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2016 Clinical Trials Roundup: The Next Generation

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Introduction

Welcome to this year's Clinical Trials Roundup where we'll reflect on research initiated in 2016, dissecting the data to survey the current trial landscape. In past roundups, our high-level overviews primarily focused on unapproved drug[1] activity within Trialtrove's six major therapeutic areas (TAs) of autoimmune/inflammation (A/I), cardiovascular (CV), CNS, infectious disease (ID), metabolic/endocrinology, and oncology. While useful in understanding competitive drug development strategies, this excluded the numerous trials supporting market or label expansion endeavors, as well as the smaller, but not insignificant, TAs of genitourinary and ophthalmology.

To capture the full universe of the competitive trial landscape, this year marks the launch of the next generation of the Clinical Trials Roundup, which will include all Phase I to III clinical research starting within 2016, regardless of the primary drug status. As usual, we'll begin with metrics by TA, trial phase, and disease, then zoom in on the most active industry sponsors, before wrapping up the roundup with a geographical survey of trial activity. Since this year's dataset is more inclusive, and has a later snapshot date than years past, minimal comparisons will be made to last year's analysis.

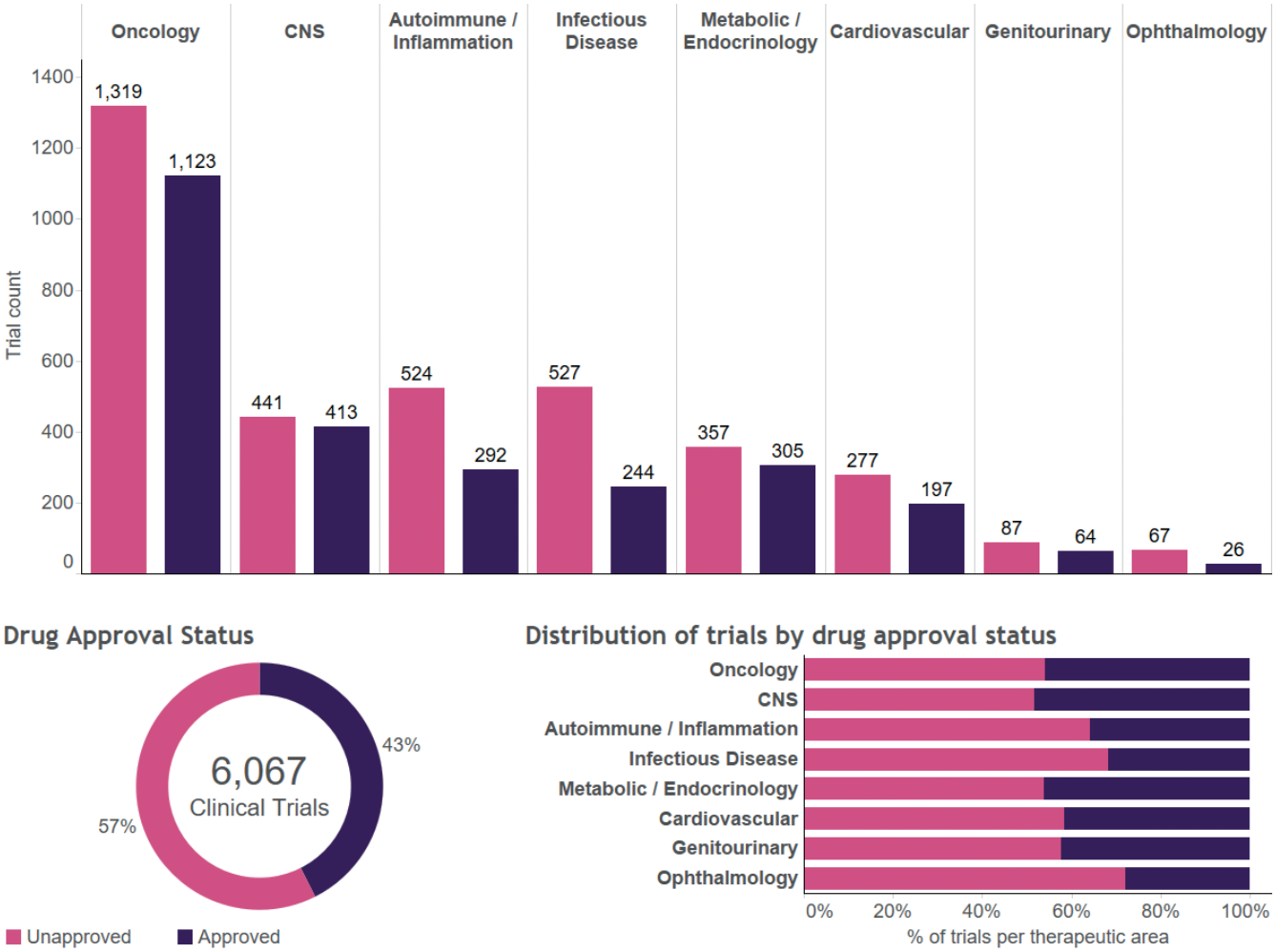
The 2016 trial landscape

As of July 6, 2017, Trialtrove captured 6,067 Phase I to III clinical trials that initiated within 2016 investigating at least one drug. While the majority of these trials do include at least one unapproved primary drug, the proportion was just 57% (3,484 of 6,067 trials). Overall, the most prolific TA[2] by far is oncology, with 2,442 trials starting in 2016. This is nearly three times more activity than the runner-up, CNS, which had 854 trials (Figure 1). These trial start trends are in line with the distribution of active drugs in the R&D pipeline by therapy group, according to Ian Lloyd's latest Pharma R&D Annual Review. Anticancer products comprise the largest portion of the R&D pipeline, with nearly twice as many neurological drugs, which is the second largest disease-specific therapy group.[3] As such, it is likely that cancer trial activity will continue to rapidly proliferate.

For all TAs, trials with unapproved drugs outnumber those focusing only on approved drugs. The TAs with the largest market expansion efforts, based on Phase I to III trial activity in 2016, were oncology, CNS, and metabolic, where nearly half of the trials involved approved drugs alone. In contrast, these types of efforts comprised approximately a third of A/I and ID research. The starkest difference is observed within the smallest TA of ophthalmology, where a mere 28% of trials were for approved compounds (Figure 1), suggesting a higher level of innovation in this area.

1 Unapproved drugs have not received regulatory approval for any indication. This excludes drugs that were approved for an initial indication but are unapproved for additional indications in other patient populations. Trials evaluating multiple drugs are classified as an unapproved drug trial if at least one primary drug is unapproved.
2 Trials that include multiple indications across different therapeutic areas will be counted for each targeted TA. As such, the sum of trial counts for the eight TAs will be higher than the total number of Phase I to III trials started in 2016.
3 Lloyd I (2017) Pharma R&D Annual Review 2017. Available from: https://pharmaintelligence.informa.com/resources/product-content/pharma-r-and-d-annual-review-2017 [Accessed July 7, 2017].

Figure 1. Phase I–III clinical trials started in 2016 by drug status



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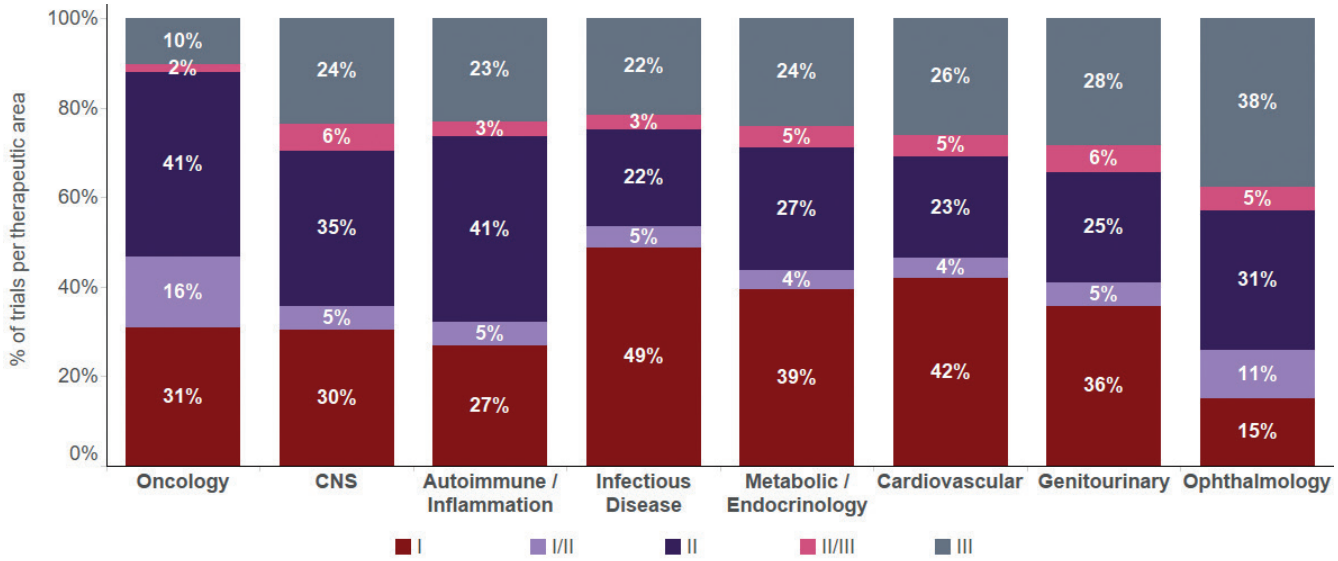
Source: Trialtrove® July 2017

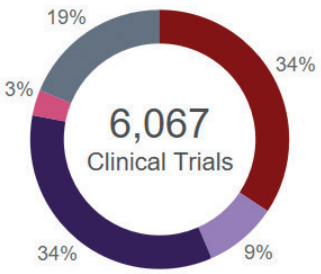
The most active TAs – oncology, CNS, and A/I – are largely driven by Phase II activity, followed by Phase I. Oncology research was particularly weighted toward early to mid-stage clinical development, with only 10% of anticancer trials in Phase III. Despite this lower proportion of late-stage research, the sheer volume of emerging cancer trials in 2016 still places the TA in first place when considering Phase III activity alone (Figure 2).

The remaining TAs tend to favor early-phase activity, and Phase I comprised between 36% and 49% of trials for ID, metabolic, CV, and genitourinary. Following this, Phase II and Phase III had somewhat similar proportions of activity, except in ID where anti-infective trials are evenly distributed between mid- and late-stage research. Again, ophthalmology distinguishes itself from the pack, with a larger focus on late-stage development, and Phase III had the largest portion of trials starting in 2016, followed by Phase II. Overall, trial hybrids were generally uncommon, but Phase I/II research was more frequent for ophthalmology, as well as oncology, reflecting the earlier movement of drugs into patients to evaluate proof of concept or initial efficacy while still establishing safety in these TAs (Figure 2).

Figure 2. Distribution of Phase I–III clinical trials started in 2016 by phase



Trial phase distribution



Trial counts by phase

	I	I/II	II	II/III	III	Total
Oncology	756	384	1,009	40	253	2,442
CNS	259	46	296	51	202	854
Autoimmune / Inflammation	220	43	338	26	189	816
Infectious Disease	375	38	166	26	166	771
Metabolic / Endocrinology	261	28	181	32	160	662
Cardiovascular	199	21	108	22	124	474
Genitourinary	54	8	37	9	43	151
Ophthalmology	14	10	29	5	35	93
Total	2,083	560	2,089	195	1,140	6,067

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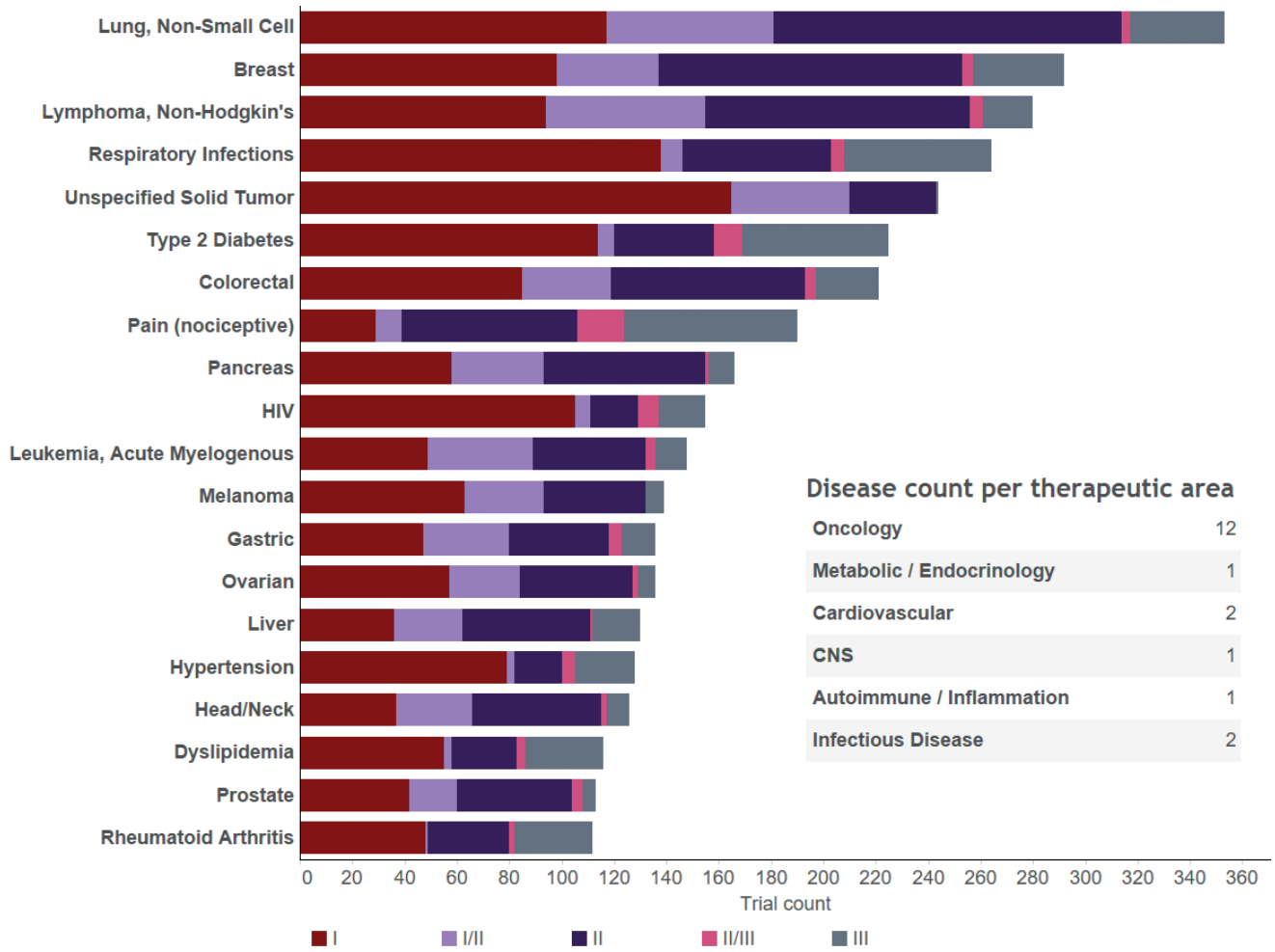
Source: Trialtrove® July 2017

Drilling down to the specific diseases,[4] multiple cancers take top billing – 12 of the top 20 diseases by trial count listed in Figure 3 are various oncology indications, with non-small cell lung cancer (NSCLC), breast cancer, and non-Hodgkin's lymphoma at the forefront, and unspecified solid tumors at fifth place. The few diseases outside of oncology span multiple TAs, including ID, metabolic, CNS, CV, and A/I, led by respiratory infections at fourth place, followed by type 2 diabetes at sixth, and nociceptive pain at eighth. The remaining non-oncology indications in the top 20, and their rankings, are HIV (10), hypertension (16), dyslipidemia (18), and rheumatoid arthritis (20) (Figure 3).

Among these active diseases, unspecified solid tumor held the largest number of Phase I trials, signaling the industry's ongoing battle with solid tumors. For most indications, the bulk of trials initiated in 2016 were in Phase I. Seven had the most activity in Phase II, including the three cancers at the top of the pack, while none had Phase III as the largest proportion of trials. Nociceptive pain, however, was close, with only a single study difference between Phase II and Phase III, and does appear to be the biggest target for late-stage development considering the disease holds the largest volume of Phase III research among these key focus areas for the industry (Figure 3).

4 Trial counts by disease represent each study that includes the specified indication, including studies that target multiple indications. As such, trials that include more than one disease will be counted for each indication.

Figure 3. Top 20 diseases of Phase I–III clinical trials started in 2016 by trial count



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The shining stars leading the way

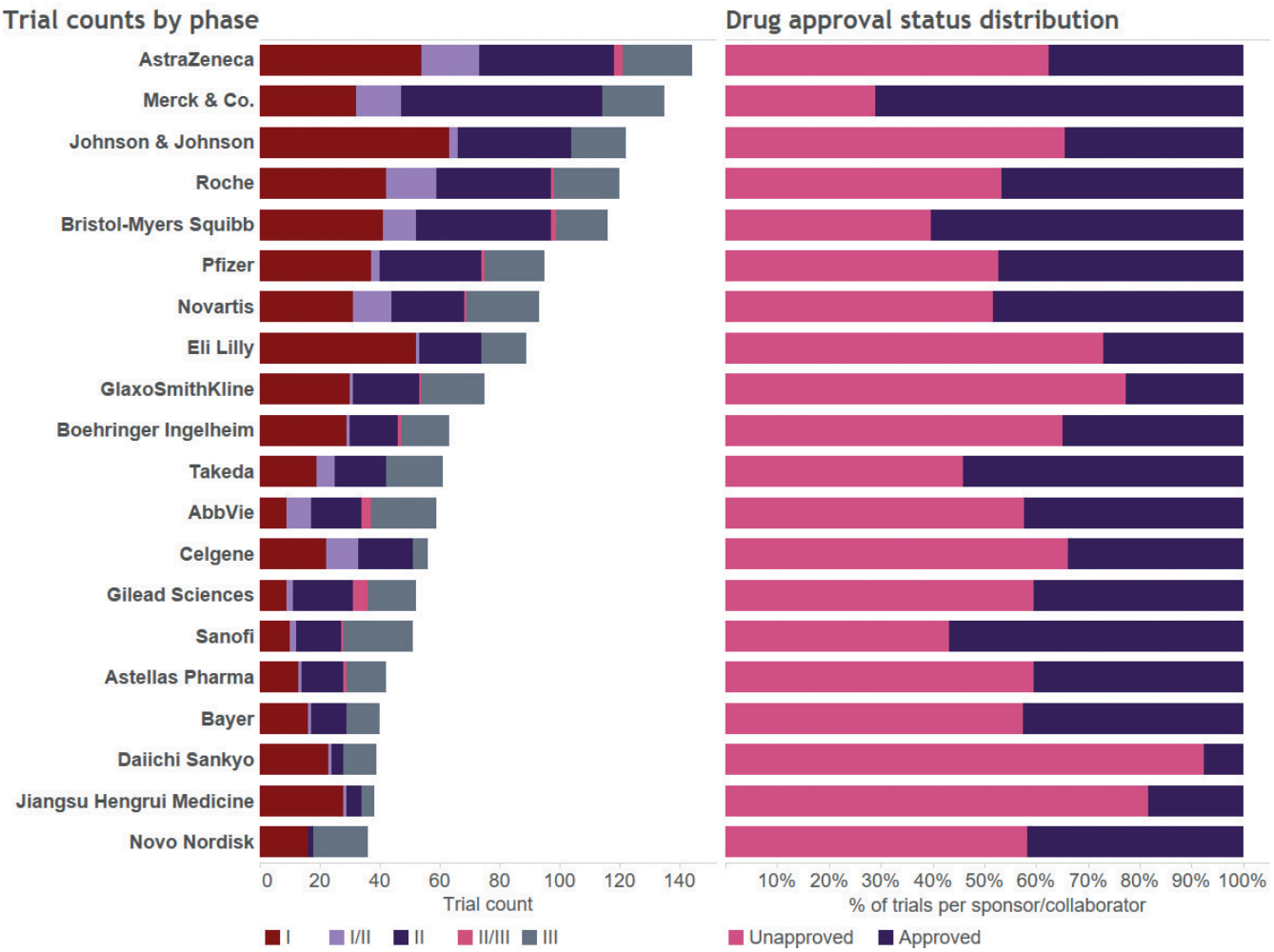
A total of 1,448 trials, or nearly a quarter of all Phase I to III trials, were initiated by the 20 most active sponsors/collaborators in 2016.[5] AstraZeneca continues to be the reigning champion, similar to years past, even though approved drug trial activity has been incorporated into the equation. Other prolific sponsors include the runner-up, Merck, and Johnson & Johnson (J&J) in third place. Nearly all the key players in Figure 4 have appeared in prior versions of the roundup, with one exception – Jiangsu Hengrui Medicine – which is the largest ethical pharmaceutical company in China. Jiangsu Hengrui, which gained approval of apatinib in late-stage gastric cancer in 2014, initiated the same volume of Phase I to III research in 2016 as Bayer and Daiichi Sankyo (Figure 4).

Trial activity was skewed toward Phase I for most of this cohort, and accounted for the biggest proportion of trials for 12 companies, including J&J, which started the largest volume of early-stage research. Four companies opted to focus efforts in Phase II, led by Merck, while three preferred Phase III trials (Figure 4). These three companies – AbbVie, Sanofi, and Novo Nordisk – initiated a mixture of unapproved and approved drug trials for their late-stage research. AbbVie tilted a larger portion of its Phase III studies toward unapproved drugs, while Sanofi and Novo Nordisk started a larger number with approved drugs (Data not shown). Meanwhile, Takeda equally split efforts between Phase I and Phase III. Also, while Astellas had its largest trial count in Phase II, the distribution among the three major phases was nearly even, with 13 trials each for Phase I and Phase III in addition to 14 Phase II trials (Figure 4).

Drug development tactics reflected in the balance between unapproved and approved drug activity varied among this cohort, but most favored unapproved drugs for the Phase I to III research initiated in 2016. Among the companies prioritizing approved drug research, Merck and Bristol-Myers Squibb (BMS) have the largest percentages, in part due to the ongoing research with their valuable immuno-oncology agents, Keytruda and Opdivo. Sanofi also has a large concentration of activity with approved drugs across a variety of indications including type 2 diabetes, multiple vaccines, and dyslipidemia. A handful of companies, namely Roche, Novartis, and Pfizer, have comparable efforts between unapproved and approved drug trials, balancing innovation and/or development of biosimilars/me-too drugs with strategic use of approved assets for new geographic and patient markets. Notably, Daiichi Sankyo devoted the vast majority (92%) of its new trials in 2016 to unapproved drugs (Figure 4).

5 Similar to disease counts, the trial counts by sponsor represent each study that the sponsor was involved in, including collaborative research. Trials that include multiple sponsors will be counted for each company.

Figure 4. Top 20 industry sponsors/collaborators by number of Phase I–III trials started in 2016



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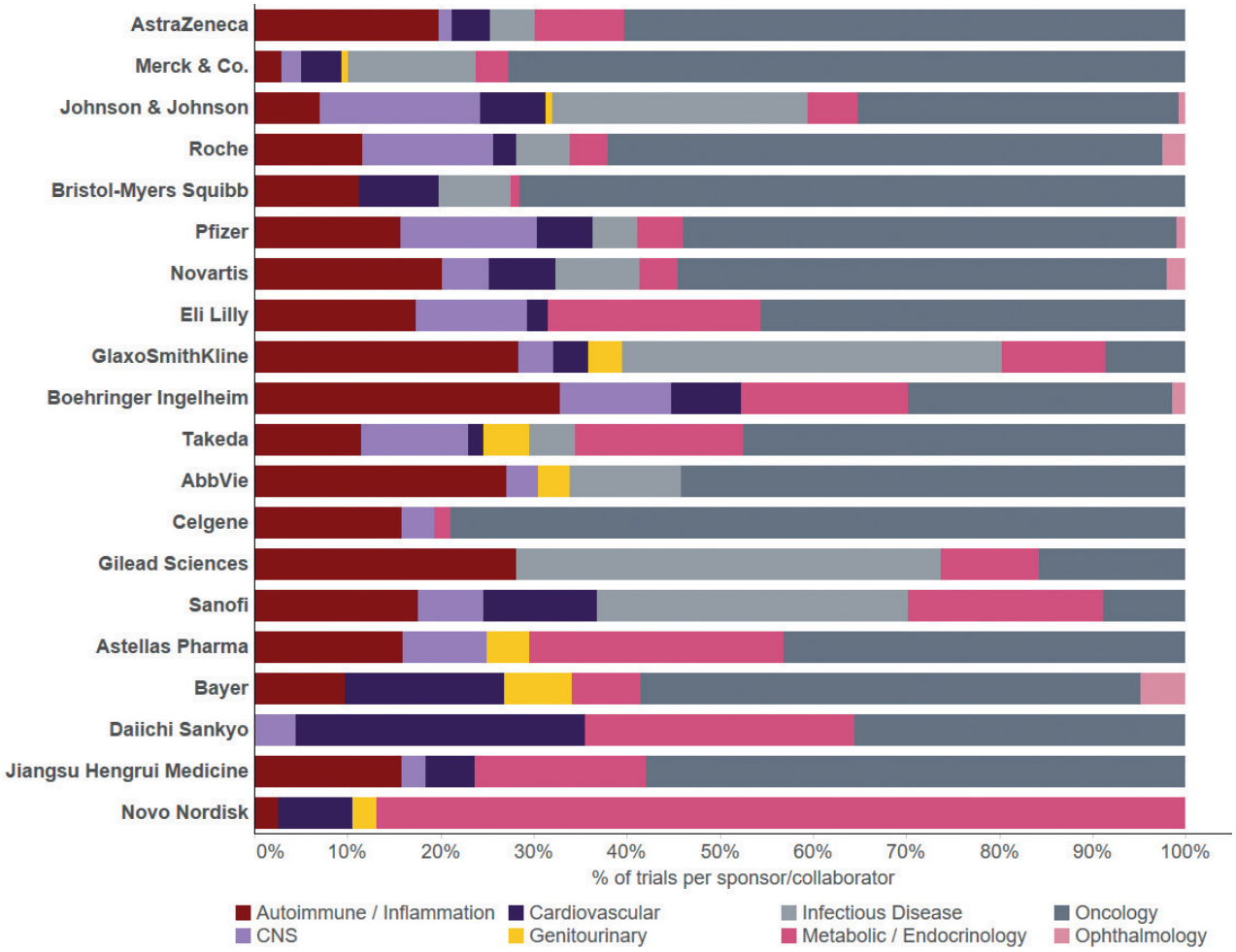
Source: Trialtrove® July 2017

Strategies around portfolio management also vary, with some companies honing in on a primary TA, while others distribute newly initiated activity across multiple areas. Novo Nordisk exemplifies therapeutic focus, and has the highest concentration of efforts in a single TA – approximately 90% of its new studies in 2016 were within the metabolic area. In contrast, Sanofi allocated its research across multiple areas, with more robust activity in ID, metabolic, and A/I, in addition to smaller efforts in CNS, CV, and oncology. Despite differing strategies, oncology is the clear priority for this cohort in general, and 15 of the 20 companies dedicated the largest portion of their trials to anticancer efforts, ranging from 34% to 79% of 2016 activity. As a distant runner-up TA, ID comprised the largest portion of trial starts for three companies, with a lower range of 33% to 46% due to comparable activity in other TAs (Figure 5).

Figure 5. Distribution of therapeutic areas for top 20 sponsors/collaborators starting trials in 2016



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Source: Trialtrove® July 2017

Turning toward the shining stars within individual TAs, generally the key players remain the same, but the leading companies shuffle in light of differing interests. While AstraZeneca remains at the top for A/I, other companies enter the limelight in other areas, with the top 20 companies dominating TA-specific rankings, including an indirect appearance in ID through ViiV Healthcare. Although ViiV has been established as its own entity, the company was created as a joint venture by Pfizer and GlaxoSmithKline (GSK) to spin out their HIV efforts into a specialty company. Companies outside the top 20 cohort are particularly present within the smaller areas of genitourinary and ophthalmology, which both have non-top 20 companies leading 2016 activity. Mithra Pharmaceuticals, Synthon, and Teva are at the forefront of genitourinary trials, while Allergan and Regeneron lead the charge for ophthalmology (Table 1).

Table 1. Top sponsors/collaborators per therapeutic area for Phase I–III clinical trials starting in 2016

Autoimmune/ Inflammation (n = 816)	
Sponsor	**Trials**
AstraZeneca	29
GlaxoSmithKline	23
Boehringer Ingelheim	22
Novartis	20
AbbVie	16
Eli Lilly	16
Gilead Sciences	16
Pfizer	16

Cardiovascular (n = 474)	
Sponsor	**Trials**
Daiichi Sankyo	14
Amgen	10
Bristol-Myers Squibb	10
Johnson & Johnson	9
Esperion Therapeutics	8

CNS (n = 854)	
Sponsor	**Trials**
Johnson & Johnson	22
Roche	17
Biogen	15
Pfizer	15
Eisai	13

Genitourinary (n = 151)	
Sponsor	**Trials**
Mithra Pharmaceuticals	6
Synthon	5
Teva	4
Bayer	3
GlaxoSmithKline	3
Lupin	3
Takeda	3

Infectious Disease (n = 771)	
Sponsor	**Trials**
Johnson & Johnson	31
GlaxoSmithKline	28
Gilead Sciences	26
Merck & Co.	18
ViiV Healthcare	15

Metabolic/Endocrinology (n = 662)	
Sponsor	**Trials**
Novo Nordisk	33
Eli Lilly	21
AstraZeneca	14
Daiichi Sankyo	13
Astellas Pharma	12
Boehringer Ingelheim	12
Sanofi	12

Oncology (n = 2,442)	
Sponsor	**Trials**
Merck & Co.	101
AstraZeneca	88
Bristol-Myers Squibb	83
Roche	72
Pfizer	54

Ophthalmology (n = 93)	
Sponsor	**Trials**
Allergan	8
Regeneron	7
Aerie Pharmaceuticals	3
Santen	3
Roche	3

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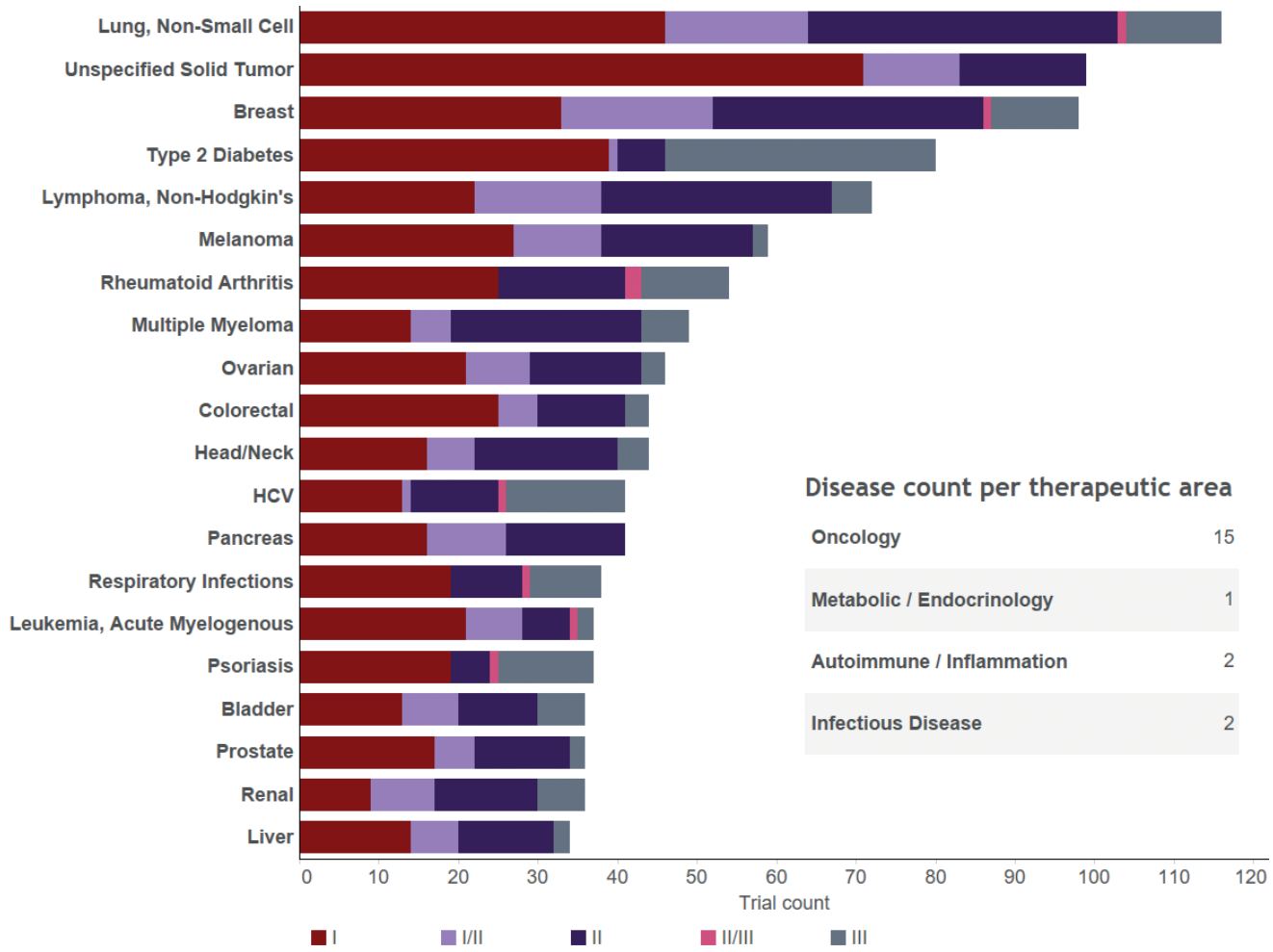
Source: Trialtrove® July 2017

Which diseases are the stars shining on?

The disease focus shifts when limiting the dataset to the activity of the top 20 sponsors (Figure 6) and comparing it to the overall rankings in Figure 3, although NSCLC remains as the leading indication, followed by unspecified solid tumor and breast cancer. Overall, the spotlight shines brighter on cancer, as the number of oncology indications increases to 15. Some changes are less dramatic, such as unspecified solid tumor's short climb to second place (from fifth place in the overall set). Other movements are more noticeable, and indicate different priorities for these prolific companies. Rheumatoid arthritis reveals itself as a larger interest for this cohort, and advances to seventh from its overall rank of 20th place. Activity is also more aggressive for melanoma, which moves up to sixth place from 12th. On the other hand, respiratory infections have been slightly deprioritized, falling 10 spots to 14th place (from fourth). Five diseases exit, namely nociceptive pain, HIV, gastric cancer, hypertension, and dyslipidemia, and are replaced by multiple myeloma, HCV, psoriasis, renal cancer, and bladder cancer (Figure 6).

Phase I continues to prevail as the most common development phase, and is the leading phase for trial volume in 14 diseases. The top 20 cohort continues to weight cancer activity toward early-stage development, particularly unspecified solid tumors as the fight against solid tumors is aggressively maintained through new activity. Five diseases have the largest volume of initiated activity in Phase II development, while HCV was the lone indication to have Phase III as their most robust area, driven by ongoing efforts from AbbVie and Gilead (Figure 6).

Figure 6. Top diseases for trials started in 2016 by the most active industry sponsors/collaborators



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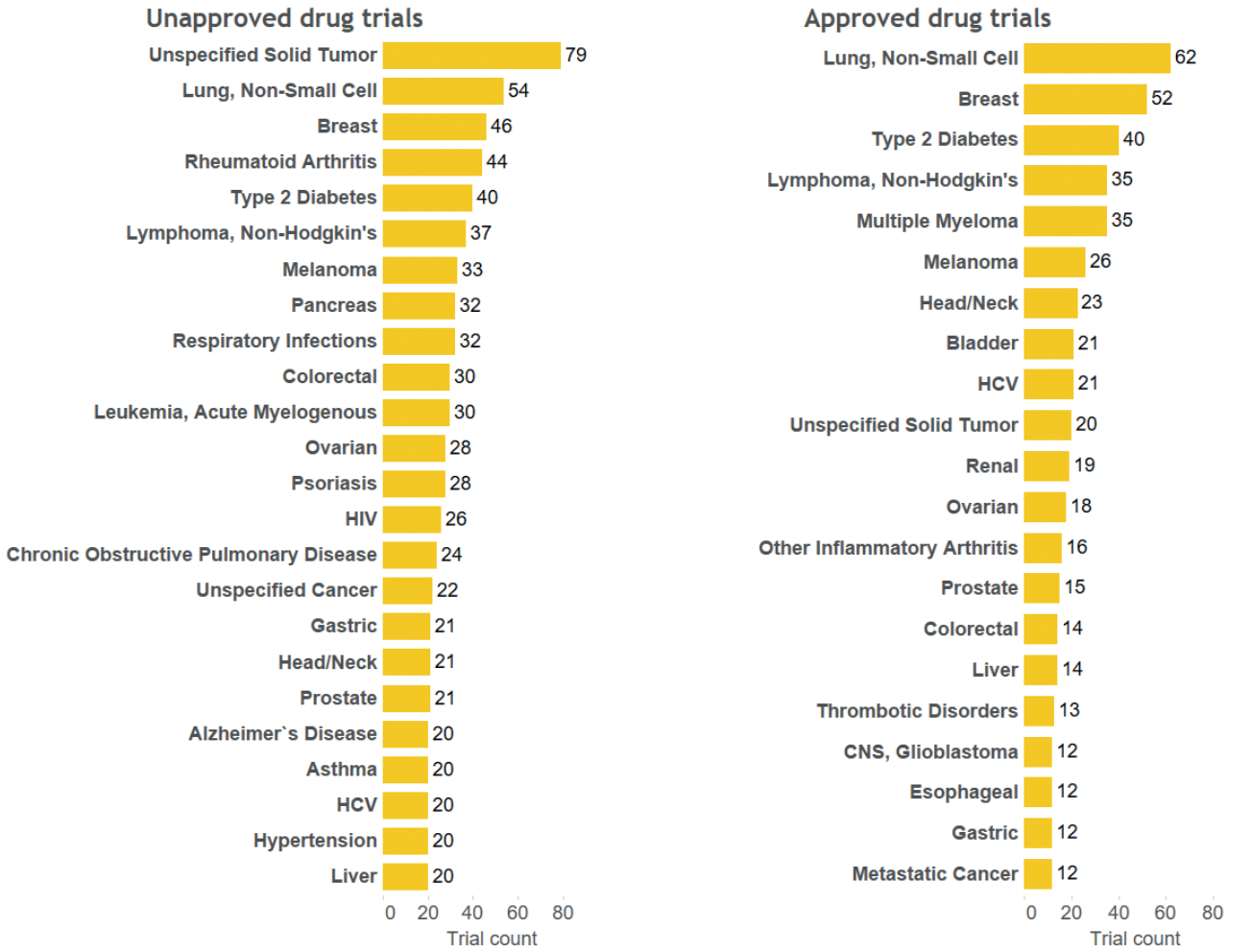
Source: Trialtrove® July 2017

In terms of indications targeted for initial approvals of pipeline drugs, the same top three cancers remain in the lead (Figure 7). Unspecified solid tumor activity is certainly driven by unapproved trials (80%; 79 of 99 trials), but less than half of NSCLC and breast cancer research from this group involves at least one unapproved drug. Since the overall volume of activity for these cancers outpaces other diseases, both remain at the top of unapproved drug research by trial count. The leading diseases largely remain the same, but smaller areas of activity reveal different indications of interest for first approvals. Besides unspecified cancer, other new diseases comprising the focus of the cohort's novel drug activity are HIV, chronic obstructive pulmonary disease, gastric cancer, Alzheimer's disease, and hypertension (Figure 7).

The number of approved drug trials was smaller, and reflects different diseases for label expansion activities. NSCLC and breast cancer continue to have the largest trial volume, but type 2 diabetes takes third place. Multiple myeloma, which does not appear in the top 20 disease list for unapproved drug activity, emerges as a key indication for market expansion efforts with 71% of new trial starts in 2016 involving only approved drugs. The tail end of the top 20 diseases includes additional targets for this cohort's efforts to evergreen their already approved assets. These include HCV, other inflammatory arthritis, liver cancer, thrombotic disorders, glioblastoma, and esophageal cancer (Figure 7).

Figure 7. Top diseases for unapproved versus approved drug trials started in 2016 by the most active industry sponsors/collaborators



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Source: Trialtrove® July 2017

Digging deeper into company-specific priorities, the leading indications for individual players are reviewed in Table 2. In all, 41 distinct indications are the primary targets of trial activity for this active group, with companies aggressively rallying against various diseases as a common cause, as well as some unique missions. Clearly, anticancer efforts are a unifying endeavor, especially for the four most active sponsors, and only four companies do not have any oncology indications as a key focus (GSK, Gilead, Sanofi, and Novo Nordisk) (Table 2).

NSCLC's top billing in overall trial activity for the cohort was primarily a concentrated effort from seven companies who have the cancer as a top disease. In fact, the total number of NSCLC trials initiated by these seven companies alone makes up 79% of all NSCLC studies from the top 20 group, and 26% of all NSCLC trials starting in 2016 regardless of sponsorship. Instead, the most common key area was unspecified solid tumor, with nine companies prioritizing the indication. Six companies also rallied behind the common cause of addressing type 2 diabetes, primarily Novo Nordisk with 20 trials and Eli Lilly with 15 (Table 2).

While multiple companies stack their efforts into the same diseases, some indications were

unique to a single company. One example is HCV, which was a top disease only for Gilead, whose concentrated efforts were the driving force in new research against the virus. Across all HCV trials initiated in 2016 by the top 20 companies, Gilead was responsible for 43%. Although AbbVie was previously mentioned for its robust Phase III HCV activity, this was the company's only effort in HCV. AbbVie spearheaded 17% of HCV research from the group as the company opted to initiate more clinical research in other areas, mostly oncology (Table 2).

Table 2. Top diseases by sponsor for clinical trials starting in 2016

AstraZeneca	Lung, Non-Small Cell (20)	Breast (16)	Asthma (13) Unspecified Solid Tumor (13)
Merck & Co.	Lung, Non-Small Cell (21)	Breast (13) Head/Neck (13) Melanoma (13) Unspecified Solid Tumor (13)	
Johnson & Johnson	Lymphoma, Non-Hodgkin's (13)	Respiratory Infections (12)	Depression (10)
Roche	Lung, Non-Small Cell (16)	Unspecified Solid Tumor (13)	Lymphoma, Non-Hodgkin's (12)
Bristol-Myers Squibb	Lung, Non-Small Cell (19)	Melanoma (17)	Multiple Myeloma (9) Renal (9)
Pfizer	Breast (19)	Ovarian (7) Unspecified Solid Tumor (7)	
Eli Lilly	Type 2 Diabetes (15)	Unspecified Cancer (12)	Type 1 Diabetes (10) Unspecified Solid Tumor (10)
Novartis	Breast (16)	Unspecified Solid Tumor (14)	Lymphoma, Non-Hodgkin's (9)
GlaxoSmithKline	HIV (10) Respiratory Infections (10)	Chronic Obstructive Pulmonary Disease (8)	Anemia (6)
Boehringer Ingelheim	Psoriasis (10)	Lung, Non-Small Cell (8)	Type 2 Diabetes (5)
Takeda	Multiple Myeloma (9)	GERD (6)	Lymphoma, Hodgkin's (5) Lymphoma, Non-Hodgkin's (5)
AbbVie	Lymphoma, Non-Hodgkin's (10)	Multiple Myeloma (8)	Leukemia, Chronic Lymphocytic (7) Psoriasis (7)
Celgene	Multiple Myeloma (15)	Crohn's Disease (7)	Leukemia, Acute Myelogenous (6)
Gilead Sciences	HCV (17)	Rheumatoid Arthritis (7)	HIV (6) NAFLD (6)
Sanofi	Type 2 Diabetes (11)	Dyslipidemia (6)	Vector-Borne Disease Vaccines (5)
Astellas Pharma	Anemia (8)	Prostate (5)	Leukemia, Acute Myelogenous (4) Rheumatoid Arthritis (4)
Bayer	Breast (4) Colorectal (4) Gastric (4) Liver (4) Lung, Non-Small Cell (4) Lymphoma, Non-Hodgkin's (4) Unspecified Solid Tumor (4)	Congestive Heart Failure (3) Diabetic Complications (3) Mesothelioma (3) Metastatic Cancer (3) Ovarian (3) Pancreas (3) Prostate (3) Thrombotic Disorders (3)	
Daiichi Sankyo	Hypertension (12)	Type 2 Diabetes (7)	Diabetic Complications (6) Unspecified Solid Tumor (6)
Jiangsu Hengrui Medicine	Unspecified Solid Tumor (6)	Type 2 Diabetes (5)	Lung, Non-Small Cell (4)
Novo Nordisk	Type 2 Diabetes (20)	Obesity (6)	Type 1 Diabetes (5)

**Top diseases limited to indications with at least 3 or more trials*

Powered by Informa's Trials API
Source: Trialtrove® July 2017

Fueling new clinical research in 2016

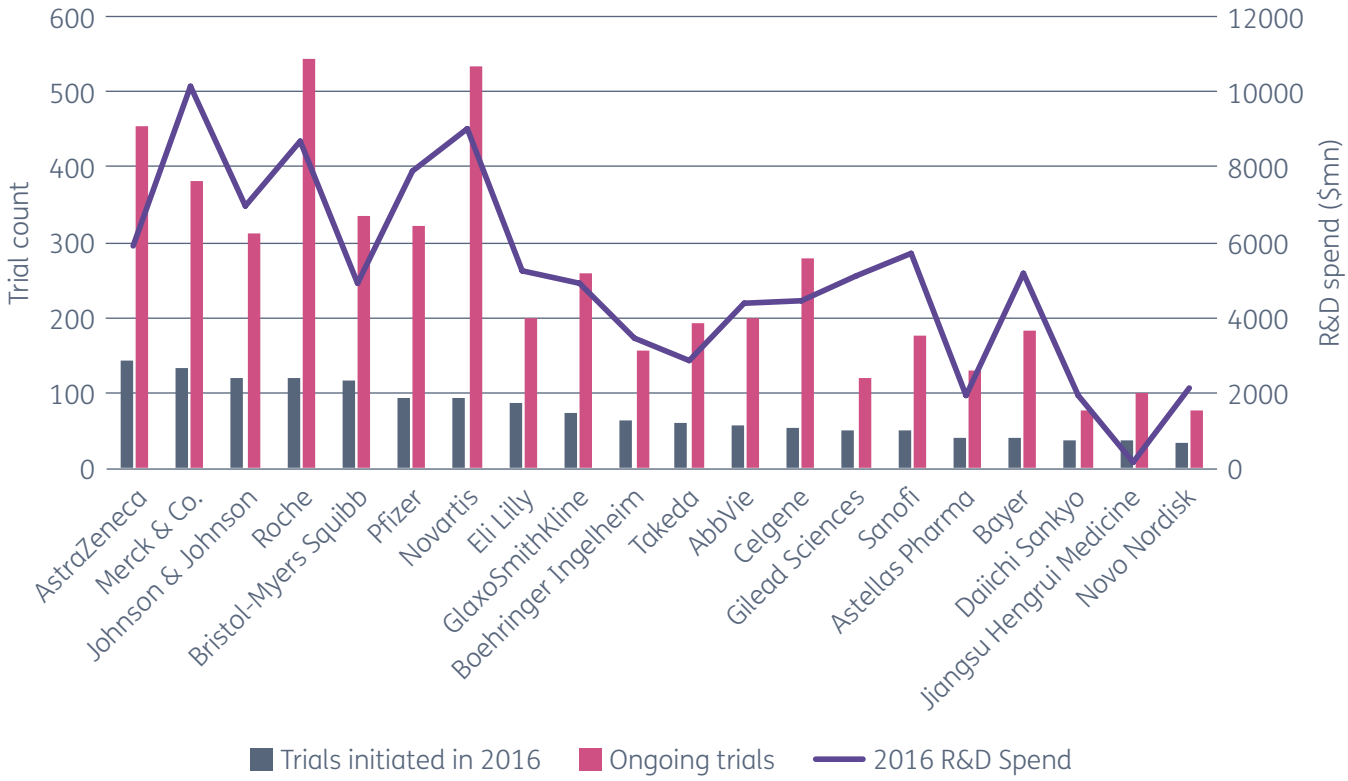
Clinical research is a complicated and costly mission, requiring immense investment. In fact, this constellation of companies invested an average of $5.1bn into R&D in 2016. To get a sense of how far these investments are going, Figure 7 compares the 2016 R&D spend of each company[6] with the total number of trials started in 2016 and the number of currently ongoing trials[7]. This analysis merely intends to provide an approximation of investment usage, since R&D spend does fund activities outside of clinical research, and we acknowledge that other factors beyond the amount of trial activity affect the price of R&D.

Merck is the largest spender by far, with a whopping $10.1bn invested into 2016 R&D – a 51% increase from the prior year. According to Merck, numerous factors contributed to the scaled-up investments, including increases in clinical development spending[8]. This is reflected in the volume of new trials and ongoing activity, as Merck is one of the most active sponsors in the peer set. Companies with the next highest R&D spends, Novartis ($9.0bn) and Roche ($8.7bn), initiated fewer trials than Merck in 2016, but support a much larger volume of ongoing research. In fact, Roche and Novartis are the leading companies for ongoing Phase I to III activity, supporting 544 and 533 trials respectively. Among the smaller stars in this constellation, Jiangsu Hengrui's investments support a somewhat similar level of activity to Daiichi Sankyo, but at a lower level of spend (Figure 8).

AstraZeneca continues to remain noteworthy as it supports, in addition to starting, a large number of clinical trials with a much smaller R&D spend than some of its counterparts (453 ongoing trials; $5.9bn). With a comparable budget, the number of trials that Sanofi initiated and currently supports are 33% and 39% of AstraZeneca's respective totals (Figure 8).

6 R&D expenditures from the calendar year of 2016 are included in the analysis, and are reported in US dollars. Due to the differing fiscal year in Japan, the R&D spend for Japan-based companies was the sum of Q4 FY2015 and Q1 to Q3 FY2016. Currency conversions are based on the average exchange rate for 2016.
7 Includes all trials, regardless of start date, that were ongoing in Trialtrove as of July 6, 2017.
8 Merck (2017) Form 10-K SEC filing. Available from: http://s21.q4cdn.com/488056881/files/doc_financials/2017/Q4/merck-q4-10k.pdf [Accessed June 30, 2017].

Figure 8. Phase I–III trials initiated in 2016 and total ongoing trials relative to R&D spend*



**Reflects R&D spend in the calendar year of 2016. Currency conversions, when applied, are based on the average exchange rate for 2016.*

Source: Company filings; Trialtrove® July 2017

Turning to a different type of fuel, Table 3 compares the counts of all active drugs in development with ongoing trials for these 20 companies, and calculates the ratio of ongoing trials conducted per drug. Overall, these companies averaged 1.9 ongoing trials for each of their active drugs in development, ranging from Daiichi Sankyo's 0.7 to Jiangsu Hengrui's 4.6. Celgene also had a high trial density for its drugs (3.2), followed by Roche (2.7). While Novartis possesses the largest number of active drugs (250 drugs), and the second largest number of ongoing trials, the company averaged 2.1 trials per drug. Other companies with higher ratios, such as Celgene and BMS, possess smaller portfolios and opt for a higher trial density with their smaller sets of assets.

Different trends emerge when dissecting the data further by drug approval status. The ratio of ongoing trials conducted per unapproved drug is much lower than the ratio for approved drugs, and the range is far less drastic. Unapproved drugs averaged 1.2 trials per drug, with a range of Sanofi's 0.5 to Jiangsu Hengrui's 3.9. On the other hand, approved drugs had an average ratio of 4.6, and a range of Daiichi Sankyo's 0.4 to Celgene's 16.2. Considering the lower average for the investigational, emerging candidates, and the fact that half of these active companies have a ratio of less than 1.0, it's apparent that most are evaluating multiple unapproved drugs within a single trial, in parallel or as combination regimens. On the other hand, approved drugs have much higher intensities as companies conduct multiple studies to expand into additional markets or indications, prolonging their investments in already approved assets. J&J is an anomaly within the cohort with comparable trial density ratios between unapproved and approved drug activity (Table 3).

Table 3. Ratio of ongoing Phase I–III trials to drugs in active clinical development

	All drugs			Unapproved drugs			Approved drugs		
Sponsor	Active drugs	Ongoing trials	# of trials per drug	Active drugs	Ongoing trials	# of trials per drug	Active drugs	Ongoing trials	# of trials per drug
AstraZeneca	220	453	2.1	170	277	1.6	50	176	3.5
Merck & Co.	222	382	1.7	156	90	0.6	66	292	4.4
Johnson & Johnson	247	312	1.3	186	210	1.1	61	102	1.7
Roche	201	544	2.7	156	183	1.2	45	361	8.0
Bristol-Myers Squibb	129	334	2.6	106	93	0.9	23	241	10.5
Pfizer	212	321	1.5	146	135	0.9	66	186	2.8
Eli Lilly	127	201	1.6	101	124	1.2	26	77	3.0
Novartis	250	533	2.1	184	210	1.1	66	323	4.9
GlaxoSmithKline	230	259	1.1	178	127	0.7	52	132	2.5
Boehringer Ingelheim	94	158	1.7	75	69	0.9	19	89	4.7
Takeda	154	192	1.2	97	68	0.7	57	124	2.2
AbbVie	98	200	2.0	75	131	1.7	23	69	3.0
Celgene	87	278	3.2	77	116	1.5	10	162	16.2
Gilead Sciences	62	122	2.0	45	67	1.5	17	55	3.2
Sanofi	190	178	0.9	129	61	0.5	61	117	1.9
Astellas Pharma	109	131	1.2	77	69	0.9	32	62	1.9
Bayer	106	183	1.7	81	70	0.9	25	113	4.5
Daiichi Sankyo	105	77	0.7	69	62	0.9	36	15	0.4
Jiangsu Hengrui Medicine	22	101	4.6	19	74	3.9	3	27	9.0
Novo Nordisk	38	78	2.1	28	45	1.6	10	33	3.3

Powered by Informa's Drugs and Trials API's
Source: Pharmaprojects® July 2017; Trialtrove® July 2017

The busiest planets in the 2016 clinical trial universe

Reviewing locations for the newly initiated trials also provides insight into potential company strategy and the markets of interest. Overall, the US remains the most frequented location, followed by China. In general, the top 10 countries for newly initiated trials in 2016, provided in Table 4, primarily span the US, Japan, and most major EU markets (France, Germany, Spain, and the UK), as well as a few emerging markets. Although Italy does not make the cut, the country just misses the mark by a few trials, and comes in 12th place.

Across the individual TAs, similar geographical areas are generally targeted, with some regional preferences. Russia, which was a top location overall, remains a key market for all TAs except oncology. East Asia is also common as all TAs include one or more countries from the region. Japan and/or China are the most frequented East Asian countries for all TAs except ophthalmology, which opts for a larger volume of trials in South Korea. Mexico also emerges as a common destination for half of the TAs: CNS, genitourinary, ID, and metabolic (Table 4).

Outside the typical universe, some unique choices are top locations for specific TAs. Eastern Europe rarely makes the top 10 locations by trial count for most TAs, but Poland and Hungary are top locations exclusive to A/I and ophthalmology, respectively. Other countries targeted by a limited number of TAs include Netherlands (CV), Iran and India (genitourinary and metabolic), and Australia (A/I and CNS) (Table 4).

Table 4. Top locations for Phase I–III trials starting in 2016 by therapeutic area

Overall	
Country	**Trials**
United States	2524
China	845
Germany	590
Japan	586
United Kingdom	550
Russia	541
Canada	528
France	504
Spain	497
South Korea	391

Autoimmune/ Inflammation	
Country	**Trials**
United States	349
Germany	142
United Kingdom	131
Canada	107
Poland	105
Japan	94
Russia	94
South Korea	86
China	82
Australia	80
France	80
Spain	80

Cardiovascular	
Country	**Trials**
United States	158
Russia	71
China	66
Canada	48
Germany	45
United Kingdom	43
Spain	42
France	41
Netherlands	40
Japan	39
South Korea	39

CNS	
Country	**Trials**
United States	396
United Kingdom	85
Germany	82
Australia	76
Canada	76
Spain	76
France	67
Japan	58
Russia	53
Mexico	51

Genitourinary	
Country	**Trials**
United States	29
China	19
Russia	18
Mexico	16
Iran	12
Egypt	10
South Korea	8
Germany	7
India	7
Japan	6

Infectious Disease	
Country	**Trials**
United States	245
Russia	125
China	106
Mexico	54
United Kingdom	51
Canada	43
Germany	43
Spain	42
France	39
Japan	33

Metabolic/Endocrinology	
Country	**Trials**
United States	216
Russia	79
Japan	73
Germany	72
Mexico	59
Canada	53
United Kingdom	51
Iran	50
China	47
India	43
South Korea	43

Oncology	
Country	**Trials**
United States	1158
China	484
Japan	293
France	244
Spain	227
Germany	209
Canada	204
United Kingdom	195
Italy	176
South Korea	155

Ophthalmology	
Country	**Trials**
United States	54
United Kingdom	11
Germany	9
France	8
Canada	7
Hungary	7
Italy	7
Russia	7
South Korea	7
Spain	7

Powered by Informa's Trials API
Source: Trialtrove® July 2017

Since companies have overlapping as well as distinct strategic plans, it follows that both common themes and outliers exist when reviewing top trial locations by company. Honing in on the most active of the top 20 sponsors/collaborators unearths Italy as a top location for all companies but Pfizer, while China drops out of the picture due to regulatory constraints. Japan is also missing as a top location for J&J and Novartis. Instead, J&J focuses their Asia-Pacific efforts on Australia, while Novartis opts for the East Asian market of South Korea (Table 5).

In comparison to the overall trial set, there is a larger Eastern European presence. Other differing markets of interest include Belgium and Netherlands for four companies each, and Australia for five. The US does continue to maintain its position as the leading market of interest for all companies except Boehringer Ingelheim, which initiated more trials in its homeland of Germany (Table 5).

Table 5. Top locations for trials starting in 2016 by most active industry sponsors/collaborators*

AstraZeneca	
Country	**Trials**
United States	84
United Kingdom	33
Germany	27
Canada	21
Spain	21
France	19
Japan	14
Hungary	13
Italy	13
Russia	12

Merck & Co.	
Country	**Trials**
United States	101
Canada	32
United Kingdom	26
Spain	23
France	21
Australia	20
Germany	20
Japan	19
Russia	18
Italy	16
South Korea	16

Johnson & Johnson	
Country	**Trials**
United States	68
Germany	27
Spain	22
United Kingdom	22
France	20
Belgium	17
Canada	17
Italy	14
Australia	13
Netherlands	13

Roche	
Country	**Trials**
United States	84
Germany	28
United Kingdom	27
Spain	26
France	24
Italy	22
South Korea	21
Canada	20
Japan	16
Poland	16

Bristol-Myers Squibb	
Country	**Trials**
United States	84
Japan	30
Australia	26
Canada	25
France	23
Germany	23
Italy	21
Spain	18
Netherlands	17
United Kingdom	14

Pfizer	
Country	**Trials**
United States	73
Canada	18
France	17
Germany	17
United Kingdom	17
Japan	15
Spain	15
Belgium	14
Hungary	12
Australia	11
Poland	11
South Korea	11

Eli Lilly	
Country	**Trials**
United States	68
Germany	30
France	26
Spain	23
United Kingdom	20
Italy	19
Japan	19
Canada	18
South Korea	16
Mexico	13
Poland	13

Novartis	
Country	**Trials**
United States	68
Germany	32
Spain	31
France	26
United Kingdom	24
Italy	23
Canada	22
Belgium	21
South Korea	21
Netherlands	19

GlaxoSmithKline	
Country	**Trials**
United States	41
Germany	22
United Kingdom	18
Canada	16
Poland	15
Spain	15
Australia	13
France	13
Japan	11
Italy	10
Netherlands	10

Boehringer Ingelheim	
Country	**Trials**
Germany	36
United States	25
France	18
Japan	18
Canada	16
Spain	16
Belgium	12
United Kingdom	11
South Korea	10
Czech Republic	9
Italy	9
Poland	9

**Sponsors/collaborators limited to top 10 companies initiating the largest number of trials in 2016.*

Powered by Informa's Trials API
Source: Trialtrove® July 2017

Across the full set of the 20 most active companies, an overall average of 4.6 countries were disclosed per trial, ranging from Jiangsu Hengrui's 1.0 to AbbVie's 7.6. This overall average is slightly higher than the typical trial size of Phase II research, which averaged 4.2 countries per trial for this cohort. Although Phase II research does have an upward range of Novo Nordisk's 15.5 countries, this appears to be an outlier as the second highest average was a more modest 6.5 countries (Table 6).

Unsurprisingly, the geographic breadth for these trials expands with the increasing phase of development to accommodate the larger target accruals required for pivotal Phase III research. Novo Nordisk and Sanofi are two rare instances of companies that utilized the largest number of countries for their Phase II studies. As previously mentioned, Novo Nordisk disclosed an average of 15.5 countries for its Phase II research, but only averaged 10.0 for Phase III. Sanofi's differences aren't quite as stark, with averages of 6.2 and 4.6 for its Phase II and Phase III trials, respectively. However, this could, in part, be attributed to delayed public disclosure of locations rather than the average scale of the studies, as some companies will gradually announce locations as trial recruitment progresses (Table 6).

The two most active companies, AstraZeneca and Merck, averaged fewer countries per trial than the overall average of 4.6. Both also had much lower averages for their Phase II trials, and AstraZeneca's Phase III country utilization was well below the mean. The reduced geographic breadth of trials initiated in 2016 could reflect a sharper focus on key markets, or perhaps suggest a strategy to mitigate costs considering the amount of new activity of both companies in comparison to their peers (Table 6).

Table 6. Average number of countries disclosed per trial across most active industry sponsors/collaborators*

	Average Number of Countries/Trial			
Sponsor	**Overall**	**I**	**II**	**III**
AstraZeneca	3.1	1.7	2.2	8.2
Merck & Co.	4.2	1.9	2.4	14.7
Johnson & Johnson	3.4	1.3	3.7	10.1
Roche	4.7	1.7	3.6	12.8
Bristol-Myers Squibb	4.3	1.1	4.4	11.1
Pfizer	4.3	1.3	2.9	11.8
Eli Lilly	5.0	2.4	6.5	11.6
Novartis	7.2	3.5	4.5	15.8
GlaxoSmithKline	4.4	1.3	3.0	10.1
Boehringer Ingelheim	4.8	1.8	6.1	8.8
Takeda	5.1	1.5	3.2	11.1
AbbVie	7.6	1.1	4.1	13.4
Celgene	3.9	1.5	3.8	15.4
Gilead Sciences	6.7	1.3	4.0	11.8
Sanofi	4.4	1.0	6.2	4.6
Astellas Pharma	4.0	1.5	2.6	7.8
Bayer	5.2	1.6	1.3	15.1
Daiichi Sankyo	1.6	1.0	1.4	2.9
Jiangsu Hengrui Medicine	1.0	1.0	1.0	1.0
Novo Nordisk	6.8	2.1	15.5	10.0

**Excludes trials with no disclosed locations. Trial hybrids rolled into calculations for higher phase of development (ie Phase I/II included in Phase II calculations)*

Powered by Informa's Trials API
Source: Trialtrove® July 2017

Closing the launch

Assessing trends in recently initiated trials supports insight into various development strategies, and where the industry stands, or what markets it may be moving toward. In order to attain a more comprehensive picture of the landscape, all drug activity does need to be accounted for. While new clinical research in 2016 primarily focused on unapproved drugs, robust levels of market expansion activities co-exist, offsetting the risk and cost of innovation slightly. (Unfortunately, approval in one indication does not guarantee success in another, as evident in a recent analysis of outcomes from completed trials. Within the active areas of oncology, A/I, and CNS, only 30–46% of label expansion trials that completed in 2016 achieved their primary endpoint(s).[9])

Within this high-level overview of the expansive clinical trial universe, oncology continues to hold the attention of the pharma industry, where a small cohort of companies drives a significant portion of trial activity. The clinical trial landscape continues to be fueled by early-stage research, particularly for unspecified solid tumors, in hopes that the viable candidates will prove their worth and progress through the R&D development cycle, and perhaps be captured in future roundups.

9 Blazynski C (2017) 2016 Completed Clinical Trials: Industry Strategies Revealed and Graded. Available from: https://pharmaintelligence.informa.com/resources/product-content/2016-completed-clinical-trials [Accessed July 8, 2017].

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