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CLINICAL TRIAL EVIDENCE SUPPORTING FDA APPROVAL OF NOVEL THERAPEUTICS, 2005–2012

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Abstract

Importance—Many patients and physicians assume that the safety and effectiveness of newly approved therapeutics is well understood; however, the strength of the clinical trial evidence supporting approval decisions by the Food and Drug Administration (FDA) has not been evaluated.

Objectives—To characterize pivotal efficacy trials, clinical trials that served as the basis of FDA approval, for newly approved novel therapeutics.

Design and Setting—Cross-sectional analysis using publicly available FDA documents for all novel therapeutics approved between 2005 and 2012.

Main Outcome Measures—We classified pivotal efficacy trials according to the following design features: randomization, blinding, comparator and trial endpoint. “Surrogate outcomes” were defined as any endpoint using a biomarker that is expected to predict clinical benefit. We also determined the number of patients, trial duration, and trial completion rates.

Results—Between 2005 and 2012, FDA approved 188 novel therapeutics for 206 indications on the basis of 448 pivotal efficacy trials. Median number of pivotal trials per indication was two (interquartile range: 1–2.5), although 74 (36.8%) indications were approved on the basis of a single pivotal trial. Nearly all trials were randomized (89.3%, 95% Confidence Interval [CI],

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Conflicts of interest: Dr. Krumholz reports that he chairs a scientific advisory board for United Healthcare. Dr. Ross reports that he is a member of a scientific advisory board for FAIR Health, Inc.

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86.4%–92.2%), double-blinded (79.5%, 95% CI, 75.7%–83.2%), and used either an active or placebo comparator (87.1%, 95% CI, 83.9%–90.2%). Median number of patients enrolled per indication among all pivotal trials was 760 (interquartile range: 270–1550). At least one pivotal trial with a duration of 6 months or greater supported the approval of 68 (33.8%, 95% CI, 27.2%–40.4%) indications. Pivotal trials using surrogate endpoints as their primary outcome formed the exclusive basis of approval for 91 (45.3%, 95% CI, 38.3%–52.2%) indications, clinical outcomes for 67 (33.3%, 95% CI, 26.8%–39.9%), and clinical scales for 36 (17.9%, 95% CI, 12.6%–23.3%). Trial features differed by therapeutic and indication characteristics, such as therapeutic area, expected length of treatment, orphan status and accelerated approval.

Conclusions and Relevance—The quality of clinical trial evidence used by the FDA as the basis of recent novel therapeutic approvals varied widely across indications.

INTRODUCTION

The approval of a drug by the Food and Drug Administration (FDA) conveys that the product is safe and effective. An Internet-based survey of a national probability sample of 4316 U.S. adults, 2944 respondents (68% response rate), found that 39% report believing that FDA only approves “extremely effective” drugs and 25% only drugs without serious side effects.¹ Some physicians make similar assumptions about effectiveness and safety, expecting that patients are likely to benefit from newly approved therapies.^{2–5}

FDA review of new drug applications is guided by the Federal Food, Drug and Cosmetic Act, which requires “adequate and well controlled investigations” to determine efficacy.⁶ FDA guidance suggests that drug manufacturers submit at least two trials, each providing independent evidence of efficacy – such studies are known as “pivotal” efficacy trials – but also implies flexibility, describing circumstances in which a single efficacy trial might be sufficient to support approval.⁷ Moreover, for certain applications, FDA provides written guidance on the design of pivotal efficacy trials, including features of trial design, such as sample selection and choice of comparator,^{8–10} and may provide further guidance in meetings with individual sponsors.¹¹ As an example, for therapeutics evaluated through the accelerated approval pathway, which aims to speed approval of therapeutics that treat life-threatening diseases, FDA permits pivotal efficacy trials to use surrogate endpoints that are “reasonably likely” to predict clinical benefit.¹²

The clinical research findings available at the time of a drug’s approval have important implications: if made public, these findings represent the only source of information available to patients and their physicians as they decide whether to use a newly approved drug. However, flexible approval standards may lead to some therapeutics being approved by FDA on the basis of numerous rigorously designed clinical trials and others on fewer or less robust studies, leading to differing levels of certainty about the risks and benefits for newly approved drugs. Accordingly, we sought to systematically examine this issue, evaluating the strength of the clinical trial evidence supporting FDA approval decisions for novel therapeutics – pharmacologics and biologics – between 2005 and 2012 by characterizing key features of pivotal efficacy trials, such as trial size, design, duration and endpoints.

METHODS

Data Sources

Drugs@FDA is a publicly accessible database available through the FDA's website that lists regulatory actions, such as approvals and drug labeling changes, for all currently approved prescription therapeutics. Records for each approved therapeutic are hyperlinked to FDA medical reviews, which are lengthy documents that outline the clinical evidence used to establish the efficacy and safety of the novel therapeutic prior to approval. The Drugs@FDA database was downloaded on January 11, 2012 and on May 1, 2013. Medical reviews were accessed several times between January 2012 and June 2013.

Study Sample

We constructed a sample of novel therapeutics (i.e., new molecular entities or novel biologic drugs) first approved by FDA between January 1, 2005 and December 31, 2012, excluding generic drugs, reformulations and combination therapies of non-novel therapeutics (Figure). We also excluded non-therapeutic agents, such as diagnostic and contrast agents (for details, see Appendix 1), and removed any duplicate records.

Therapeutic and Indication Characteristics

Using information provided within the Drugs@FDA database, we categorized each novel therapeutic by year of approval and as a pharmacologic (i.e., small molecule) or biologic.¹³ Additionally, therapeutics were classified by orphan status, a designation made by FDA that affords extended market exclusivity for drugs that treat rare diseases (n.b., the Drugs@FDA database only indicates orphan status for biologics approved after 2010). Using FDA approval letters, which are also hyperlinked in the Drugs@FDA database, we identified therapeutics approved through the accelerated approval pathway, and the indication for which all novel therapeutics were initially approved for use. Subsequently, indications were categorized by expected length of treatment: acute, intermediate, or chronic. The expected length of use for acute treatments was less than one month, between one month, and two years for intermediate treatments and greater than two years for chronic treatments (for details, see Appendix 2). Additionally, we used the World Health Organization's Anatomic Therapeutic Classification system, contextualized for clinical relevance, to categorize each indication into one of eight therapeutic areas.¹⁴ Finally, two investigators (NSD and JSR) determined the total number of patients exposed to the novel therapeutic during clinical development, the total safety population (for details, see Appendix 3).

Identification of Pivotal Efficacy Trials

For each novel therapeutic, one investigator (JAA) identified the pivotal efficacy trials used as the basis for approval. Generally, these trials are labeled in FDA medical reviews as "pivotal" and their design and findings are discussed in detail. For approvals where no trial was explicitly labeled "pivotal" in the FDA medical review, we identified trials described as essential to approval or those that were prioritized within the review, using criteria like substantial discussion of study design (i.e., inclusion and exclusion criteria, thorough description of study protocol) and independent analysis of results (i.e., not pooled with other

studies). Additionally, any efficacy trial reviewed as part of a resubmitted application was considered pivotal to approval. Two investigators (NSD and JSR) subsequently validated identification of all pivotal efficacy trials through independent review, resolving conflicts by consensus.

Pivotal Efficacy Trial Features

Each pivotal trial was categorized according to its use of randomization and blinding based on the FDA reviewer's description of the trial. In addition, we also recorded the type of comparator, primary trial endpoint(s), the number of treated patients (overall and intervention group), trial duration and completion rate (Appendix 3). Completion rate was calculated by dividing the number of patients completing the trial by the number of treated patients (overall and intervention group). Primary trial endpoints were classified as "clinical outcomes", "clinical scales" or "surrogate outcomes" based on an established framework and a recent Institute of Medicine Report (Appendix 3).^{15,16} Clinical outcomes, such as death or rate of hospitalization, measure patient survival or function. Clinical scales, such as the Crohn's Disease Activity Index or the visual analogue scale for pain, represent rubrics for the quantification of subjective patient-reported symptoms. Surrogate outcomes, such as hemoglobin A1C or hepatitis C ribonucleic acid levels, represent biomarkers expected to predict clinical benefit. The initial abstraction was performed by one investigator (JAA). Again, two investigators (NSD and JSR) subsequently validated characterization of all pivotal trials through independent review and abstraction, resolving conflicts by consensus.

Statistical analysis

Using descriptive statistics, we characterized the novel therapeutics included in our sample and the indications for which they were initially approved for use. Next, we used descriptive statistics to characterize features across the overall sample of pivotal efficacy trials as well as the features of these trials aggregated at the indication level, the summary of all pivotal efficacy trials used to support the approval of each indication. We then used chi-square, Wilcoxon and Kruskal-Wallis tests as appropriate to examine differences among novel therapeutic and indication characteristics, including therapeutic area, expected length of therapy, drug type, orphan status, and accelerated approval, all of which were pre-planned prior to data collection. Analyses were performed using Microsoft Excel 2010 (Microsoft Corporation; Redmond, WA) and JMP 7.0.1 (SAS Institute; Cary, NC). All statistical tests were two-tailed and used a type I error rate of 0.01 to account for multiple comparisons across 5 therapeutic/indication characteristics.

RESULTS

Between 2005 and 2012, FDA approved 188 novel therapeutics: 154 (81.9%) were pharmacologics, 34 (18.1%) biologics. FDA had granted orphan status to 31 (16.5%) and 22 (11.7%) were approved through the accelerated approval pathway (Table 1). These 188 novel therapeutics were approved for use for 206 indications: 171 (91.0%) for a single indication, 16 (8.5%) for two indications and one (0.5%) for three. Over half of indications required chronic treatment (n=108; 52.4%), 58 (28.2%) intermediate-length treatment, and 40 (19.4%) acute treatment. Three therapeutic areas accounted for nearly half of indications:

41 (19.9%) were used to treat cancer, 29 (14.1%) infectious disease and 23 (11.2%) cardiovascular disease, diabetes mellitus or hyperlipidemia. Median safety population, total number of patients exposed to the novel therapeutic during clinical development, was 1143 (Inter-Quartile Range [IQR]: 503–2600).

Pivotal Efficacy Trial Features

Pivotal efficacy trials were identified for 201 of 206 indications (Figure); four novel therapeutics were approved (one for two indications) without a pivotal efficacy trial. A total of 448 pivotal trials were identified: 283 (63.2%) were explicitly labeled “pivotal”, 165 (36.8%) were inferred as pivotal based on the criteria described previously. The vast majority of pivotal trials were randomized (n=400; 89.3%, 95% Confidence Interval [CI], 86.4%–92.2%) and double-blinded (n=356; 79.5%, 95% CI, 75.7%–83.2%) (Table 2). Over half of trials used a placebo comparator (n=247; 55.1%, 95% CI, 50.5%–59.8%), 143 (31.9%, 95% CI, 27.6%–36.3%) used an active comparator, and 58 (12.9%, 95% CI, 9.8%–16.1%) had no comparator. The primary endpoint was a surrogate outcome for 219 (48.9%, 95% CI, 44.2%–53.5%) trials, 130 (29.0%, 95% CI, 24.8%–33.2%) used clinical outcomes and 99 (22.1%, 95% CI, 18.2%–26.0%) used clinical scales. Median total and intervention group patient populations were 446 (IQR: 205–678) and 271 (IQR: 133–426), while median trial duration was 14.0 weeks (IQR: 6.0–26.0 weeks); 113 (25.2%, 95% CI, 21.2%–29.3%) lasted 6 months or longer (Table 3). The median completion rate was 86.6% (IQR: 77.9%–93.1%).

Trial Features by Therapeutic & Indication Characteristics

Features of pivotal efficacy trials differed by therapeutic and indication characteristics. Trials of therapeutics used for cancer were least likely to be randomized (47.3%, 95% CI, 33.7%–60.9% vs. 95.2%, 95% CI, 93.0%–97.3%; $p<0.001$) and double-blinded (27.3%, 95% CI, 15.1%–39.4% vs. 86.8%, 95% CI, 83.4%–90.1%; $p<0.001$) (Table 2). An active comparator was used more frequently in trials of therapeutics approved for infectious disease indications when compared with therapeutics for other indications (68.4%, 95% CI, 56.0%–80.9% vs. 26.6%, 95% CI, 22.2%–31.0%; $p<0.001$). Clinical outcomes and scales were infrequently used in trials of therapeutics approved for cancer (n=9; 16.4%, 95% CI, 6.3%–26.5%) and cardiovascular disease, diabetes mellitus, and hyperlipidemia (n=11; 15.1%, 95% CI, 6.7%–23.5%). Surrogate endpoints were used in nearly all trials among therapeutics approved through the accelerated approval pathway (n=38; 95.0%, 95% CI, 87.9%–100%), in contrast to fewer than half (n=181; 44.4%, 95% CI, 39.5%–49.2%) of trials among non-accelerated approval therapeutics.

The median intervention group patient population was smaller among therapeutics with orphan status when compared with those without (98 [IQR: 53–184] vs. 294 [IQR: 157–454]; $p<0.001$), and in trials of therapeutics approved via the accelerated approval pathway when compared to non-accelerated approval therapeutics (142 [IQR: 78–260] vs. 289 [IQR: 142–446]; $p<0.001$) (Table 3). Trial duration varied according to expected length of treatment ($p<0.001$) and was shorter for pharmacologics when compared with biologics (12.0 [IQR: 6.0–24.0] vs. 24.0 [IQR: 18.0–49.6] weeks; $p<0.001$).

Aggregated Pivotal Efficacy Trial Features Supporting Approved Indications

Among 201 indications, median number of trials per indication was 2 (IQR: 1–2.5; Table 4); 74 (36.8%) indications were approved on the basis of a single trial, 77 (38.3%) on two, and 50 (24.9%) on three or more. Among the aggregated pivotal efficacy trials supporting these indications, median total and intervention group patient populations were 760 (IQR: 270–1550) and 445 (IQR: 169–936). Although at least one trial using clinical outcomes or clinical scales supported the approval of 73 (36.3%, 95% CI, 29.6%–43.0%) and 39 (19.4%, 95% CI, 13.9%–24.9%) indications, respectively (Table 5), trials using clinical outcomes or clinical scales formed the exclusive basis of approval for slightly fewer: 67 (33.3%, 95% CI, 26.8%–39.9%) and 36 (17.9%, 95% CI, 12.6%–23.3%) indications. In addition, trials using surrogate endpoints as their primary outcome formed the exclusive basis of approval for 91 (45.3%, 95% CI, 38.3%–52.2%) indications. At least one trial of at least 6 months in duration supported the approval of 68 (33.8%, 95% CI, 27.2%–40.4%) indications.

Aggregated Trial Features Supporting Approved Indications by Therapeutic & Indication Characteristics

The features of the aggregated pivotal efficacy trials supporting approved indications differed by therapeutic and indication characteristics. Most therapeutics approved for cancer indications were on the basis of a single trial, while the approval of therapeutics for cardiovascular disease, diabetes mellitus, and hyperlipidemia and psychiatric indications often relied upon at least three trials (Tables 4 and 5). Median numbers of overall and intervention group patients were larger among aggregated trials supporting indications within these therapeutic areas.

There was no difference in the proportion of indications approved through the accelerated approval pathway on the basis of multiple trials when compared with non-accelerated approval indications (56.5%, 95% CI, 34.6%–78.4% vs. 64.0%, 95% CI, 56.9%–71.2%; $p=0.48$). More therapeutics indicated for chronic treatment were supported by at least one trial of 6 months duration when compared with therapeutics indicated for acute or intermediate-length treatment (44.4%, 95% CI, 34.9%–54.0% vs. 2.8%, 95% CI, 0%–8.4% and 33.3%, 95% CI, 20.7%–46.0%, respectively; $p<0.001$).

DISCUSSION

Our characterization of pivotal efficacy trials, trials that serve as the basis of FDA approval, for all novel therapeutics approved between 2005 and 2012 demonstrates that the quality of clinical trial evidence used by the FDA to make approval decisions varied widely across indications. While the vast majority of indications were supported by at least one randomized, double-blinded trial, there was wide variation in trials' choice of comparators and endpoints, duration, size, and completion rate. In addition, just over one third of indications were approved on the basis of a single pivotal efficacy trial.

The variation in the quality of clinical trial evidence used by FDA to assess novel therapeutic efficacy highlights the agency's flexible standards for approval. Such regulatory flexibility allows for a customized approach to approval, including the ability to rapidly

approve potentially effective therapies for life-threatening diseases, such as certain cancers, or those diseases for which there is no existing effective treatment, such as orphan diseases. These approvals can be made without requiring costly and time-consuming randomized, double-blinded, controlled trials, despite their being regarded as the gold standard for evaluation.^{17–19} Indeed, FDA has provided guidance on approaches to accelerate clinical development of novel therapeutics^{8–10,20} and has cited its willingness to rapidly approve new drugs in recent year-end reviews of drug approvals.^{21,22} Substantial variation has been described among pivotal efficacy trials supporting the approval of cancer drugs,²³ and this flexibility may well be warranted given the limited number of effective therapies and poor prognosis associated with cancer.

Understanding the strength of clinical trial evidence of newly approved therapeutics has important implications for patients and physicians. When medications become available on the market, decisions must be made about their use, likely informed by how well safety and effectiveness are understood. Comparative effectiveness information, which is not required as part of FDA approval and involves comparison of an intervention to an active control, was available for less than half of indications, consistent with prior research,²⁴ but leaving uncertainty about the benefits and safety of these medications when compared with other available therapeutics. Similarly, while patient-important clinical outcomes and scales were used in many pivotal trials, trials using surrogate endpoints as their primary outcome formed the exclusive basis of approval for nearly half of the approved indications in our study. This reliance on surrogate outcomes leaves patients and physicians to extrapolate clinical benefits from trials, again raising questions about the certainty of the medications' benefits in practice.²⁵ Finally, we found that the majority of trials evaluating therapeutics indicated for chronic treatment lasted less than one year, raising questions about the certainty of these medications' long-term efficacy and safety.

Because comprehensive safety evaluations are difficult to undertake as part of randomized controlled trials, particularly smaller trials, these findings clarify the importance of adopting a “life-cycle” approach, both for drug safety and for improved understanding of drug effectiveness. In 2006, the Institute of Medicine's Report on the Future of Drug Safety recommended that the FDA monitor and evaluate the benefits and risks of drug therapies not only prior to their approval but throughout their entire market life.²⁶ This so-called life-cycle approach suggests that new information on therapeutics' benefits and safety be continually collected. It also requires adequate and robust post-market surveillance systems that allow reassessments of drug efficacy and safety after market introduction.

However, communicating this updated information to patients and physicians is critical. A recent Institute of Medicine committee report similarly recommended that the FDA implement a benefit and risk assessment and management plan that would summarize the FDA's evaluation of a drug's benefit-risk profile in a single document and be continuously updated during the entire market life of the product.^{27,28} Alternatively, or as part of this effort, FDA could provide a summative statement, or even a grade, for each approval to signal the quality of clinical trial evidence used to determine safety and efficacy, allowing therapeutics approved on the basis of more robust evidence to be distinguished from those approved on less robust evidence. As the FDA has publicly declared its intention to

encourage investigators to use innovative trial designs that are as effective as standard designs but less burdensome and time-consuming and to identify qualifying biomarkers that accurately predict outcomes to make clinical trials more efficient,²⁹ it must also ensure that patients and physicians understand how to interpret these trials and the likelihood of experiencing benefit or harm when deciding to use these newly approved therapeutics.

Our study has several limitations. Although pivotal efficacy trials represent the primary source of information about novel therapeutic efficacy at approval, other trials that provide supplementary efficacy data are discussed transiently in FDA medical reviews, but were not systematically assessed. While FDA is more likely to first approve novel therapeutics for use,³⁰ the agency may also rely on information from use of the drugs in other countries when evaluating these therapeutics for approval, which we did not assess. Additionally, efficacy represents just one component of FDA review, which also covers safety, pharmacology, chemistry and manufacturing. Finally, our study was limited to the approval of new molecular entities and novel biologics; since reformulated and generic drugs can be approved on the basis of bioequivalence studies, it is likely that our study captured the majority of pivotal efficacy trials used for novel therapeutic evaluations. Moreover, our findings are consistent with a prior study of high-risk cardiovascular devices, which found many to be approved on the basis of trials that lack adequate strength and may be prone to bias.³¹

In conclusion, the quality of clinical trial evidence used by the FDA as the basis of novel therapeutic approvals between 2005 and 2012 varied widely across indications. This variation has important implications for patients and physicians as they make decisions about the use of newly approved therapeutics and has the potential to inform both the current FDA regulatory approval standards and post-market surveillance initiatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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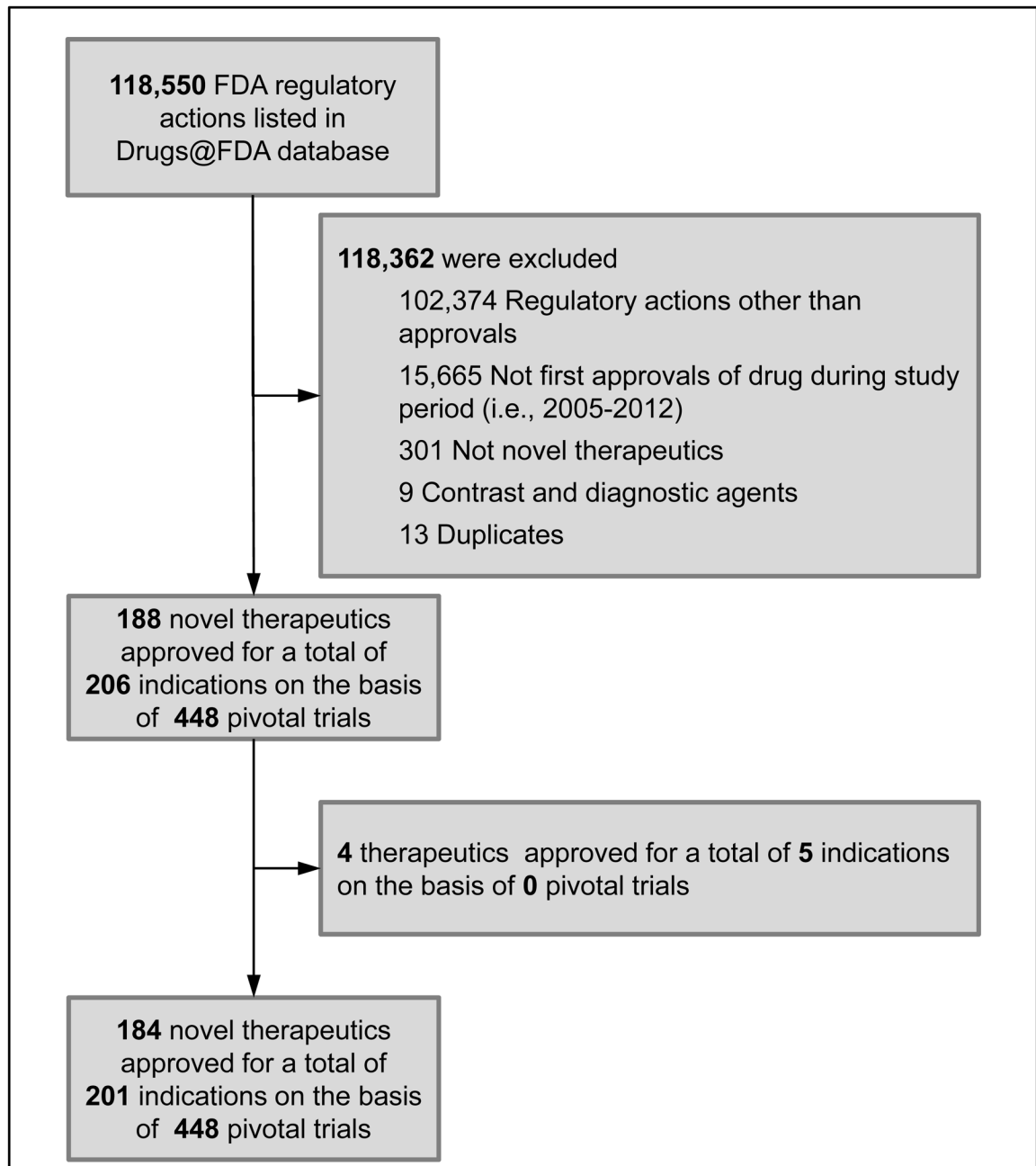


Figure.
Flow diagram showing sample construction of novel therapeutics approved by the Food and Drug Administration between 2005 and 2012.

Table 1

Novel therapeutics and associated indications approved by the Food and Drug Administration between 2005 and 2012.

Novel Therapeutics (n=188)	
Approval Year	
2005	19 (10.1)
2006	22 (11.7)
2007	17 (9.0)
2008	20 (10.6)
2009	25 (13.3)
2010	20 (10.6)
2011	28 (14.9)
2012	37 (19.7)
Review Cycles Required for Approval	
Single	134 (71.3)
Multiple	54 (28.7)
Novel Therapeutic Type	
Pharmacologic	154 (81.9)
Biologic	34 (18.1)
Orphan Status	
Orphan designation	31 (16.5)
No orphan designation	157 (83.5)
Accelerated Approval	
Accelerated approval	22 (11.7)
Regular approval	166 (88.3)
Associated Indications (n=206)	
Therapeutic Area	
Cancer	41 (19.9)
Infectious disease	29 (14.1)
Cardiovascular disease, diabetes mellitus and hyperlipidemia	23 (11.2)
Neurologic	17 (8.3)
Dermatologic	15 (7.3)
Autoimmune and musculoskeletal	13 (6.3)
Psychiatric	10 (4.9)
Other	58 (28.2)
Expected Length of Treatment	
Acute	40 (19.4)
Intermediate	58 (28.2)
Chronic	108 (52.4)

Table 2 Design of pivotal efficacy trials providing the basis for approval of novel therapeutics by the Food and Drug Administration between 2005 and 2012, stratified by therapeutic and indication characteristics.

Therapeutic/Indication Characteristic	Pivotal Trials, No.	Randomized, No. % (95% CI)	Double-Blinded, No. % (95% CI)	Comparator, No. % (95% CI)			Endpoint, No. % (95% CI)		
				Active	Placebo	None	Surrogate Outcome	Clinical Outcome	Clinical Scale
All	448	400 (89.3% (86.4%–92.2%))	356 (79.5% (75.7%–83.2%))	143 (31.9% (27.6%–36.3%))	247 (55.1% (50.5%–59.8%))	58 (12.9% (9.8%–16.1%))	219 (48.9% (44.2%–53.5%))	130 (29.0% (24.8%–33.2%))	99 (22.1% (18.2%–26.0%))
Therapeutic Area									
Cancer	55	26 (47.3% (33.7%–60.9%))	15 (27.3% (15.1%–39.4%))	10 (18.2% (7.7%–28.7%))	16 (29.1% (16.7%–41.5%))	29 (52.7% (39.1%–66.3%))	46 (83.6% (73.5%–93.7%))	9 (16.4% (6.3%–26.5%))	0 (0.0% (0.0%–0.0%))
Infectious Disease	57	53 (93.0% (86.1%–99.8%))	45 (78.9% (68.0%–89.9%))	39 (68.4% (56.0%–80.9%))	13 (22.8% (11.6%–34.0%))	5 (8.8% (1.2%–16.3%))	33 (57.9% (44.7%–71.1%))	24 (42.1% (28.9%–55.3%))	0 (0.0% (0.0%–0.0%))
CV/DMLipids	73	72 (98.6% (95.9%–100.0%))	68 (93.2% (87.2%–99.1%))	26 (35.6% (24.4%–46.9%))	45 (61.6% (50.2%–73.1%))	2 (2.7% (0.0%–6.6%))	62 (84.9% (76.5%–93.3%))	11 (15.1% (6.7%–23.5%))	0 (0.0% (0.0%–0.0%))
Neurology	38	38 (100.0% (100.0%–100.0%))	38 (100.0% (100.0%–100.0%))	6 (15.8% (3.6%–27.9%))	30 (78.9% (65.4%–92.5%))	2 (5.3% (0.0%–12.7%))	0 (0.0% (0.0%–0.0%))	25 (65.8% (50.0%–81.6%))	13 (34.2% (18.4%–50.0%))
Dermatology	29	27 (93.1% (83.3%–100.0%))	22 (75.9% (59.3%–92.4%))	5 (17.2% (2.6%–31.9%))	20 (69.0% (51.1%–86.9%))	4 (13.8% (0.4%–27.1%))	5 (17.2% (2.6%–31.9%))	15 (51.7% (32.4%–71.1%))	9 (31.0% (13.1%–48.9%))
Autoimmune/Musculoskeletal	36	36 (100.0% (100.0%–100.0%))	34 (94.4% (86.6%–100%))	11 (30.6% (14.7%–46.3%))	25 (69.4% (53.6%–85.3%))	0 (0.0% (0.0%–0.0%))	6 (16.7% (3.9%–29.5%))	2 (5.6% (0.0%–13.4%))	28 (77.8% (63.5%–92.0%))
Psychiatry	43	43 (100.0% (100.0%–100.0%))	43 (100.0% (100.0%–100.0%))	19 (44.2% (28.7%–60.0%))	24 (55.8% (40.3%–71.3%))	0 (0.0% (0.0%–0.0%))	5 (11.6% (1.6%–21.6%))	7 (16.3% (4.8%–27.8%))	31 (72.1% (58.1%–86.1%))
Other	117	105 (89.7% (84.2%–95.3%))	91 (77.8% (70.1%–85.4%))	27 (23.1% (15.3%–30.8%))	74 (63.2% (54.4%–72.1%))	16 (13.7% (7.4%–20.0%))	62 (53.0% (43.8%–62.2%))	37 (31.6% (23.1%–40.2%))	18 (15.4% (8.7%–22.0%))
P value		< 0.001	< 0.001		< 0.001			< 0.001	
Expected Length of Treatment									
Acute	78	72 (92.3% (86.3%–98.4%))	63 (80.8% (71.8%–89.7%))	32 (41.0% (29.9%–52.1%))	35 (44.9% (33.6%–56.2%))	11 (14.1% (6.2%–22.0%))	31 (39.7% (28.6%–50.8%))	41 (52.6% (41.2%–63.9%))	6 (7.7% (1.6%–13.7%))
Intermediate	99	68 (68.7% (59.4%–78.0%))	54 (54.5% (44.6%–64.5%))	30 (30.3% (21.1%–39.5%))	38 (38.4% (28.6%–48.1%))	31 (31.3% (22.0%–40.6%))	53 (53.5% (43.5%–63.5%))	22 (22.2% (13.9%–30.6%))	24 (24.2% (15.7%–32.8%))
Chronic	271	260 (95.9% (93.6%–98.3%))	239 (88.2% (84.3%–92.1%))	81 (29.9% (24.4%–35.4%))	174 (64.2% (58.5%–70.0%))	16 (5.9% (3.1%–8.7%))	135 (49.8% (43.8%–55.8%))	67 (24.7% (19.6%–29.9%))	69 (25.5% (20.2%–30.7%))
P value		< 0.001	< 0.001		< 0.001			< 0.001	
Novel Therapeutic Type									
Pharmacologic	384	340 (88.5% (85.3%–91.7%))	307 (79.9% (75.9%–84.0%))	127 (33.1% (28.3%–37.8%))	204 (53.1% (48.1%–58.1%))	53 (13.8% (10.3%–17.3%))	196 (51.0% (46.0%–56.1%))	121 (31.5% (26.8%–36.2%))	67 (17.4% (13.6%–21.2%))
Biologic	64	60 (93.8% (87.7%–99.8%))	49 (76.6% (65.9%–87.2%))	16 (25.0% (14.1%–35.9%))	43 (67.2% (55.4%–79.0%))	5 (7.8% (1.1%–14.6%))	23 (35.9% (23.6%–48.0%))	9 (14.1% (5.3%–22.8%))	32 (50.0% (37.4%–62.6%))
P value		0.28	0.51		0.10			< 0.001	
Orphan Status									
Yes	56	30 (53.6% (40.0%–67.0%))	21 (37.5% (24.4%–50.6%))	12 (21.4% (10.3%–32.5%))	16 (28.6% (16.4%–40.8%))	28 (50.0% (36.5%–63.5%))	41 (73.2% (61.2%–85.2%))	10 (17.9% (7.5%–28.2%))	5 (8.9% (1.2%–16.6%))

Therapeutic/Indication Characteristic	Pivotal Trials, No.	Randomized, No. % (95% CI)	Double-Blinded, No. % (95% CI)	Comparator, No. % (95% CI)			Endpoint, No. % (95% CI)		
				Active	Placebo	None	Surrogate Outcome	Clinical Outcome	Clinical Scale
No	392	370 94.4% (92.1%–96.7%)	335 85.5% (82.0%–89.0%)	131 33.4% (28.7%–38.1%)	231 58.9% (54.0%–63.8%)	30 7.7% (5.0%–10.3%)	178 45.4% (40.5%–50.4%)	120 30.6% (26.0%–35.2%)	94 24.0% (19.7%–28.2%)
P value									
< 0.001									
Accelerated Approval									
Yes	40	18 45.0% (28.9%–61.1%)	12 30.0% (15.2%–44.8%)	6 15.0% (3.4%–26.6%)	12 30.0% (15.2%–44.8%)	22 55.0% (38.9%–71.1%)	38 95.0% (87.9%–100.0%)	2 5.0% (0.0%–12.1%)	0 0.0% (0.0%–0.0%)
No	408	382 93.6% (91.2%–96.0%)	344 84.3% (80.8%–87.9%)	137 33.6% (29.0%–38.2%)	235 57.6% (52.8%–62.4%)	36 8.8% (6.1%–11.6%)	181 44.4% (39.5%–49.2%)	128 31.4% (26.9%–35.9%)	99 24.3% (20.1%–28.4%)
P value									
< 0.001									

Notes: CI=Confidence Interval; CV/DM/Lipids=Cardiovascular disease, diabetes mellitus, and hyperlipidemia.

Table 3

Exposure to novel therapeutics approved by the Food and Drug Administration between 2005 and 2012 during pivotal efficacy trials that provided the basis for approval, stratified by therapeutic and indication characteristics.

Therapeutic/Indication Characteristic	Pivotal Trials, No.	Median Patients, No. (IQR)		Duration* 6 Months, No. % (95% CI)	Median Overall Completion Rate (IQR)
		Overall	Intervention Group		
All Trials (n=448)	448	446 (205-678)	271 (133-426)	113 25.2% (21.2%-29.3%)	86.6 (77.9-93.1)
Therapeutic Area					
Cancer	55	266 (84-610)	154 (84-359)	17 30.9% (18.3%-43.5%)	82.5 (75.0-91.3)
Infectious Disease	57	585 (319-697)	305 (234-366)	10 17.5% (7.4%-27.7%)	91.6 (87.1-96.0)
CV/DM/Lipids	73	651 (406-926)	441 (271-710)	23 31.5% (20.6%-42.4%)	88.0 (76.8-92.4)
Neurology	38	358 (234-613)	253 (127-333)	7 18.4% (5.5%-31.3%)	83.9 (76.7-88.5)
Dermatology	29	233 (121-491)	126 (64-204)	3 10.3% (0.0%-22.1%)	94.4 (90.5-98.0)
Autoimmune/Musculoskeletal	36	525 (362-749)	345 (230-502)	12 33.3% (17.2%-49.5%)	82.8 (76.9-92.2)
Psychiatry	43	432 (275-590)	231 (128-343)	0 0% (0.0%-0.0%)	70.1 (54.8-83.6)
Other	117	416 (122-695)	238 (83-451)	41 35.0% (26.3%-43.8%)	87.0 (79.4-93.1)
P value		< 0.001	< 0.001	< 0.001	< 0.001
Expected Length of Treatment					
Acute	78	312 (154-599)	212 (97-318)	1 1.3% (0.0%-3.8%)	93.1 (82.4-98.1)
Intermediate	99	296 (108-625)	196 (86-365)	22 22.2% (13.9%-30.6%)	82.4 (67.5-91.3)
Chronic	271	499 (312-745)	311 (168-499)	90 33.2% (27.6%-38.9%)	86.0 (79.2-92.1)
P value		< 0.001	< 0.001	< 0.001	< 0.001
Novel Therapeutic Type					
Pharmacologic	384	461 (222-693)	275 (138-426)	86 22.4% (18.2%-26.6%)	85.8 (77.5-92.9)

Therapeutic/Indication Characteristic	Pivotal Trials, No.	Median Patients, No. (IQR)		Median Weeks (IQR)	Duration*		Median Overall Completion Rate (IQR)
		Overall	Intervention Group		6 Months, No. % (95% CI)		
Biologic	64	344 (108–658)	217 (70–410)	24.0 (18.0–49.6)	27 42.2% (29.7%–54.6%)	90.8 (81.3–94.5)	
P value		0.07	0.05	< 0.001	0.002	0.03	
Orphan Status							
Yes	56	150 (71–288)	98 (53–184)	13.5 (4.0–37.5)	16 28.6% (16.4%–40.8%)	88.7 (81.1–94.7)	
No	392	480 (276–717)	294 (157–454)	14.0 (6.0–26.0)	97 24.7% (20.5%–29.0%)	86.3 (77.7–93.1)	
P value		< 0.001	< 0.001	0.70	0.52	0.18	
Accelerated Approval							
Yes	40	157 (89–342)	142 (78–260)	23.7 (9.4–24.0)	9 22.5% (9.0%–36.0%)	87.4 (76.0–94.8)	
No	408	470 (240–711)	289 (142–446)	12.0 (6.0–26.0)	104 25.5% (21.2%–29.7%)	86.6 (78.0–93.1)	
P value		< 0.001	< 0.001	0.13	0.85	0.61	

Notes: IQR=Interquartile Range; CI=Confidence Interval; CV/DMLipids=Cardiovascular disease, diabetes mellitus, and hyperlipidemia.

* Excludes “single administration” trials, in which the investigational drug was given only once.

Table 4

Number of aggregated pivotal efficacy trials and total number of patients providing the basis for approval of indications for novel therapeutics by the Food and Drug Administration between 2005 and 2012, stratified by therapeutic and indication characteristics.

Therapeutic/Indication Characteristic	Indications, No.	Median Pivotal Efficacy Trials, No. (IQR)	Median Patients in Aggregated Pivotal Efficacy Trials, No. (IQR)		Median Total Safety Population,* No. (IQR)
			Overall	Intervention Group	
All Indications	201	2 (1.0–2.5)	760 (270–1550)	445 (169–936)	1143 (503–2600)
Therapeutic Area					
Cancer	41	1 (1.0–1.0)	397 (180–634)	277 (159–414)	511 (295–1100)
Infectious Disease	27	2 (2.0–2.0)	1171 (763–1408)	605 (462–817)	1408 (840–1979)
CV/DM/Lipids	23	3 (1.0–5.0)	3645 (1446–5942)	2291 (832–3947)	3422 (1579–6570)
Neurology	17	2 (2.0–3.0)	1088 (448–1394)	661 (279–877)	2315 (1729–3145)
Dermatology	15	2 (1.0–2.0)	374 (233–1005)	187 (127–376)	1193 (1048–2228)
Autoimmune/Musculoskeletal	13	2 (2.0–3.0)	1209 (289–2893)	804 (223–1906)	1955 (379–3233)
Psychiatry	10	4 (2.0–5.5)	1492 (947–3000)	878 (417–1812)	3290 (1596–4099)
Other	55	2 (1.0–2.0)	418 (105–1608)	238 (78–968)	700 (296–1781)
P value		< 0.001	< 0.001	< 0.001	< 0.001
Expected Length of Treatment					
Acute	36	2 (2.0–2.0)	586 (305–1194)	349 (155–613)	889 (471–1560)
Intermediate	57	1 (1.0–2.0)	435 (192–787)	290 (159–507)	645 (365–1319)
Chronic	108	2 (1.0–3.0)	1203 (361–2062)	694 (234–1407)	1857 (698–3262)
P value		< 0.001	< 0.001	< 0.001	< 0.001
Novel Therapeutic Type					
Pharmacologic	164	2 (1.0–3.0)	825 (322–1607)	503 (209–956)	1206 (554–2806)
Biologic	37	1 (1.0–2.0)	374 (105–1213)	229 (70–683)	890 (288–1839)
P value		0.01	0.009	0.003	0.05
Orphan Status					
Yes	29	1 (1.0–2.0)	238 (162–576)	190 (107–361)	483 (290–651)
No	172	2 (1.0–3.0)	961 (339–1659)	516 (214–1021)	1371 (663–2909)
P value		0.05	< 0.001	< 0.001	< 0.001
Accelerated Approval					

Therapeutic/Indication Characteristic	Indications, No.	Median Pivotal Efficacy Trials, No. (IQR)	Median Patients in Aggregated Pivotal Efficacy Trials, No. (IQR)		Median Total Safety Population,* No. (IQR)
			Overall	Intervention Group	
Yes	23	2 (1.0–2.0)	266 (160–586)	207 (154–462)	497 (299–856)
No	178	2 (1.0–3.0)	862 (323–1648)	503 (180–986)	1323 (593–2761)
P value		0.11	< 0.001	0.008	< 0.001

Notes: IQR=Interquartile Range; CV/DM/Lipids=Cardiovascular disease, diabetes mellitus, and hyperlipidemia.

* For therapeutics approved for multiple indications, the safety population is the pooled number of patients exposed to the drug.

Proportion of novel therapeutic indications approved by the Food and Drug Administration between 2005 and 2012 on the basis of at least one trial that met the criteria below, stratified by therapeutic and indication characteristics.

Table 5

Therapeutic/Indication Characteristic	Indications, No.	2 Pivotal Trials No. % (95% CI)		Trial Duration [†] No. % (95% CI)		Comparator No. % (95% CI)			Trial Endpoint No. % (95% CI)	
		6 months	12 months	Active	Placebo	Clinical Outcome	Clinical Scale			
All Indications	201	68 33.8% (27.2%-40.4%)	17 8.5% (4.6%-12.3%)	79 39.3% (32.5%-46.1%)	119 59.2% (52.4%-66.0%)	73 36.3% (29.6%-43.0%)	39 19.4% (13.9%-24.9%)			
Therapeutic Area										
Cancer	41	16 39.0% (23.4%-54.6%)	2 4.9% (0.0%-11.8%)	10 24.4% (10.7%-38.1%)	15 36.6% (21.2%-52.0%)	9 22.0% (8.7%-35.2%)	0 0.0% (0.0%-0.0%)			
Infectious Disease	27	5 18.5% (2.9%-34.1%)	1 3.7% (0.0%-11.3%)	21 77.8% (61.1%-94.5%)	7 25.9% (8.3%-43.6%)	13 48.1% (28.0%-68.3%)	0 0.0% (0.0%-0.0%)			
CV/DMLipids	23	12 52.2% (30.0%-74.3%)	4 17.4% (0.0%-34.2%)	13 56.5% (34.6%-78.4%)	16 69.6% (49.2%-89.9%)	8 34.8% (13.7%-55.8%)	0 0.0% (0.0%-0.0%)			
Neurology	17	4 23.5% (1.0%-46.0%)	2 11.8% (0.0%-28.8%)	5 29.4% (5.3%-53.6%)	15 88.2% (71.1%-100.0%)	11 64.7% (39.4%-90.0%)	7 41.2% (15.1%-67.2%)			
Dermatology	15	2 13.3% (0.0%-32.8%)	0 0.0% (0.0%-0.0%)	3 20.0% (0.0%-42.9%)	11 73.3% (48.0%-98.7%)	8 53.3% (24.7%-81.9%)	5 33.3% (6.3%-60.3%)			
Autoimmune/Musculoskeletal	13	6 46.2% (14.8%-77.5%)	1 7.7% (0.0%-24.5%)	6 46.2% (14.8%-77.5%)	11 84.6% (61.9%-100.0%)	1 7.7% (0.0%-24.5%)	10 76.9% (50.4%-100.0%)			
Psychiatry	10	0 0.0% (0.0%-0.0%)	0 0.0% (0.0%-0.0%)	8 80.0% (49.8%-100.0%)	7 70.0% (35.4%-100.0%)	2 20.0% (0.0%-50.2%)	8 80.0% (49.8%-100.0%)			
Other	55	23 41.8% (28.4%-55.3%)	7 12.7% (3.6%-21.8%)	13 23.6% (12.0%-35.2%)	37 67.3% (54.5%-80.0%)	21 38.2% (24.9%-51.4%)	9 16.4% (6.3%-26.5%)			
P value		0.01	0.36	< 0.001	< 0.001	0.008	< 0.001			
Expected Length of Treatment										
Acute	36	1 2.8% (0.0%-8.4%)	0 0.0% (0.0%-0.0%)	20 55.6% (38.5%-72.6%)	17 47.2% (30.0%-64.4%)	22 61.1% (44.4%-77.8%)	3 8.3% (0.0%-17.8%)			
Intermediate	57	19 33.3% (20.7%-46.0%)	4 7.0% (0.0%-13.8%)	17 29.8% (17.6%-42.1%)	25 43.9% (30.6%-57.1%)	14 24.6% (13.0%-36.1%)	10 17.5% (7.4%-27.7%)			
Chronic	108	48 44.4% (34.9%-54.0%)	13 12.0% (5.8%-18.3%)	42 38.9% (29.5%-48.2%)	77 71.3% (62.6%-80.0%)	37 34.3% (25.2%-43.4%)	26 24.1% (15.9%-32.3%)			
P value		< 0.001	0.07	0.05	0.001	0.001	0.11			
Novel Therapeutic Type										
Pharmacologic	164	52 31.7% (24.5%-38.9%)	15 9.1% (4.7%-13.6%)	71 43.3% (35.6%-51.0%)	92 56.1% (48.4%-63.8%)	66 40.2% (32.7%-47.8%)	23 14.0% (8.7%-19.4%)			
Biologic	37	16 43.2% (26.5%-60.0%)	2 5.4% (0.0%-13.0%)	8 21.6% (7.7%-35.5%)	27 73.0% (58.0%-88.0%)	7 18.9% (5.7%-32.2%)	16 43.2% (26.5%-60.0%)			
P value		0.02	0.46	0.01	0.06	0.01	< 0.001			

Therapeutic/Indication Characteristic	Indications, No.	2 Pivotal Trials No. % (95% CI) *	Trial Duration [†] No. % (95% CI)		Comparator No. % (95% CI)		Trial Endpoint No. % (95% CI)	
			6 months	12 months	Active	Placebo	Clinical Outcome	Clinical Scale
Orphan Status								
Yes	29	13 44.8% (25.6%–64.0%)	12 41.4% (22.3%–60.4%)	5 17.2% (2.6%–31.9%)	8 27.6% (10.3%–44.9%)	11 37.9% (19.1%–56.7%)	8 27.6% (10.3%–44.9%)	2 6.9% (0.0%–16.7%)
No	172	114 66.3% (59.1%–73.4%)	56 32.6% (25.5%–39.6%)	12 7.0% (3.1%–10.8%)	71 41.3% (33.8%–48.7%)	108 62.8% (55.5%–70.9%)	65 37.8% (30.5%–45.1%)	37 21.5% (15.3%–27.7%)
P value		0.03	0.35	0.07	0.16	0.01	0.29	0.07
Accelerated Approval								
Yes	23	13 56.5% (34.6%–78.4%)	8 34.8% (13.7%–55.8%)	2 8.7% (0.0%–21.2%)	4 17.4% (0.0%–34.2%)	7 30.4% (10.0%–50.8%)	1 4.3% (0.0%–13.4%)	0 0.0% (0.0%–0.0%)
No	178	114 64.0% (56.9%–71.2%)	60 33.7% (26.7%–40.7%)	15 8.4% (4.3%–12.5%)	75 42.1% (34.8%–49.5%)	112 62.9% (55.8%–70.0%)	72 40.4% (35.2%–47.7%)	39 21.9% (15.8%–28.0%)
P value		0.48	0.92	0.97	0.02	0.003	0.001	0.001

Notes: CI=Confidence Interval; CV/DM/Lipids=Cardiovascular disease, diabetes mellitus, and hypertension.

* Two or more pivotal trials served as the basis of FDA approval

† Excludes “single administration” trials, in which the investigational drug was given only once.