (27.4%)	769 (66.3%)	391 (33.7%)
Study phase	Missing data	1052	554	498
	0	34 (0.6%)	13 (38.2%)	21 (61.8%)
	I	933 (16.6%)	651 (69.8%)	282 (30.2%)
	I/II	423 (7.5%)	245 (58.0%)	178 (42.0%)
	II	1837 (32.6%)	1047 (57.0%)	790 (43.0%)
	II/III	109 (1.9%)	52 (47.7%)	57 (52.3%)
	III	1246 (22.1%)	1018 (81.7%)	228 (18.3%)
	IV	1045 (18.6%)	596 (57.0%)	449 (43.0%)
Centers	Missing data	503	428	75
	Min/max	1/1616	1/1616	1/922
	Median [Q1-Q3]	2 [1-12]	4 [1-23]	1 [1-2]
	Mean (SD)	19.9 (62.1)	26.4 (70.5)	9.8 (44.7)
Countries	Missing data	501	427	74
	Min/max	1/46	1/46	1/15
	Median [Q1-Q3]	1 [1-1]	1 [1-2]	1 [1-1]

	Mean (SD)	2.6 (4.7)	3.6 (5.8)	1.1 (0.7)
Planned enrollment	Missing data	14	9	5
	Min/max	1/904585	1/904585	1/61050
	Median [Q1-Q3]	60 [28-183]	72 [30-248]	48 [24-100]
	Mean (SD)	649.6 (12812.2)	943.8 (16167.1)	158.9 (1274.7)
Status at the time of data exportation	Not yet recruiting	319 (4.8%)	136 (42.6%)	183 (57.4%)
	Recruiting	1895 (28.4%)	886 (46.8%)	1009 (53.2%)
	Active, not recruiting	1013 (15.2%)	627 (61.9%)	386 (38.1%)
	Enrolling by invitation	64 (1.0%)	42 (65.6%)	22 (34.4%)
	Completed	2901 (43.4%)	2147 (74.0%)	754 (26.0%)
	Terminated	487 (7.3%)	338 (69.4%)	149 (30.6%)

NIH, US National Institutes of Health

*includes cardiovascular system, dermatological, genitourinary system and sex hormones, musculoskeletal system, sensory organs, systemic hormonal preparations, excluding sex hormones, and other

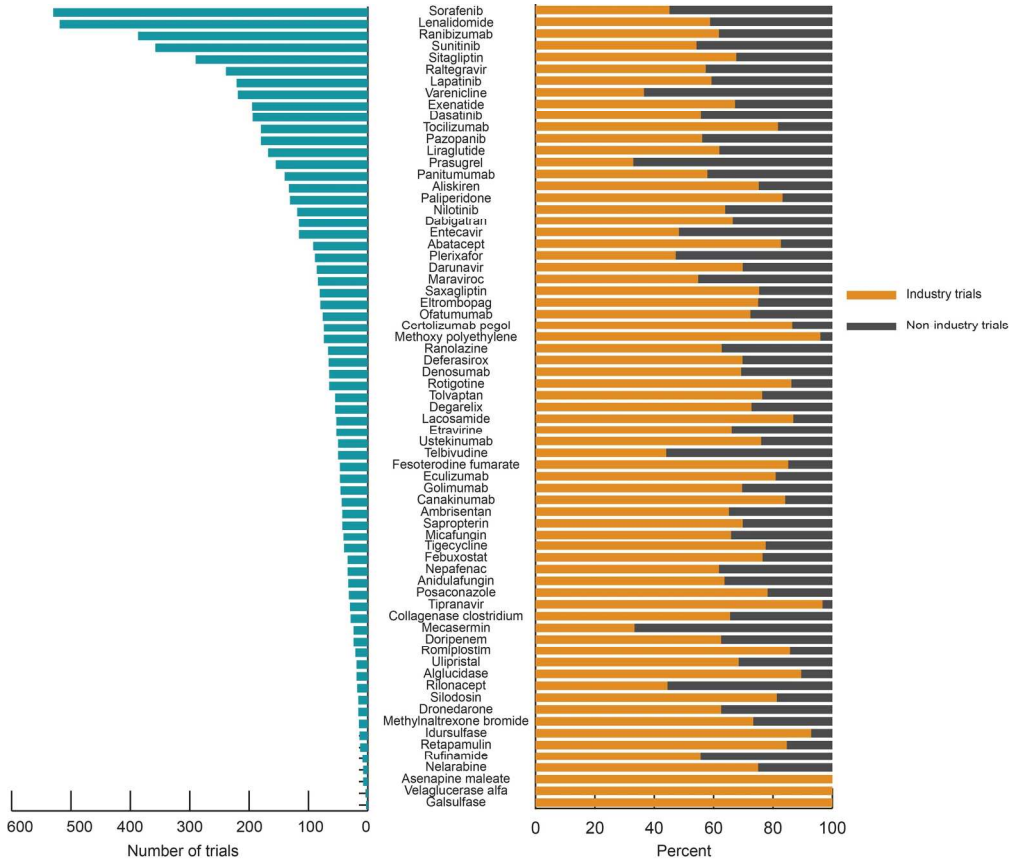


Figure 1

179x153mm (300 x 300 DPI)

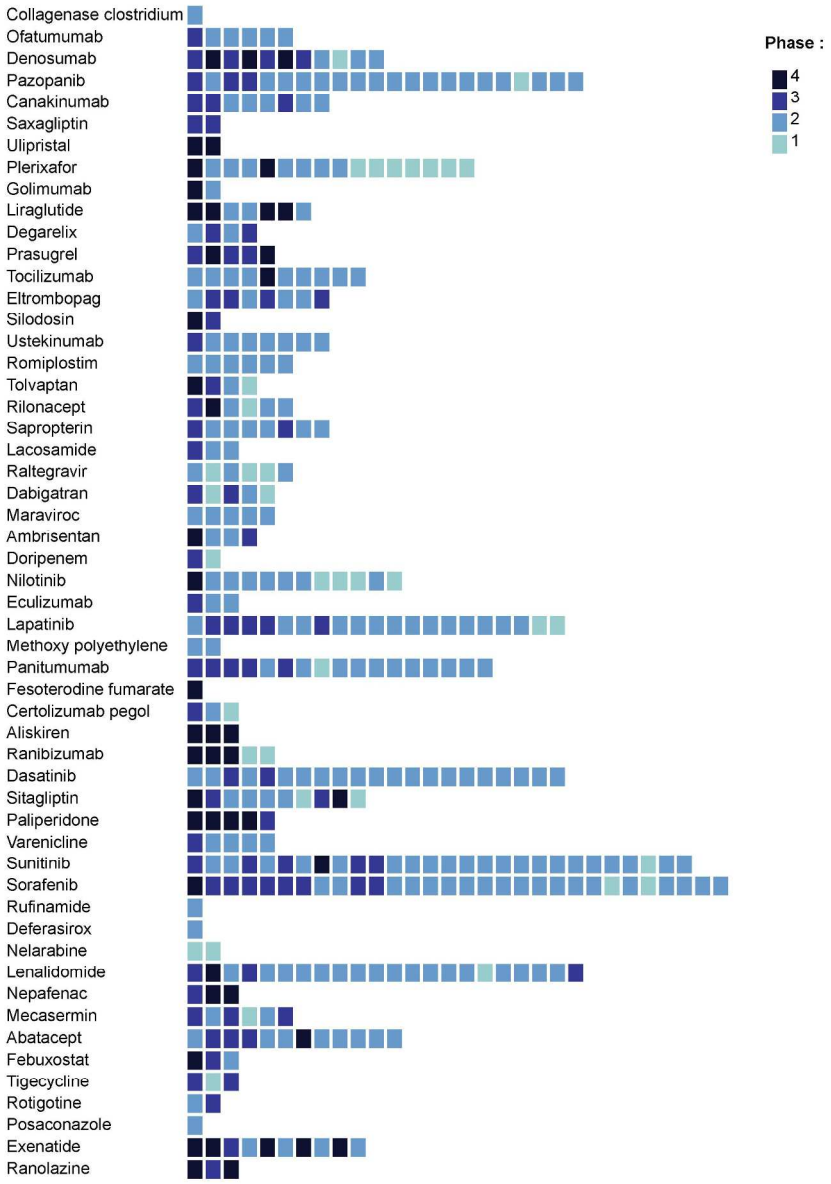


Figure 2

215x279mm (300 x 300 DPI)

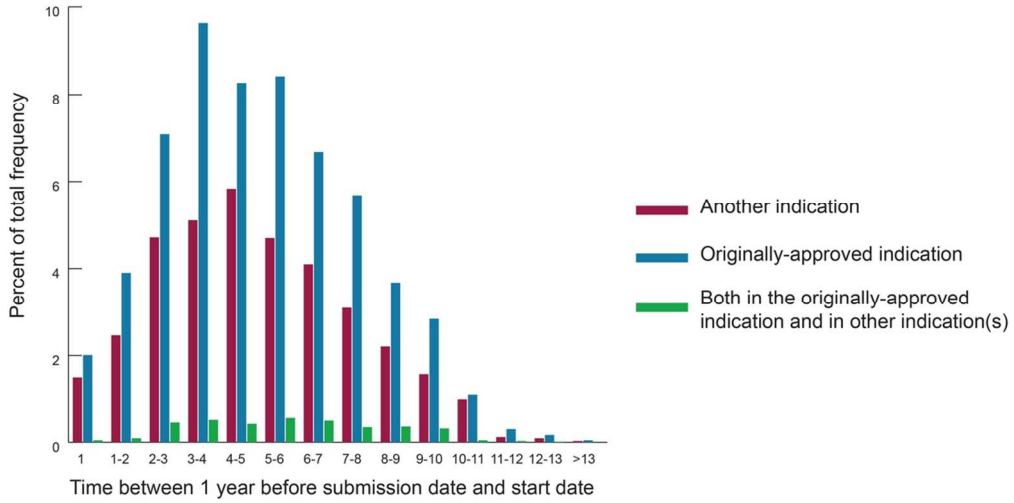
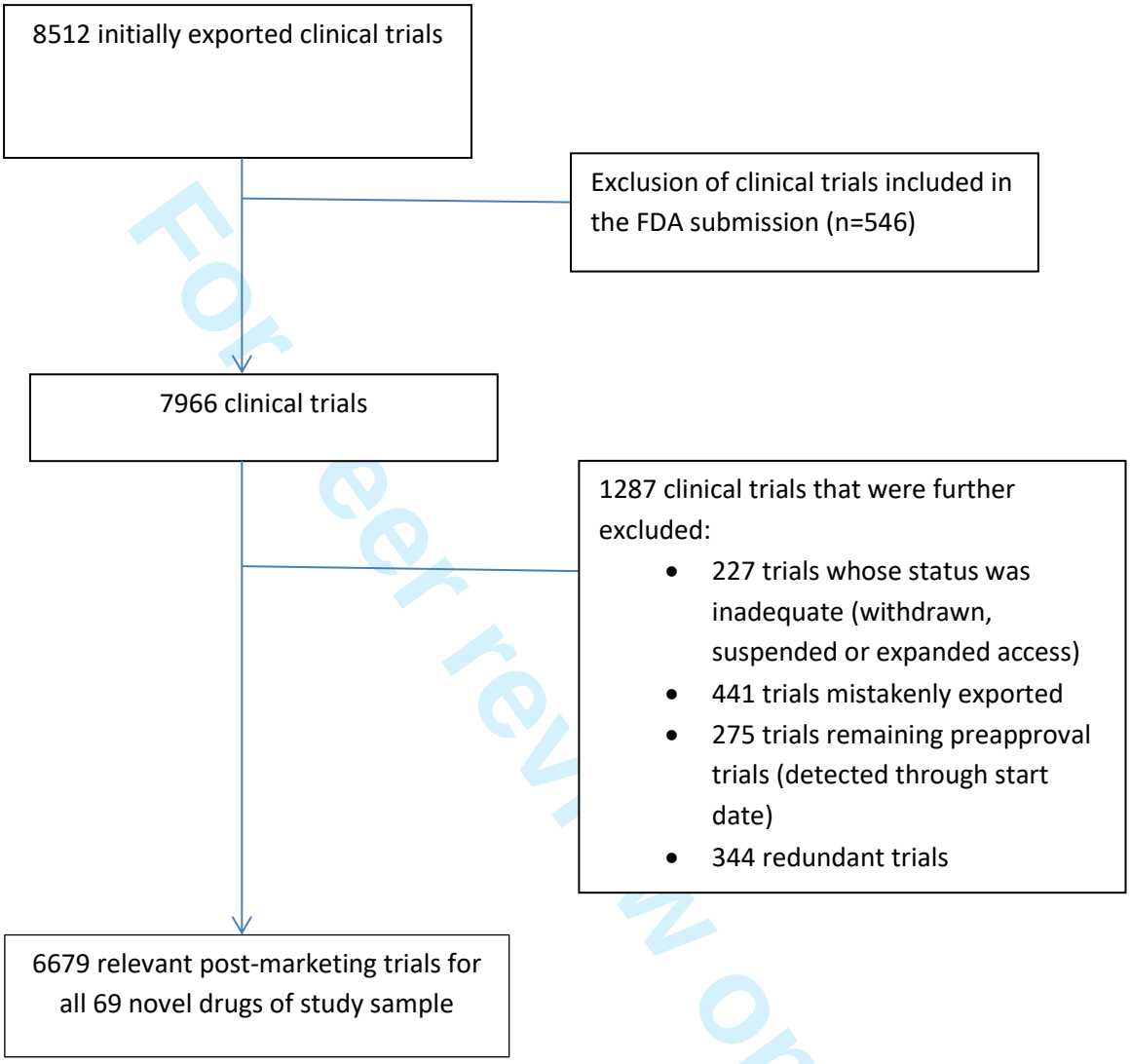
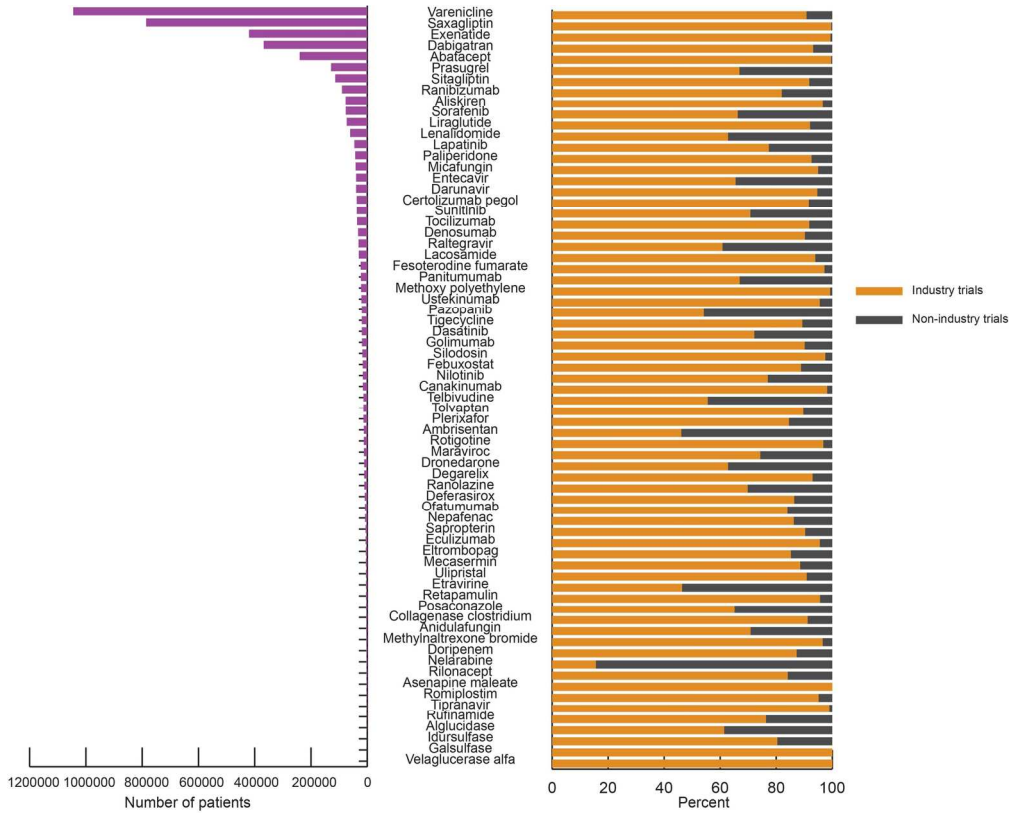


Figure 3

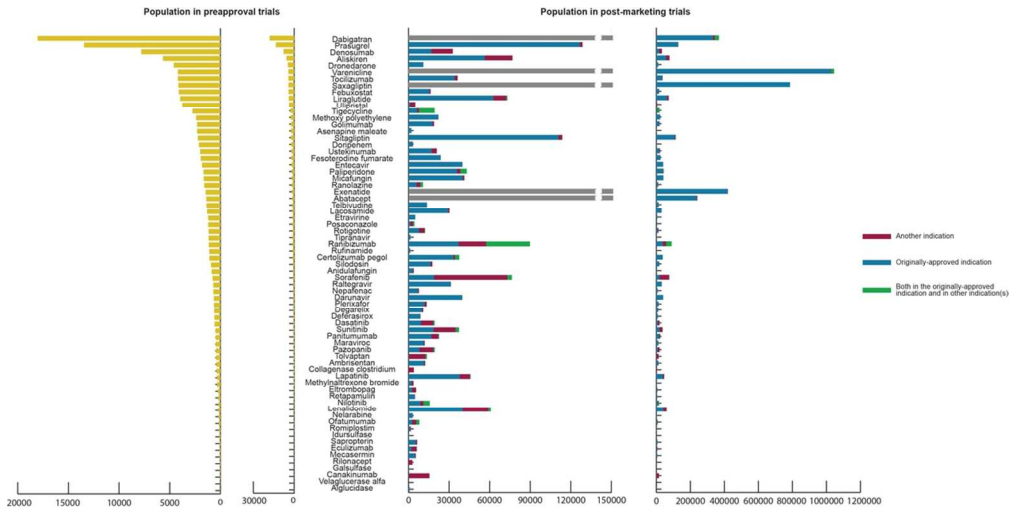
105x51mm (300 x 300 DPI)

Supplemental Material 1. Sample construction of relevant post-marketing trials related to all 69 novel drugs both approved by the FDA and the EMA between 2005 and 2010, after exclusion of everolimus and temsirolimus

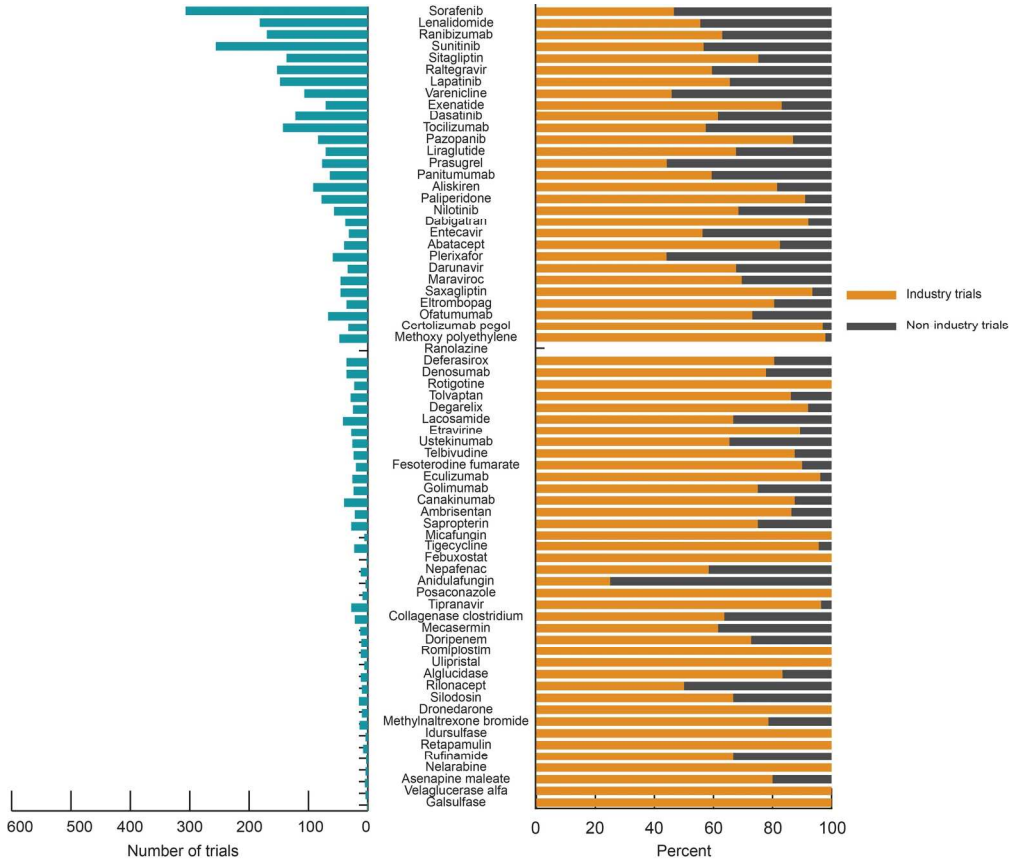




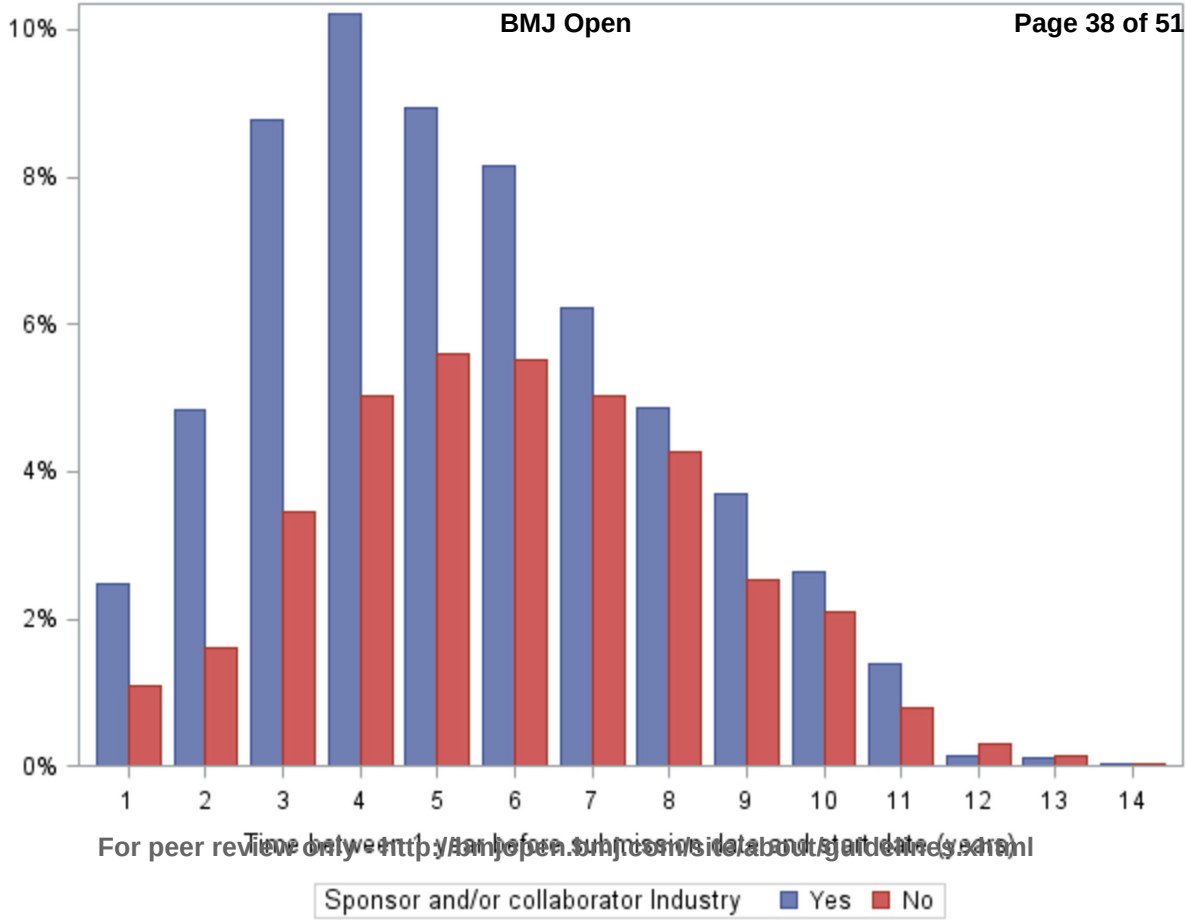
165x133mm (300 x 300 DPI)

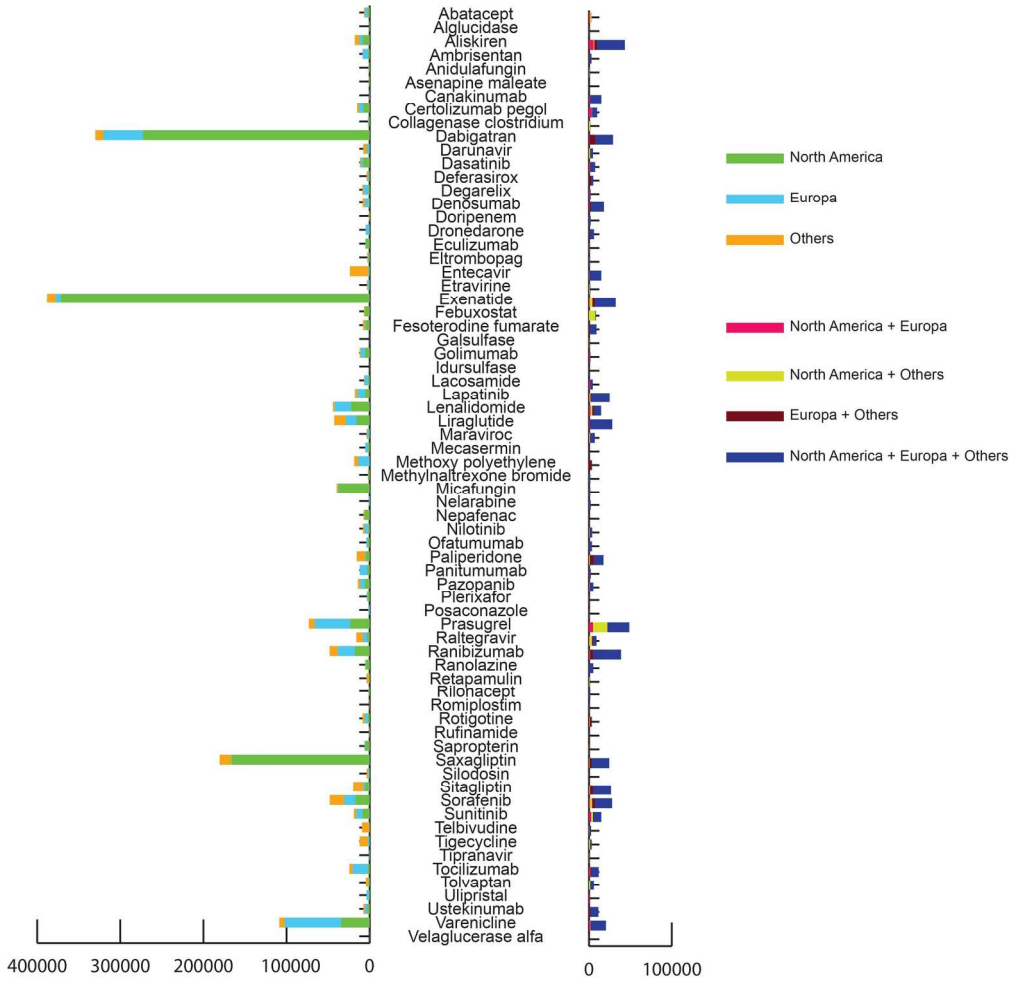


106x53mm (300 x 300 DPI)



179x153mm (300 x 300 DPI)





184x179mm (300 x 300 DPI)

Supplemental file S2 **bis**: Total number of patients to be included in post-marketing studies for each drug

Drug	Total number of patients to be included in post-marketing studies	Percentage of industry funders	Percentage of non-industry funders
Varenicline	1045002	90.8	9.2
Saxagliptin	785853	99.6	0.4
Exenatide	420256	99.3	0.7
Dabigatran	368063	93.1	6.9
Abatacept	240227	99.6	0.4
Prasugrel	128744	66.9	33.1
Sitagliptin	113824	91.8	8.2
Ranibizumab	89765	81.9	18.1
Aliskiren	76864	96.6	3.4
Sorafenib	76434	66.2	33.8
Liraglutide	73106	92.0	8.0
Lenalidomide	60805	62.8	37.2
Lapatinib	45881	77.4	22.6
Paliperidone	43024	92.6	7.4
Micafungin	41363	95.0	5.0
Entecavir	39787	65.5	34.5
Darunavir	39773	94.7	5.3
Certolizumab pegol	37523	91.6	8.4
Sunitinib	37320	70.7	29.3
Tocilizumab	36262	91.8	8.2
Denosumab	32688	90.2	9.8
Raltegravir	31285	60.8	39.2
Lacosamide	30236	93.9	6.1
Fesoterodine fumarate	23699	97.2	2.8
Panitumumab	22585	66.9	33.1
Methoxy polyethylene	22102	99.2	0.8
Ustekinumab	20873	95.5	4.5
Pazopanib	19332	54.1	45.9
Tigecycline	19322	89.3	10.7
Dasatinib	19320	72.2	27.8
Golimumab	18801	90.1	9.9
Silodosin	17591	97.5	2.5
Febuxostat	16330	88.8	11.2
Nilotinib	15657	77.0	23.0
Canakinumab	15418	98.2	1.8
Telbivudine	13590	55.6	44.4
Tolvaptan	13552	89.7	10.3
Plerixafor	13450	84.6	15.4
Ambrisentan	12300	46.1	53.9

Drug	Total number of patients to be included in post-marketing studies	Percentage of industry funders	Percentage of non-industry funders
Rotigotine	12258	96.8	3.2
Maraviroc	11957	74.3	25.7
Dronedarone	10947	62.7	37.3
Degarelix	10811	93.0	7.0
Ranolazine	10614	69.8	30.2
Deferasirox	8812	86.4	13.6
Ofatumumab	7988	84.0	16.0
Nepafenac	7627	86.2	13.8
Sapropterin	6328	90.3	9.7
Eculizumab	6065	95.5	4.5
Eltrombopag	5590	85.2	14.8
Mecasermin	5291	88.5	11.5
Ulipristal	4932	90.9	9.1
Etravirine	4881	46.4	53.6
Retapamulin	4819	95.6	4.4
Posaconazole	4391	65.1	34.9
Collagenase clostridium	3897	91.2	8.8
Anidulafungin	3819	70.8	29.2
Methylnaltrexone bromide	3581	96.6	3.4
Doripenem	3204	87.3	12.7
Nelarabine	3104	15.6	84.4
Rilonacept	2790	84.1	15.9
Asenapine maleate	2179	100.0	0.0
Romiplostim	1627	95.1	4.9
Tipranavir	1401	98.9	1.1
Rufinamide	1174	76.3	23.7
Alglucidase	803	61.4	38.6
Idursulfase	408	80.4	19.6
Galsulfase	269	100.0	0.0
Velaglucerase alfa	67	100.0	0.0

Supplemental file S3 **bis**: Population in preapproval pivotal trials and post-marketing studies

Drug	Population in preapproval pivotal trials	Population in post-marketing studies			
		Another indication	Originally-approved indication	Both in originally approved indication and in other(s) indication	Total
Dabigatran	18040	10896	332151	25016	368063
Prasugrel	13457	1960	126669	115	128744
Denosumab	7808	15825	16863	0	32688
Aliskiren	5663	20625	56239	0	76864
Dronedarone	4604	20	10927	0	10947
Varenicline	4198	1847	1024229	18926	1045002
Tocilizumab	4190	2201	34061	0	36262
Saxagliptin	4148	396	785457	0	785853
Febuxostat	4101	854	15476	0	16330
Liraglutide	3978	9509	62587	1010	73106
Ulipristal	3754	4012	920	0	4932
Tigecycline	2758	1339	6291	11692	19322
Methoxy polyethylene	2398	8	22094	0	22102
Golimumab	2297	1222	17579	0	18801
Asenapine maleate	2294	0	2179	0	2179
Sitagliptin	2220	2794	110745	285	113824
Doripenem	2117	267	2937	0	3204
Ustekinumab	1996	3793	17080	0	20873
Fesoterodine fumarate	1935	182	23517	0	23699
Entecavir	1814	0	39787	0	39787
Paliperidone	1665	2548	35755	4721	43024
Micafungin	1643	1105	39983	275	41363
Ranolazine	1593	2945	5773	1896	10614
Exenatide	1446	2810	417301	145	420256
Abatacept	1382	5622	234605	0	240227
Telbivudine	1367	0	13590	0	13590
Lacosamide	1308	1133	29103	0	30236
Etravirine	1203	0	4881	0	4881
Posaconazole	1202	1949	1282	1160	4391
Rotigotine	1163	4067	7671	520	12258
Tipranavir	1159	0	1365	36	1401
Ranibizumab	1139	20541	36906	32318	89765
Rufinamide	1097	288	886	0	1174
Certolizumab pegol	1088	1200	33077	3246	37523
Silodosin	923	1339	16252	0	17591
Anidulafungin	857	792	2993	34	3819
Sorafenib	769	54317	18809	3308	76434
Raltegravir	699	83	31202	0	31285
Nepafenac	688	815	6812	0	7627
Darunavir	637	0	39773	0	39773

Drug	Population in preapproval pivotal trials	Population in post-marketing studies			
		Another indication	Originally-approved indication	Both in originally approved indication and in other(s) indication	Total
Plerixafor	623	1467	11644	339	13450
Degarelix	610	791	10020	0	10811
Deferasirox	586	153	8609	50	8812
Dasatinib	565	9267	9090	963	19320
Sunitinib	481	16462	18362	2496	37320
Panitumumab	461	5197	16874	514	22585
Maraviroc	448	560	11397	0	11957
Pazopanib	435	10363	8060	909	19332
Tolvaptan	418	12221	356	975	13552
Ambrisentan	393	715	11585	0	12300
Collagenase clostridium	374	3897	0	0	3897
Lapatinib	324	7678	37714	489	45881
Methylnaltrexone bromide	321	1359	2222	0	3581
Eltrombopag	232	2957	2533	100	5590
Retapamulin	210	267	4417	135	4819
Nilotinib	196	2431	8531	4695	15657
Lenalidomide	193	19105	39873	1827	60805
Nelarabine	190	35	3069	0	3104
Ofatumumab	154	3076	2595	2317	7988
Romiplostim	125	543	1084	0	1627
Idursulfase	96	0	408	0	408
Sapropterin	88	1133	5195	0	6328
Eculizumab	87	3861	2204	0	6065
Mecasermin	70	623	4668	0	5291
Rilonacept	47	2765	25	0	2790
Galsulfase	39	0	269	0	269
Canakinumab	31	15157	261	0	15418
Velaglucerase alfa	25	0	67	0	67
Alglucidase	18	0	803	0	803

Supplemental file S6 **bis**: Location of post-marketing studies (sample size by location)

	Location						
	North America	Europa	Others	North America + Europa	North America + Others	Europa + Others	North America + Europa + Others
Abatacept	2267	2801	1575	1255	1715	0	9390
Alglucidase	633	5	0	83	22	20	40
Aliskiren	8269	3870	5760	5467	975	3097	33667
Ambrisentan	2128	6116	196	64	524	0	2330
Anidulafungin	1115	225	214	0	282	21	776
Asenapine maleate	950	0	0	0	0		0
Canakinumab	164	320	34	1037	0	274	13569
Certolizumab pegol	7278	5383	2401	3225	271	0	6265
Collagenase clostridium	1402	541	79	0	1286	0	400
Dabigatran	272415	47930	9639	636	0	7096	21220
Darunavir	755	2880	4076	12	1213	576	2940
Dasatinib	7476	2941	1139	768	195	484	5866
Deferasirox	1473	1023	1148	0	0	2506	2575
Degarelix	1613	5646	1522	783	0	0	1147
Denosumab	1168	4547	2692	427	0	1439	16134
Doripenem	82	195	818	52	0	0	1911
Dronedarone	480	4143	279	0	0	556	5436
Eculizumab	4683	447	52	60	92	80	463
Eltrombopag	1486	458	992	82	0	100	1059
Entecavir	807	1096	21848	4	200	184	14460
Etravirine	857	1730	570	30	671	279	536
Exenatide	371779	5876	10283	736	3323	2963	25151
Febuxostat	5473	0	1424	0	7500	0	744
Fesoterodine fumarate	4555	1231	2245	0	0	794	8210

	Location						
	North America	Europa	Others	North America + Europa	North America + Others	Europa + Others	North America + Europa + Others
Galsulfase	10	0	0	0	200	0	59
Golimumab	5459	5031	1361	706	11	120	811
Idursulfase	0	0	81	79	0	108	118
Lacosamide	1597	4167	946	1210	0	0	3281
Lapatinib	5446	9359	2989	502	1106	876	22398
Lenalidomide	22422	19825	1874	1804	1916	1972	8846
Liraglutide	15787	12960	13865	717	0	415	26892
Maraviroc	1268	1849	561	129	876	186	5698
Mecasermin	2073	3198	0	0	0	0	0
Methoxy polyethylene	340	13375	4841	0	0	2828	718
Methylnaltrexone bromide	1968	31	0	0	0	0	1462
Micafungin	37521	664	1518	0	84	619	836
Nelarabine	95	720	13	0	36	40	1900
Nepafenac	5927	227	1021	0	0	0	0
Nilotinib	1660	4393	1964	175	512	218	2882
Ofatumumab	2401	1549	20	60	14	122	3294
Paliperidone	4400	1064	10125	0	838	4753	11816
Panitumumab	2888	8858	164	375	0	0	1700
Pazopanib	5947	5436	2684	374	207	102	4518
Plerixafor	2374	850	164	0	61	46	0
Posaconazole	154	1370	126	96	0	0	600
Prasugrel	23597	42550	7015	4760	17372	0	26550
Raltegravir	3106	4949	8048	366	3156	1173	4308
Ranibizumab	17679	20576	9883	694	232	3832	33851
Ranolazine	4524	551	310	0	0	0	5102

	Location						
	North America	Europa	Others	North America + Europa	North America + Others	Europa + Others	North America + Europa + Others
Retapamulin	784	0	3000	0	508	465	60
Rilonacept	1242	30	0	0	0	244	1274
Romiplostim	280	119	76	63	62	0	175
Rotigotine	2229	3696	2553	220	601	2197	371
Rufinamide	230	278	366	75	0	0	0
Sapropterin	5120	1018	0	0	190	0	0
Saxagliptin	166072	594	13757	0	501	2670	21205
Silodosin	885	1196	1559	0	0	0	0
Sitagliptin	5577	2079	12049	164	804	3770	21728
Sorafenib	17405	13223	17312	973	2681	3230	20954
Sunitinib	8448	7676	2806	2557	2006	167	10074
Telbivudine	159	132	8934	0	308	367	1790
Tigecycline	473	1987	9632	0	1175	473	1588
Tipranavir	71	504	0	0	246	0	84
Tocilizumab	2511	17868	4033	1054	228	1270	9070
Tolvaptan	1227	304	3131	0	1300	0	4500
Ulipristal	855	2845	51	579	60	542	0
Ustekinumab	2823	2649	2004	166	0	1290	9859
Varenicline	34574	67592	6523	1307	360	0	18706
Velaglucerase alfa	0	50	17	0	0	0	0

Supplemental File S8. Characteristics of industry and non-industry post-marketing studies when only incorporating those whose launch started after the first regulatory approval.

Characteristics		All (n=6443)	Industry studies (n=4012)	Non-industry studies (n=2431)
Primary sponsor	Industry NIH US Fed Other	2564 (39.8%) 244 (3.8%) 15 (0.2%) 3620 (56.2%)		
Industry involved either as a primary sponsor or a collaborator		4012 (62.5%)		
No. of post-marketing studies per drug	Min/max Median [Q1-Q3] Mean (SD)	3/498 51 [19-118] 93.4 (105.5)		
Population size per drug	Min/max Median [Q1-Q3] Mean (SD)	67/1.04E6 15212 [4819-36262] 61719 (166183)		

Therapeutic class according to the ATC				
Alimentary tract and metabolism		809 (12.6%)	547 (67.6%)	262 (32.4%)
Anti-infectives for systemic use		814 (12.6%)	495 (60.8%)	319 (39.2%)
Antineoplastic and immunomodulating agents		2900 (45.5%)	1742 (60.1%)	1158 (39.9%)
Blood and blood forming organs		429 (6.7%)	261 (60.8%)	168 (39.2%)
Nervous system		468 (7.3%)	288 (61.5%)	180 (38.5%)
Other*		1023 (15.9%)	679 (66.4%)	344 (33.6%)
Study design with respect to primary label	Another indication than the originally approved indication	2342 (36.4%)	1259 (53.8%)	1083 (46.2%)
	Originally approved indication	3859 (59.9%)	2631 (68.2%)	1228 (31.8%)
	Both the originally approved indication and another indication	242 (3.7%)	122 (50.4%)	120 (49.6%)
Study type	Observational	703 (10.9%)	466 (66.3%)	237 (33.7%)
	Interventional	5740 (89.1%)	3546 (61.8%)	2194 (38.2%)

Randomization	Missing data	2393	1412	981
	Yes	2950 (72.8%)	1875 (63.6%)	1075 (36.4%)
	No	1100 (27.2%)	725 (65.9%)	375 (34.1%)
Study phase	Missing data	1046	551	495
	0	33 (0.6%)	12 (36.4%)	21 (63.6%)
	I	886 (16.4%)	622 (70.2%)	264 (29.8%)
	I/II	406 (7.5%)	235 (57.9%)	171 (42.1%)
	II	1746 (32.4%)	992 (56.8%)	754 (43.2%)
	II/III	104 (1.9%)	49 (47.1%)	55 (52.9%)
	III	1180 (21.9%)	957 (81.1%)	223 (18.9%)
	IV	1042 (19.3%)	594 (57.0%)	448 (43.0%)
Centers	Missing data	468	394	74
	Min/max	1/1616	1/1616	1/922
	Median [Q1-Q3]	2 [1-12]	4 [1-23]	1 [1-2]
	Mean (SD)	19.7 (62.2)	26.1 (70.4)	9.8 (45.0)
Countries	Missing data	466	393	73
	Min/max	1/45	1/46	1/15
	Median [Q1-Q3]	1 [1-1]	1 [1-2]	1 [1-1]

	Mean (SD)	2.6 (4.6)	3.5 (5.7)	1.1 (0.7)
Planned enrollment	Missing data	14	9	5
	Min/max	1/904585	1/904585	1/61050
	Median [Q1-Q3]	60 [27-180]	70 [29-241]	48 [24-100]
	Mean (SD)	662.4 (13044.2)	966.4 (16495.6)	160.9 (1293.2)
Status at the time of data exportation	Not yet recruiting	319 (4.8%)	136 (42.6%)	183 (57.4%)
	Recruiting	1888 (29.3%)	883 (46.8%)	1005 (53.2%)
	Active, not recruiting	991 (15.4%)	619 (62.5%)	372 (37.5%)
	Enrolling by invitation	64 (1.0%)	42 (65.6%)	22 (34.4%)
	Completed	2705 (42.0%)	2000 (73.9%)	705 (26.1%)
	Terminated	476 (7.4%)	332 (69.8%)	144 (30.3%)

NIH, US National Institutes of Health

*includes cardiovascular system, dermatological, genitourinary system and sex hormones, musculoskeletal system, sensory organs, systemic hormonal preparations, excluding sex hormones, and other

eTable. Planned enrollment of post-marketing trials by industry and non-industry funding for indications targeted in trials.

Indication	Industry funding		Non-industry funding	
	No. of trials	Planned enrollment	No. of trials	Planned enrollment
Originally approved indication	2742	Median [Q1-Q3]: 100 [33-323] Mean (SD): 1322.0 (19921.8)	1251	Median [Q1-Q3]: 60 [29.5-150] Mean (SD): 230.9 (1771.2)
Other indication(s)	1310	Median [Q1-Q3]: 45 [24-128] Mean (SD): 167.7 (SD: 544.1)	1131	Median [Q1-Q3]: 40 [21-70] Mean (SD): 72.9 (148.0)
Both the originally approved indication and another indication	124	Median [Q1-Q3]: 60 [30-224] Mean (SD): 765.2 (2961.8)	121	Median [Q1-Q3]: 50 [30-120] Mean (SD): 218.1 (934.9)

Data were missing for 9 industry-funded trials and 5 other trials.