Clinical Trials in Russia
Orange Paper
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Contents

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Executive Summary – English

The Ministry of Health of the Russian Federation approved 241 new clinical trials of all types, including local and bioequivalence studies, during Q3 2016. This represents a 18% increase over Q3 2015.

The main contribution into the total number of studies in Q3 2016 was made by multinational multi-center clinical trials (MMCT), the number of these studies is 89 and it is 3.5% more than in Q3 2015. The number of bioequivalence studies (BE) decreased from 77 studies in Q3 2015 to 72 in Q3 2016, a 6.5% decrease from last year's figure. The number of local clinical trials (LCT) significantly increased from 40 in Q3 2015 to 80 in Q3 2016.

Clinical trials in Russia in Q3 2016 were sponsored by companies from 28 countries. The maximum number of trials (93) were initiated by Russian sponsors. American sponsors with 33 new studies took the runner-up place; they are followed by Indian sponsors (22 trials), and Swiss sponsors (15 trials).

The number of Phase I clinical trials has increased from 12 studies to 23 new studies in Q3 2016 (92% increase). The number of Phase II trials (23 new studies) was similar to that in Q3 2015 (21 studies). The number of Phase III trials increased from 90 to 115 studies, 28% more than in Q3 2015. The number of Phase IV trials increased in comparison with Q3 2015 from three to eight studies.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q3 2016 is 22,226, two-fold more than Q3 2015 figure, when 10,689 subjects were planned to be enrolled.

Novartis is on the top of the heap of foreign pharmaceutical manufacturers in Q3 2016 by sponsoring seven new studies. They are followed by *Merck & Co.,* having six new trials, *H. Lundbeck A/S* and *Bristol-Myers Squibb*, each with five new studies in Q3 2016, differentiating in number of patients, and *Teva Pharmaceutical Industries Ltd*, having four new trials.

Top five domestic pharmaceutical manufacturers by the number of new studies in Q3 2016 is headed by *Biocad,* having six new trials. They are followed by *Sotex* and *Atoll* with five and four new trials, respectively. Top five is concluded by companies *R-Pharm* and *Materia Medica Holding*, each having three new studies and differentiating in the number of patients.

In this issue we decided to make two research centers ratings according to phases of their clinical trials to get a more objective overview.

The top five Russian research sites (BE and Phase I studies) include: *Ecosafety Ltd.* (16 new studies), *Bioeq Ltd.* (12 studies), *Clinical Hospital N2 of the Yaroslav Region* (8 studies).

The top Russian research sites (Phase II-IV studies) include: *Russian Oncological Scientific Center named after N.N. Blokhin* (26 new studies), *Kazan State Medical University* (23 studies), *Ryazan State Medical University named after I.P. Pavlov* (19 studies).

The top five CROs in Russia are: *Quintiles* (10 new studies), *MSD Pharmaceuticals, Covance Clinical* and *Trokas Pharma Ltd.* (six studies each), and *Parexel* (four studies).

The top therapeutic areas were: Oncology (44 new studies); Neurology (30 new studies), Therapy (25 studies), Cardiology and Infectious diseases (23 studies each), Rheumatology and Psychiatry (16 studies each).

The Center for Drug Evaluation and Research (CDER) of the FDA approved 22 new drugs during Q3 2016, and **four** of them were (or are being) studied in clinical trials conducted in Russia.

During Q3 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 18 new drug applications[1]. **Twelve** of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

[1] Positive opinions on new generic, hybrid and biosimilar medicines are not included.

Executive Summary – Russian

В третьем квартале 2016 года Министерством здравоохранения Российской Федерации было выдано 241 разрешение на все виды клинических исследований (КИ), что на 18% больше, чем за аналогичный период 2015 года.

При этом количество новых международных многоцентровых КИ, инициированных в третьем квартале 2016 года, составило 89, что на 3,5% больше по сравнению с аналогичным периодом прошлого года. Количество исследований биоэквивалентности уменьшилось на 6,5% по сравнению с 2015 годом и составило 72 против 77. Количество локальных КИ, проводимых на территории России, значительно увеличилось по сравнению с третьим кварталом 2015 года и составило 80 исследований против 40.

Спонсорами КИ, разрешенных к проведению в России в третьем квартале 2016 года, выступили компании из 28 стран. На первое место вышли российские производители с 93 КИ, за ними идут американские спонсоры с 33 КИ, Индия (21 КИ) и Швейцария (15 КИ).

В третьем квартале 2016 года было инициировано 23 новых КИ I фазы, что на 92% больше, чем за тот же период 2015 года (12 КИ). Количество исследований II фазы (23 новых исследования) было примерно таким же, как в третьем квартале 2015 года (21 КИ). Количество КИ III фазы увеличилось с 90 до 115, что на 28% больше по сравнению с аналогичным периодом прошлого года. Количество исследований IV фазы увеличилось по сравнению с третьим кварталом 2015 года с трех до восьми исследований.

Количество субъектов для участия в исследованиях I-IV фаз в третьем квартале 2016 года составило 22 226, что в два раза больше, чем в третьем квартале 2015 года, когда планировалось участие 10 689 субъектов.

В третьем квартале 2016 года лидирующие позиции среди иностранных производителей по количеству новых исследований заняла компания *Novartis* с семью новыми исследованиями. Далее следуют компании *Merck & Co.* с шестью новыми КИ, *H. Lundbeck A/S* и *Bristol-Myers Squibb*, каждая с пятью новыми КИ, но с разным количеством пациентов, и *Teva Pharmaceutical Industries Ltd* с четырьмя исследованиями.

Список пяти лидирующих отечественных производителей по количеству новых исследований в третьем квартале 2016 года возглавила компания *Биокад* с шестью исследованиями. Далее следуют компании *Сотекс* и *Атолл* (пять и четыре новых КИ соответственно), *Р-Фарм* и *Материа Медика Холдинг* (три исследования каждая).

В этом выпуске мы решили составить два рейтинга исследовательских центров по фазам проводимых в них исследований, чтобы получить более объективную оценку.

В пятерку передовиков по исследованиям биоэквивалентности и I фазы в третьем квартале 2016 года вошли следующие центры: *ООО «НИЦ Эко-безопасность»* (16 новых КИ), *ООО «БиоЭк»* (12 КИ), *Клиническая больница №2 Ярославской области* (8 КИ).

Лидирующие центры по исследованиям II-IV фаз: *Российский онкологический научный центр имени Н.Н. Блохина* (26 новых исследований), *Казанский государственный медицинский университет* (23 исследования), *Рязанский государственный медицинский университет имени академика И.П. Павлова* (19 исследований).

Пятерка лидеров среди КИО в России: *Quintiles* (10 новых КИ), *MSD Pharmaceuticals, Covance Clinical* и *Trokas Pharma Ltd.* (по шесть КИ), *Parexel* (четыре КИ).

Наибольшее количество исследований проведено в следующих областях: онкология – 44, неврология – 30, терапия – 25, кардиология и инфекционные болезни – по 23 новых КИ, ревматология и психиатрия – по 16 новых КИ.

FDA одобрено в третьем квартале 2016 года 22 новых лекарственных препарата, по **четырем** из которых в России проводились (или проводятся) КИ. EMA одобрено в третьем квартале 2016 года 18 новых лекарственных препаратов, по **12** из которых в России проводились (или проводятся) КИ.

Clinical Trials by Type and Manufacturing Country

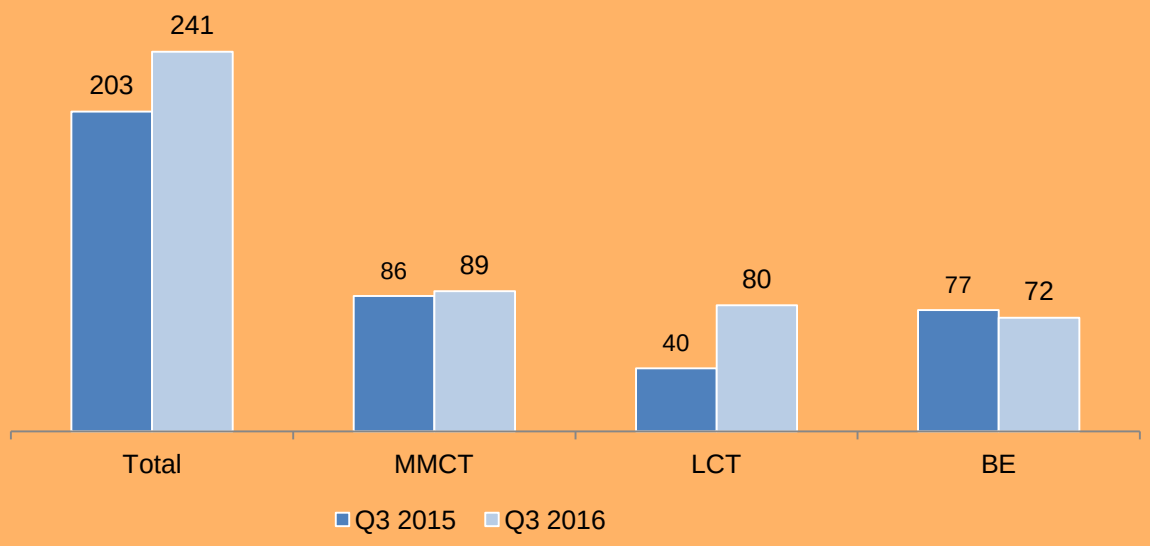
The Russian MoH approved 241 new clinical trials of all types including local and bioequivalence studies during Q3 2016, demonstrating a 18% increase in comparison with the same point of the last year.

As shown in **Figure 1**, the main contribution into the total number of studies was made by multinational multi-center clinical trials (MMCT); the number of these studies has increased from 86 studies in Q3 2015 to 89 in Q3 2016, a 3.5% increase from last year's figure.

The number of bioequivalence studies (BE) decreased from 77 studies in Q3 2015 to 72 in Q3 2016, a 6.5% decrease from last year's figure.

The number of local clinical trials (LCT) has significantly increased from 40 in Q3 2015 to 80 in Q3 2016, a 100% increase from last year's figure.

Figure 1. Clinical Trials in Russia in Q3 2016

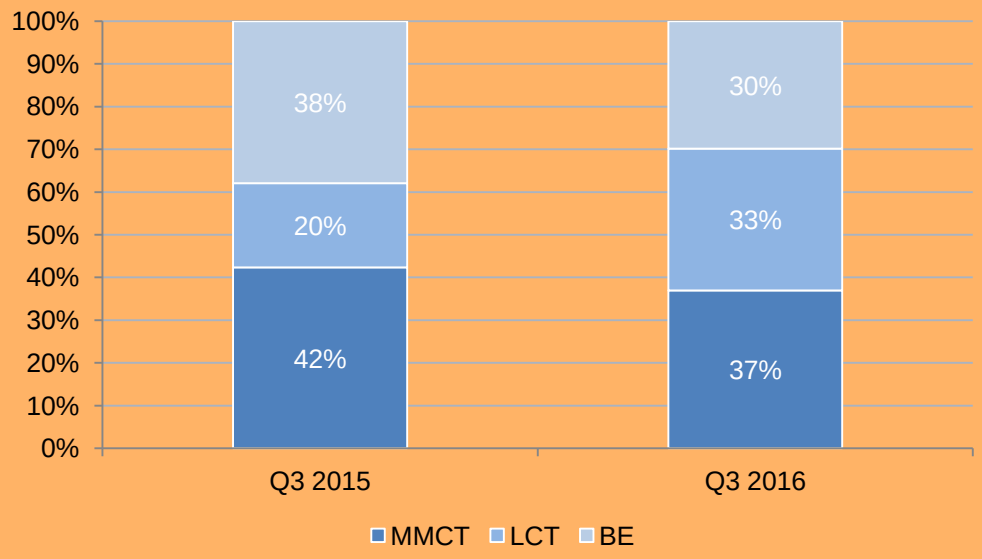


The proportions between different study types (multinational multi-center clinical trials, local clinical trials and bioequivalence studies) changed since last year (see **Figure 2**).

The share of bioequivalence studies decreased from 38% to 30% of the total number of clinical trials approved in Q3 2016.

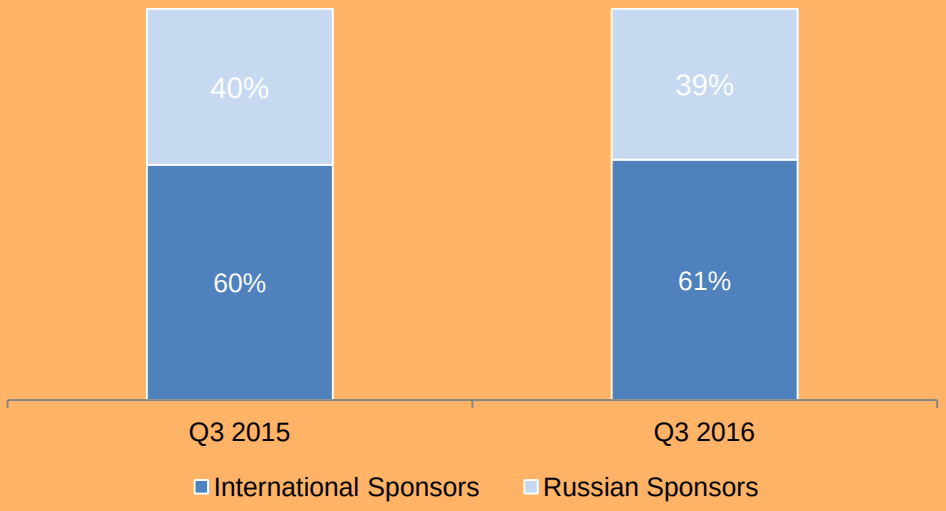
The share of the local clinical trials increased from 20% in Q3 2015 to 33% in Q3 2016, and the share of multinational multi-center clinical trials was 37% of the total number of trials approved during Q3 2016 (42% in Q3 2015).

Figure 2. Clinical Trials by Type in Q3 2016



The geographic origins of sponsors changed slightly in comparison with last year. 61% of the total number of new studies in Q3 2016 were sponsored by foreign companies which received 148 study approvals (60% in Q3 2015). The share of studies of local manufacturers decreased from 40% in Q3 2015 to 39% in Q3 2016, and amounted to 93 studies (**Figure 3**).

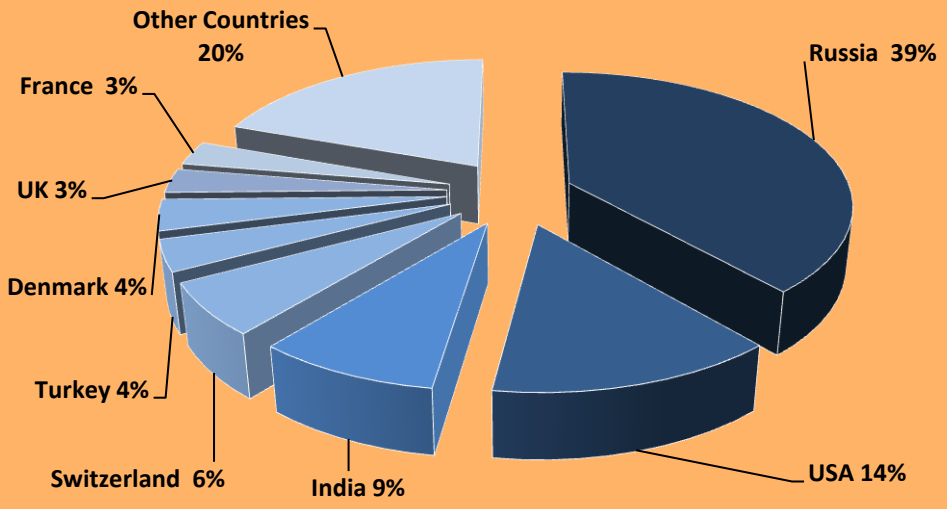
Figure 3. Russian vs International Sponsors in Q3 2016



Clinical trials in Russia in Q3 2016 were sponsored by companies from 28 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (93) were initiated by Russian sponsors. American sponsors with 33 new studies took the runner-up place; they are followed by Indian sponsors with 21 trials, then by Swiss sponsors with 15 new studies. The group of leaders is concluded by Turkish and Danish Sponsors, each having nine studies, United Kingdom and France (each having seven studies).

Figure 4. Sponsors' Country of Origin for Q3 2016 Clinical Trials in Russia



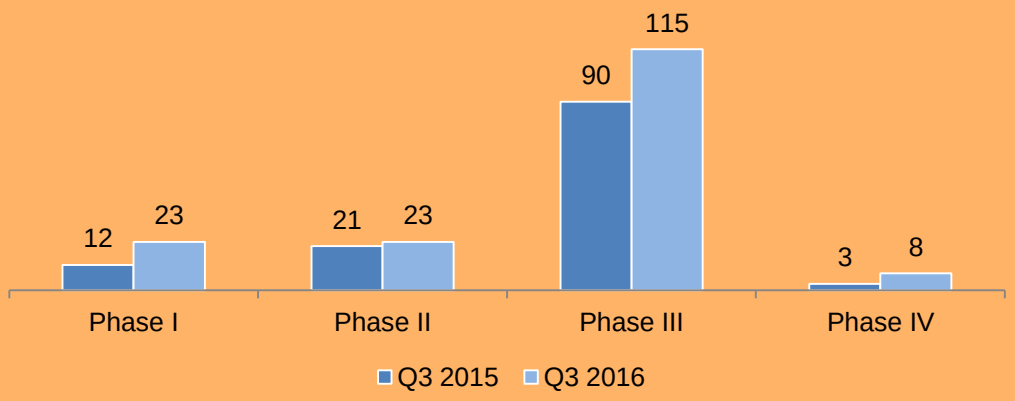
Other sponsors include: Poland (five studies), Belgium, Croatia, Germany, Israel (four studies each), Czech Republic, Iceland and Sweden (three studies each), Austria, Hungary, Italy, Netherlands and Slovenia (two studies each), and Brazil, Latvia, Luxembourg, Republic of Belarus, Republic of Korea, Romania, Ukraine, each started one new study in Q3 2016.

Clinical trials by Phase

The number of Phase I clinical trials increased to 92% compared to Q3 2015: from 12 studies to 23 new studies in Q3 2016. The number of Phase II trials increased to 9% compared to Q3 2015 from 21 studies to 23 new studies (**Figure 5**).

The number of Phase III trials increased from 90 to 115 studies, 28% more than in Q3 2015. The number of Phase IV trials increased in comparison with Q3 2015 from three to eight studies in Q3 2016.

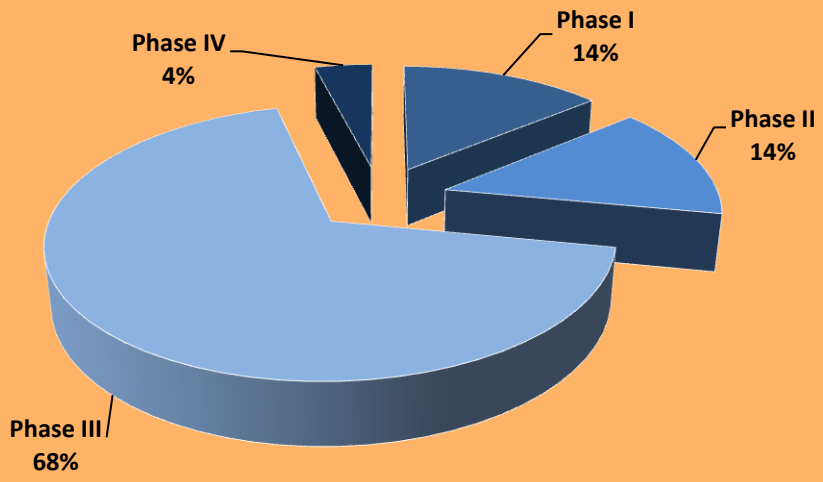
Figure 5. Clinical Trials in Russia in Q3 2016 by Phase[1]



[1] Studies indicated by sponsors as Phase I-II in the applications submitted to MoH, are shown in Phase II studies group; Phase II-III – in Phase III group; Phase III-IV – in Phase IV group. BE studies were not included in any phase group.

As shown in **Figure 6**, the share of Phase III trials in Q3 2016 is 68% of the total number of studies, the share of Phase I trials is 14%, Phase II trials is 14% and the share of Phase IV studies accounted to 4%.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



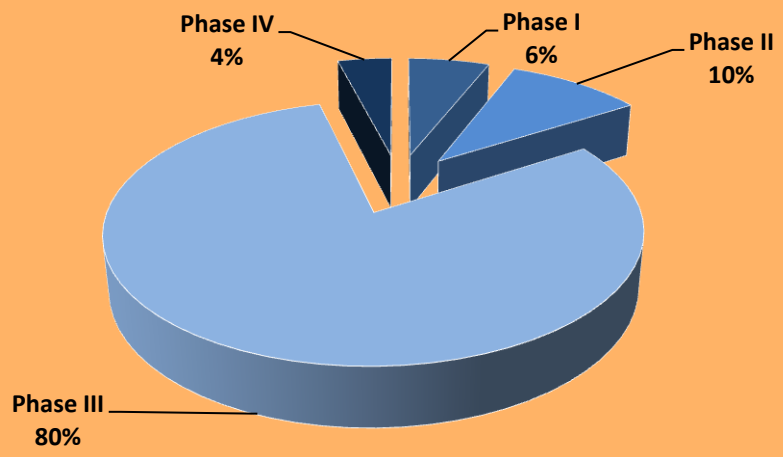
The number of subjects planned to be enrolled in Phase I-IV trials launched in Q3 2016 is 22,226, two-fold more than in Q3 2015, when 10,689 subjects were planned to be enrolled.

1,277 subjects will be recruited in Phase I trials; 2,235 – in Phase II trials; 17,721 – in Phase III studies and 993 subjects will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is two, the maximum number is 1,910.

Figure 7 indicates the distribution of subjects by study phase (only studies in which phase is specified were included), with Phase III clearly enrolling the majority of patients, as is to be expected.

Figure 7. Number of Study Subjects in Q3 2016 by Study Phase



The Top Five: Sponsors, Sites and CROs

Table 1. Top-5 International Study Sponsors in Q3 2016

№	Company Name	No. studies[1]	No. patients
1	Novartis	7	792
2	Merck & Co.	6	1360
3	H. Lundbeck A/S	5	560
4	Bristol-Myers Squibb	5	235
5	Teva Pharmaceutical Industries Ltd	4	730

Table 2. Top-5 Russian Study Sponsors in Q3 2016

№	Company Name	No. studies	No. patients
1	Biocad	6	411
2	Sotex	5	538
3	Atoll	4	210
4	R-Pharm	3	621
5	Materia Medica Holding	3	615

Table 3. Top-5 Russian Research Sites (BE and Phase I studies) in Q3 2016

№	Site Name	City	No. studies
1	Ecosafety Ltd.	Saint-Petersburg	16
2	Bioeq Ltd.	Saint-Petersburg	12
3	Clinical Hospital N2, Yaroslavl	Yaroslavl	8
4	Clinical Hospital N3, Yaroslavl	Yaroslavl	6
5	Road Clinical Hospital at the station Yaroslavl of Russian Railways	Yaroslavl	6

[1] Excluding BE studies.

Table 4. Top-5 Russian Research Sites (Phase II-IV studies) in Q3 2016

№	*Site Name*	*City*	*No. studies*
1	N.N. Blokhin Russian Oncological Scientific Center	Moscow	26
2	Kazan State Medical University	Kazan	23
3	Ryazan State Medical University named after I.P.Pavlov	Ryazan	19
4	I.P. Pavlov First St.Petersburg State Medical University	Saint-Petersburg	18
5	I.M. Sechenov First Moscow State Medical University	Moscow	17

Table 5. Top-5 Russian Research Sites (all studies) in Q3 2016

№	*Site Name*	*City*	*No. studies*
1	N.N. Blokhin Russian Oncological Scientific Center	Moscow	31
2	Kazan State Medical University	Kazan	24
3	Ecosafety Ltd.	Saint-Petersburg	21
4	I.P. Pavlov First St.Petersburg State Medical University	Saint-Petersburg	20
5	I.M. Sechenov First Moscow State Medical University	Moscow	20

Table 6. Top-CROs in Russia in Q3 2016

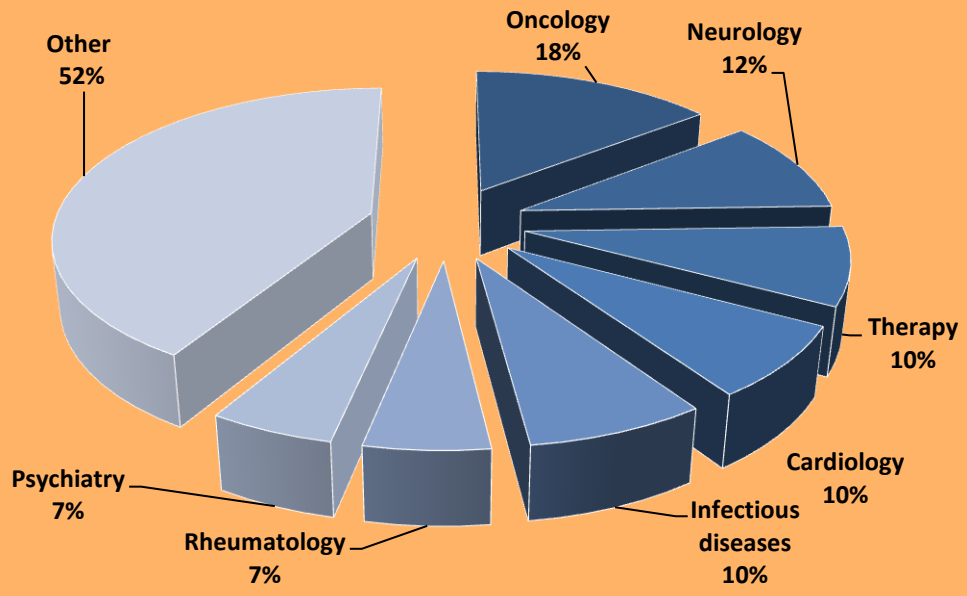
№	*CRO Name*	*No. studies*	*No. patients*
1	Quintiles	10	839
2	MSD Pharmaceuticals	6	1,360
3	Trokas Pharma Ltd.	6	574
4	Covance Clinical and Periapproval Services Ltd	6	550
5	Parexel	4	413

Therapeutic Areas of Russian Clinical Trials in Q3 2016

The largest number of studies were initiated in Oncology (44 studies); and is followed by Neurology (30 new studies), Therapy (25 studies), Cardiology and Infectious diseases (23 studies each), Rheumatology and Psychiatry (16 studies each).

The breakdown of therapeutic areas is shown in **Figure 8**.

Figure 8. Clinical Trials in Russia in Q3 2016 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 22 new drugs during Q3 2016; three of them are new molecular entities (NME); other approvals concern new dosages, combinations or manufacturers. Four of 22 drugs were (or are being) studied in clinical trials involving Russian sites.

The **Table 7** shows the drugs which were approved by FDA in Q3 2016 that were (or are being) tested in clinical trials in Russia.

Table 7. New Drugs Approved by FDA in Q3 2016 and Tested in Russian Sites

Appr.date	*Drug (active ingredient)*	*Company*
07/27/2016	Adlyxin (lixisenatide)	Sanofi-Aventis US
09/16/2016	Kyleena (levonorgestrel)	Bayer Healthcare Pharms
09/20/2016	Invokamet XR (canagliflozin / metformin hydrochloride)	Janssen Pharms
09/23/2016	Stelara (ustekinumab)	Janssen Biotech
		Source: FDA

During Q3 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 18 new drug applications[1], five positive recommendations on new generic medicines, one for new hybrid medicines and two for new biosimilar medicines. 12 of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

The **Table 8** represents those of them which were, or are being tested in clinical trials in Russia in Q3 2016.

Table 8. New Drugs Approved by EMA in Q3 2016 and Tested in Russian Sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
07/21/2016	Imbruvica (ibrutinib)	Janssen-Cilag International NV
07/21/2016	Orencia (abatacept)	Bristol-Myers Squibb Pharma EEIG
07/21/2016	Truvada (emtricitabine / tenofovir disoproxil)	Gilead Sciences International Ltd
07/21/2016	Xalkori (crizotinib)	Pfizer Limited
07/21/2016	Kisplyx (lenvatinib)	Eisai Europe Ltd
09/15/2016	NovoRapid (insulin aspart)	Novo Nordisk A/S
09/15/2016	Stelara (ustekinumab)	Janssen-Cilag International NV
09/15/2016	Glyxambi (empagliflozin / linagliptin)	Boehringer Ingelheim International GmbH
09/15/2016	Ibrance (palbociclib)	Pfizer Limited
09/15/2016	Lartruvo (olaratumab)	Eli Lilly Nederland B.V.
09/15/2016	Ninlaro (ixazomib)	Takeda Pharma A/S
09/15/2016	Parsabiv (etelcalcetide)	Amgen Europe B.V.
		Source: EMA

About Synergy Research Group

Synergy Research Group is a Russian contract research organization successfully operating in Russia since 2002. Synergy provides a full range of CRO services to help Russian and foreign pharmaceutical and biotechnological companies conduct cost-effective clinical trials. Today, Synergy is represented in Moscow, Saint-Petersburg, Novosibirsk, Yekaterinburg, Perm, Krasnodar, and also in Almaty and Astana (Kazakhstan) and Kyiv (Ukraine). The company's headquarters are in Moscow.

[1] Positive opinions on new generic, hybrid and biosimilar medicines are not included.