SYNERGY
ORANGE
PAPER

RESEARCH REPORT

CLINICAL TRIALS IN UKRAINE

2017 Annual Summary

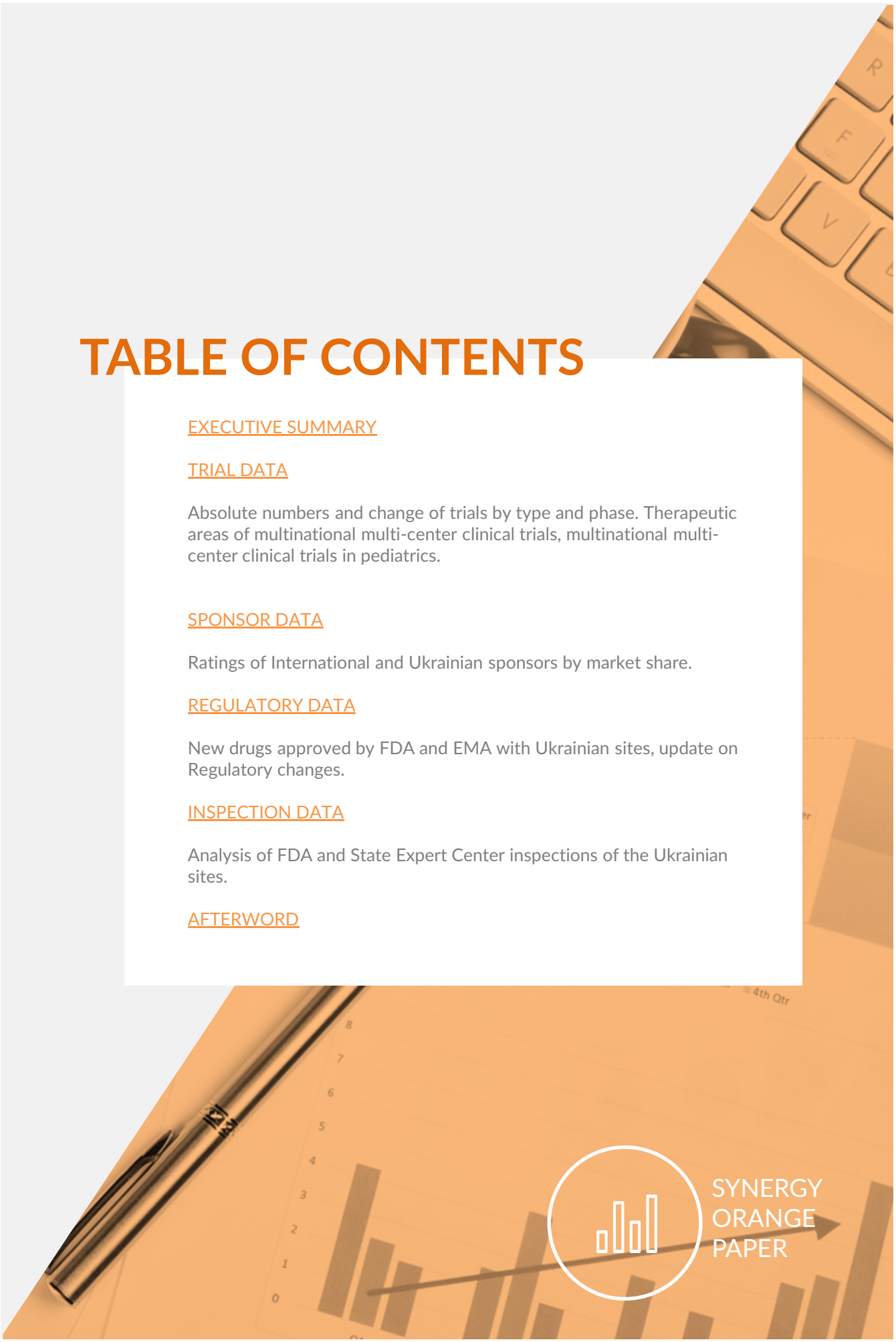
WWW.SRGCRO.COM

FOREWORD

The Orange Paper is a free publication produced by Synergy Research Group for the pharmaceutical industry since 2006. It pulls together data from numerous public sources into a single brief document to aid decision makers planning to conduct clinical trials. In Ukraine it is produced semi-annually, with an annual summary at the close of each year.

SYNERGY
ORANGE
PAPER

TABLE OF CONTENTS



EXECUTIVE SUMMARY

The Ministry of Health of Ukraine (MoH) approved 230 new clinical trials during 2017 (approximately 27% increases in comparison to 2016).

The share of multinational multi-center clinical trials (MMCT) was 79% of the total number of clinical trials in 2017, while the share of local clinical trials amounted to 16% and bioequivalence studies 5% respectively.

Among international CROs Quintiles Ukraine, which holds 15% of the market share, was in the top position in 2017. Second position was held by PRA Ukraine which had 9%, whilst in third place was InnoPharm Ukraine (PPD) with 6% followed by AbbVie Biopharmaceuticals GmbH and Astra Zeneca Ukraine with 5% each. The remaining companies combined had a total market share of 60%.

Among local Sponsors the Ukrainian company PJSC “Farmak” held 21% of the market share and was ranked number one among domestic pharmaceutical Applicants in 2017. It is followed by PrJSC “Darnitsa” and LLC “Zdorovya” with 15% each, PJSC "Chervona zirka" with 7%, “Microkhim” LTD with 6% market share, and the remaining companies combined had a market share of 36%.

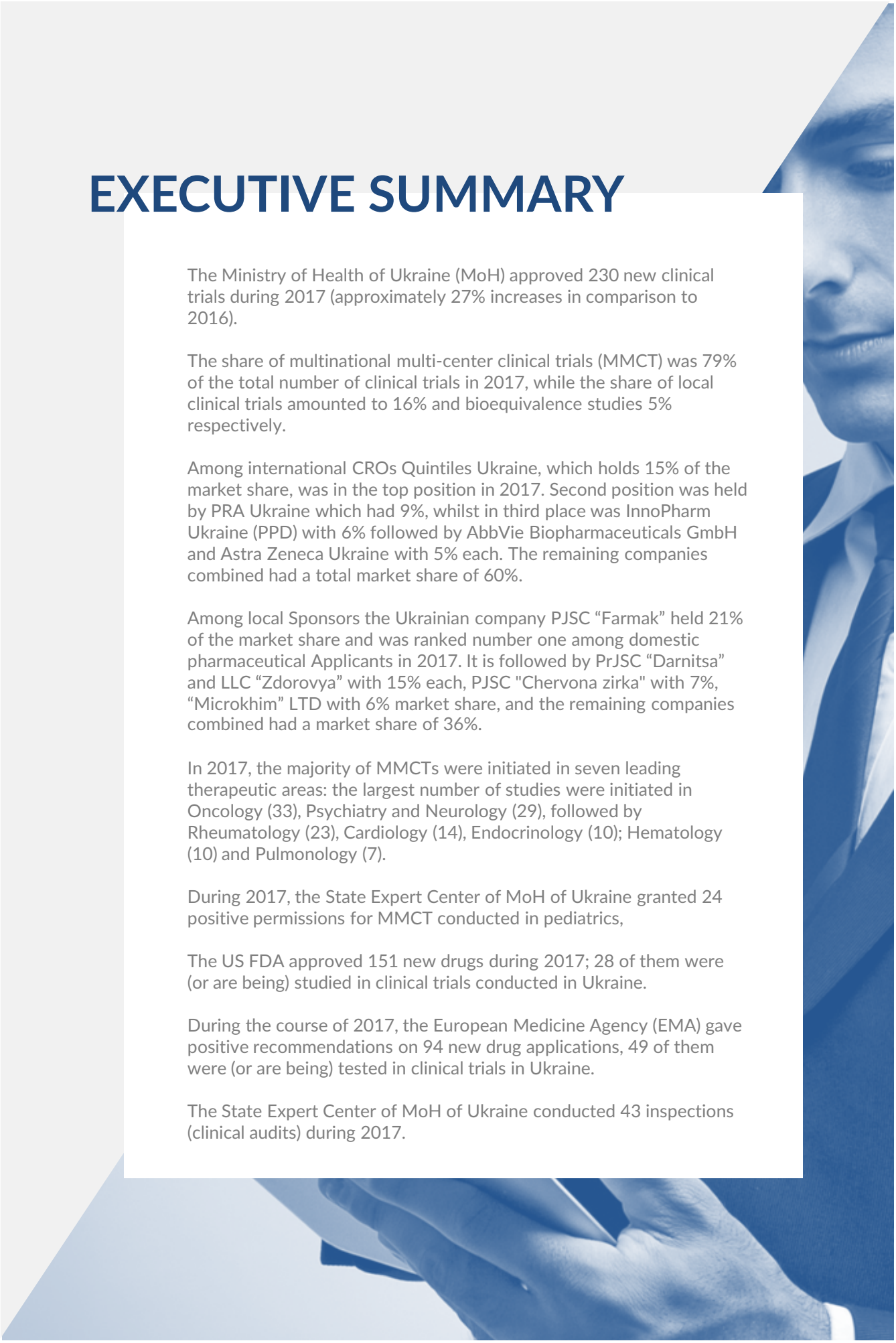
In 2017, the majority of MMCTs were initiated in seven leading therapeutic areas: the largest number of studies were initiated in Oncology (33), Psychiatry and Neurology (29), followed by Rheumatology (23), Cardiology (14), Endocrinology (10); Hematology (10) and Pulmonology (7).

During 2017, the State Expert Center of MoH of Ukraine granted 24 positive permissions for MMCT conducted in pediatrics,

The US FDA approved 151 new drugs during 2017; 28 of them were (or are being) studied in clinical trials conducted in Ukraine.

During the course of 2017, the European Medicine Agency (EMA) gave positive recommendations on 94 new drug applications, 49 of them were (or are being) tested in clinical trials in Ukraine.

The State Expert Center of MoH of Ukraine conducted 43 inspections (clinical audits) during 2017.



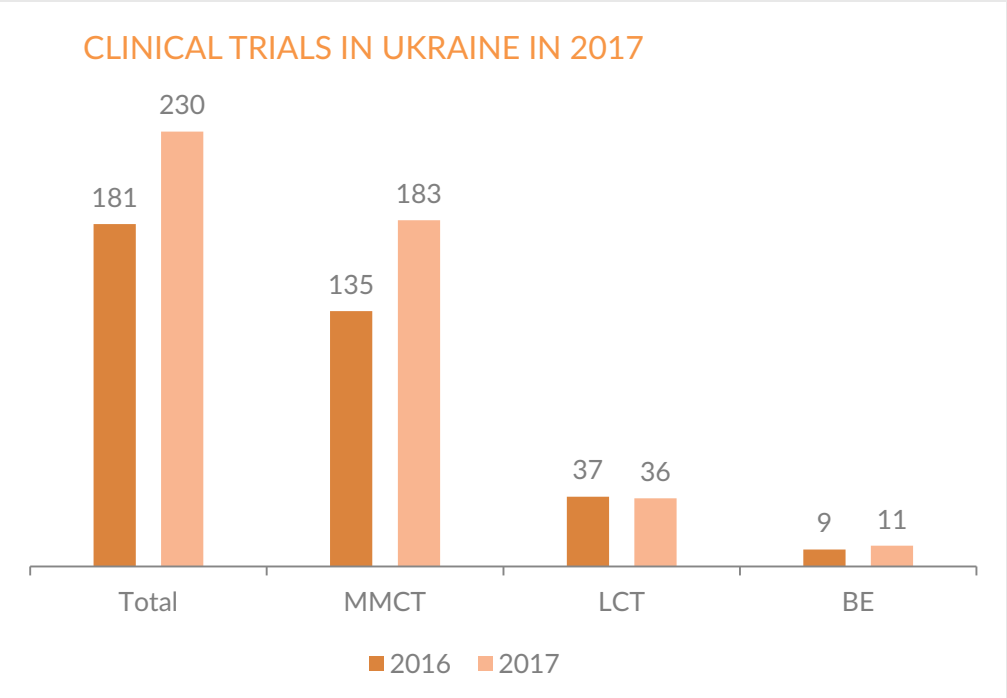
TRIAL DATA

The MoH of Ukraine approved 230 new clinical trials of all types including local and bioequivalence studies during 2017, demonstrating a 27% increase in comparison to the previous 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 also increased from 135 studies in 2016 to 183 in 2017.

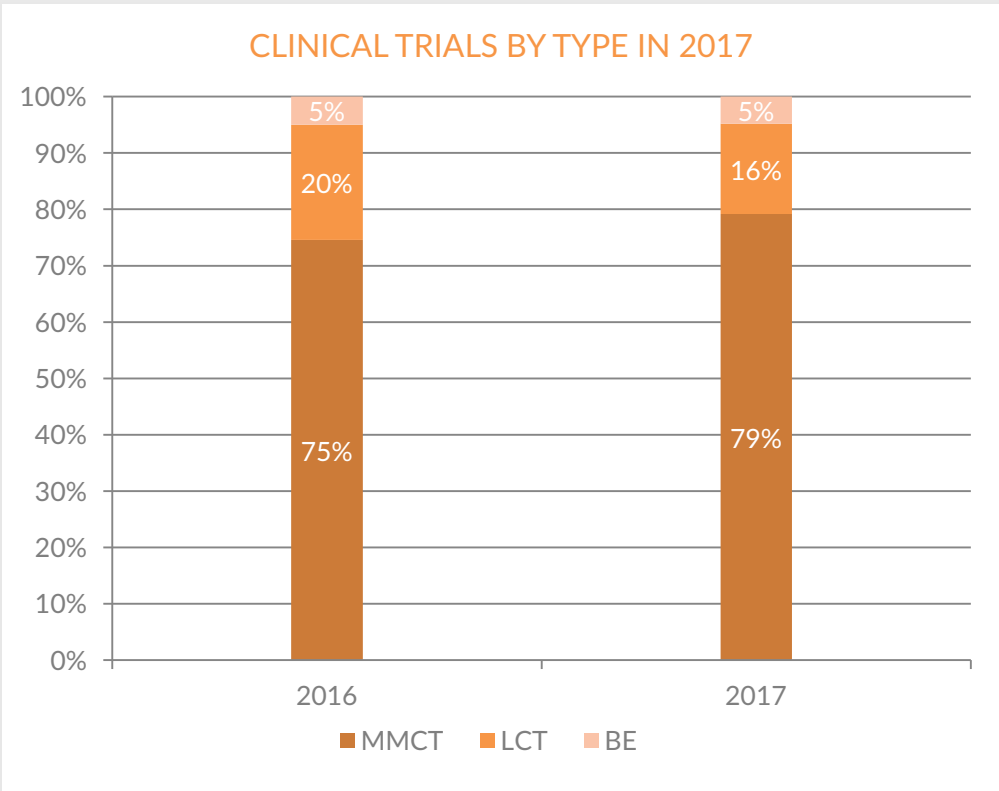
The number of local clinical trials (LCT) decreased from 37 in 2016 to 36 clinical trials in 2017.

The number of bioequivalence studies (BE) increased from 9 in 2016 to 11 clinical trials in 2017, an increase of 22% over last year's figure.



BREAKDOWN BY TYPE

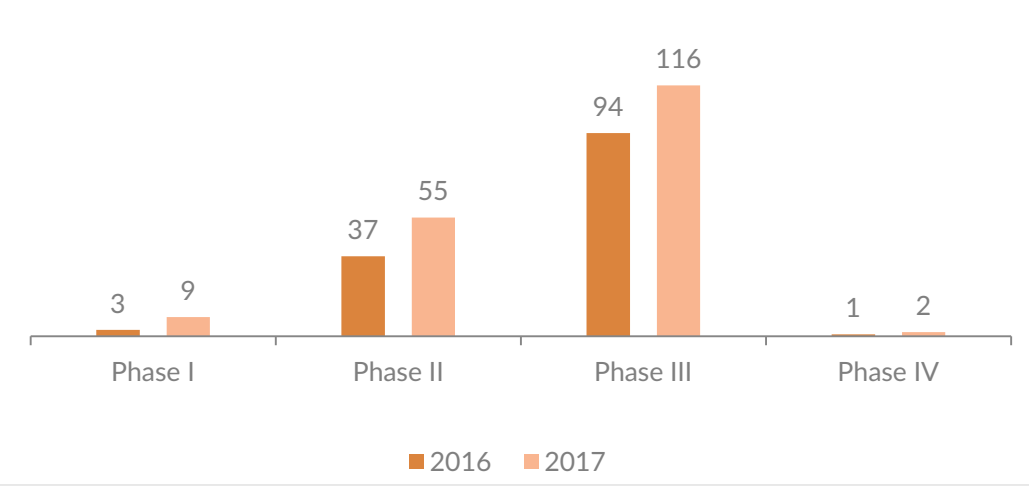
The proportions between different study types (multinational multi-center clinical trials and local studies) changed noticeably from 2016 to 2017.
The share of bioequivalence studies remained at the same level as in 2016 - 5% of the total number of clinical trials approved in 2017.
The share of the local trials decreased from 20% in 2016 to 16% in 2017 whilst the share of multinational multi-center clinical trials increased from 75% in 2016 to 79% in 2017 of the total number of trials approved during 2017.



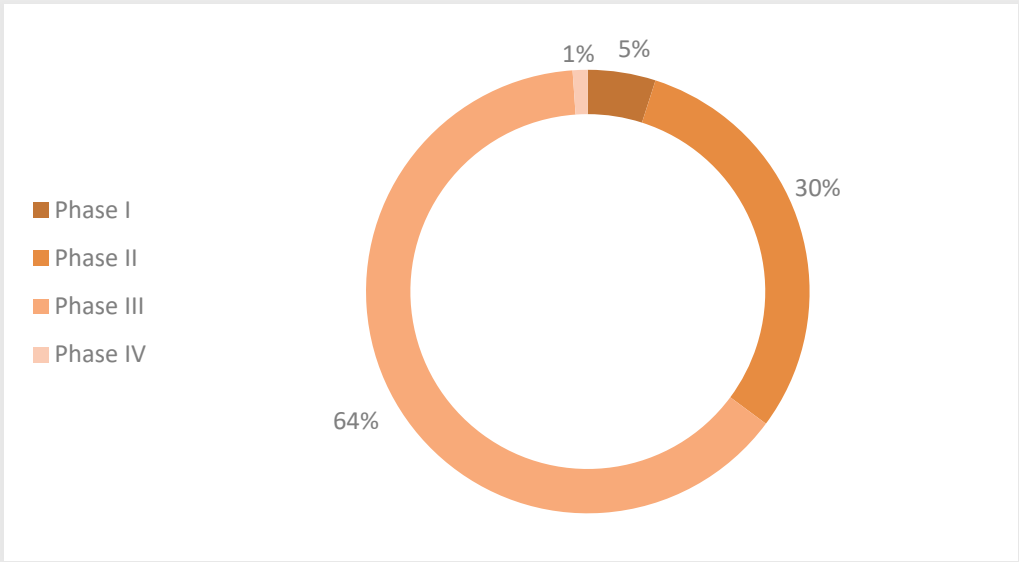
During the course of a clinical trial, an applicant may submit to the State Expert Center of MoH of Ukraine (Center) for significant amendments to the clinical trial protocol (additions or changes of existing information) which are reviewed according to current local legislation. During 2017, the Center issued 1,373 positive conclusions for MMCT amendments, representing an increase of 12% compared to 2016 with 1,222 positive conclusions.

MULTINATIONAL MULTI-CENTER CLINICAL TRIALS BY PHASE

2017 saw the approval of 9 new Phase I MMCT an increase of 6 studies compared to 2016. Phase IV trials increased from one study in 2016 to two new studies in 2017.

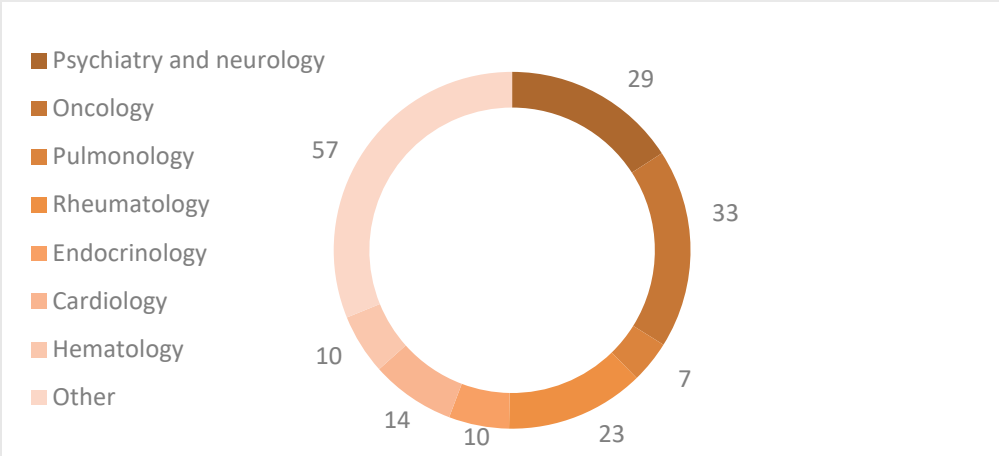


The share of Phase III trials in Q1 2018 is 61% of the total number of studies, the share of Phase I trials is 9%, Phase II trials is 16% and the share of Phase IV studies accounted to 14%.



THERAPEUTIC AREAS OF MULTINATIONAL MULTI-CENTER CLINICAL TRIALS IN 2017

In 2017, the majority of MMCTs were initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology (33) and Psychiatry and Neurology (29); and is followed by Rheumatology (23); Cardiology (14), Endocrinology (10); Hematology (10) and Pulmonology (7).

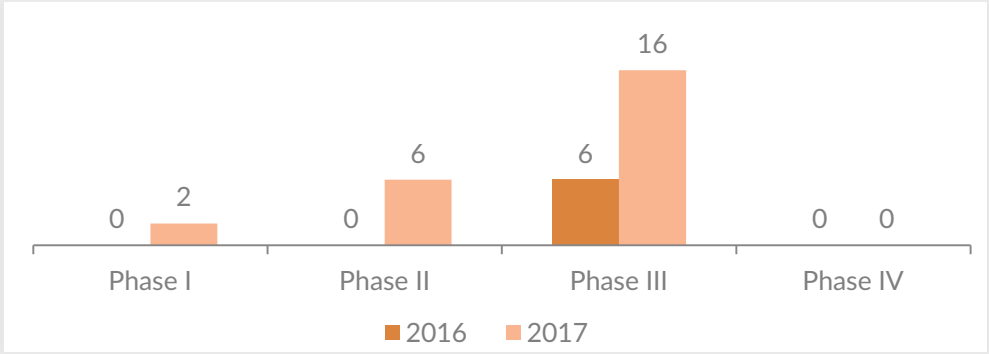


MULTINATIONAL MULTI-CENTER CLINICAL TRIALS IN PEDIATRICS

During 2017, the State Expert Center of MoH of Ukraine granted 24 positive permissions for MMCT conduct in pediatrics, 18 more than in 2016. The number of Phase I studies approved in pediatric patients in 2017 was two, an increase over 2016 when no such studies were approved.

The number of pediatric Phase II trials increased to 6 studies in 2017, whereas no Phase II trials were approved in 2016. Phase III trials increased from 6 to 16 respectively. Phase III trials in pediatric patients accounted approximately for 67% in 2017 compared with 100% in 2016.

POSITIVE CONCLUSIONS REGARDING MMCT IN PEDIATRICS (2016-2017 YEARS)



POSITIVE CONCLUSIONS REGARDING MMCT IN PEDIATRICS (2016-2017 YEARS)

Nosology	2016	2017
Psychiatry	1	0
Hematology	1	2
Infectious diseases	2	3
Endocrinology	2	3
Surgery	0	2
Neurology	0	1
Pulmonology	0	2
Oncology	0	1
Urology/Nephrology	0	1
Immunology	0	2
Gastroenterology	0	2
Dermatology	0	2
Cardiology	0	1
Rheumatology	0	1
Metabolic disorders	0	1

SPONSOR DATA

APPLICANTS OF MULTINATIONAL MULTI-CENTER CLINICAL TRIALS IN UKRAINE IN 2017

№	Company Name	Market share
1	Quintiles Ukraine	15%
2	PRA Ukraine	9%
3	InnoPharm Ukraine (PPD)	6%
4	AbbVie Biopharmaceuticals GmbH	5%
5	Astra Zeneca Ukraine	5%
6	Remaining Applicants	60%

APPLICANTS OF LOCAL CLINICAL TRIALS IN UKRAINE IN 2017

№	Company Name	Market share
1	PJSC “Farmak”	21%
2	PrJSC “Darnitsa”	15%
3	LLC “Zdorovya”	15%
4	PJSC "Chervona zirka"	7%
5	“Microkhim” LTD	6%
6	Remaining Applicants	36%

REGULATORY DATA

CLINICAL TRIAL RESULTS

The Center for Drug Evaluation and Research (CDER) of the US-FDA approved 151 new drugs during 2017; 39 of these were new molecular entities (NME); other approvals concerned new dosages, combinations or manufacturers. 28 of the 151 new drugs were (or are being) studied in clinical trials conducted in Ukraine.
Table shows the drugs which were approved by FDA in 2017 that were (or are being) tested in clinical trials in Ukraine.

NEW DRUGS APPROVED BY FDA IN 2017 AND TESTED IN UKRAINIAN SITES

Approval date	Drug (active ingredient)	Company
27/01/2017	AIRDUO RESPICLICK (FLUTICASONE PROPIONATE; SALMETEROL XINAFOATE)	TEVA PHARM
27/01/2017	ARMONAIR RESPICLICK (FLUTICASONE PROPIONATE)	TEVA PHARM
28/03/2017	DUPIXENT (DUPILUMAB)	REGENERON PHARMACEUTICALS
28/03/2017	OCREVUS (OCRELIZUMAB)	GENENTECH INC
01/05/2017	IMFINZI (DURVALUMAB)	ASTRAZENECA UK LTD
22/05/2017	KEVZARA (SARILUMAB)	SANOFI SYNTHELABO
23/06/2017	BEVYXXA (BETRIXABAN)	PORTOLA PHARMS INC
13/07/2017	TREMFYA (GUSELKUMAB)	JANSSEN BIOTECH
17/07/2017	NERLYNX (NERATINIB MALEATE)	PUMA BIOTECH

Approval date	Drug (active ingredient)	Company
19/07/2017	LUSDUNA (INSULIN GLARGINE)	MERCK SHARP DOHME
20/07/2017	BENLYSTA (BELIMUMAB)	GLAXOSMITHKLINE LLC
17/08/2017	LYNPARZA (OLAPARIB)	ASTRAZENECA PHARMS
18/08/2017	DUZALLO (ALLOPURINOL; LESINURAD)	ARDEA BIOSCIENCES
25/08/2017	CYLTEZO (ADALIMUMAB-ADBM)	BOEHRINGER INGELHEIM
29/08/2017	VABOMERE (MEROPENEM; VABORBACTAM)	REMPEX PHARMS MEDCNS
05/09/2017	TRACLEER (BOSENTAN)	ACTELION PHARMACEUTICALS LTD
14/09/2017	ALIQOPA (COPANLISIB)	BAYER HEALTHCARE PHARMS
18/09/2017	TRELEGY ELLIPTA (FLUTICASONE FUROATE; UMECLIDINIUM; VILANTEROL)	GLAXOSMITHKLINE
28/09/2017	VERZENIO (ABEMACICLIB)	ELI LILLY AND CO
29/09/2017	FIASP (INSULIN ASPART)	NOVO NORDISK INC
11/10/2017	LYRICA CR (PREGABALIN)	PFIZER INC
20/10/2017	BYDUREON BCISE (EXENATIDE)	ASTRAZENECA AB
13/11/2017	ABILIFY MYCITE KIT (ARIPIPRAZOLE)	OTSUKA PHARM CO LTD
14/11/2017	FASENRA (BENRALIZUMAB)	ASTRAZENECA AB
05/12/2017	OZEMPIC (SEMAGLUTIDE)	NOVO NORDISK INC
13/12/2017	IXIFI (INFLIXIMAB-QBTX)	PFIZER INC
19/12/2017	STEGLATRO (ERTUGLIFLOZIN)	MERCK SHARP DOHME
19/12/2017	SEGLUROMET (ERTUGLIFLOZIN; METFORMIN HYDROCHLORIDE)	MERCK SHARP DOHME
		Source: FDA

During the course of 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 94 new drug applications, 21 positive recommendations on new generic medicines, two for new hybrid medicines and 13 for new biosimilar medicines. A negative opinion was adopted for 12 drugs. 49 new drugs which received positive opinions were tested in clinical trials in Ukraine.
Table shows the drugs which were approved by EMA in 2017 that were (or are being) tested in clinical trials in Ukraine. Positive opinions on new generic, hybrid and biosimilar medicines are not included.

NEW DRUGS APPROVED BY EMA IN 2017 AND TESTED IN UKRAINIAN SITES

Approval date	Drug	Company
26/01/2017	Xeljanz	Pfizer Limited
26/01/2017	Revlimid	Celgene Europe Limited
26/01/2017	Synjardy	Boehringer Ingelheim GmbH
23/02/2017	Darzalex	Janssen-Cilag International NV
23/02/2017	Mekinist	Novartis Europharm Ltd
23/02/2017	Tafinlar	Novartis Europharm Ltd
23/03/2017	Keytruda	Merck Sharp & Dohme Limited
23/03/2017	Zebinix	Bial - Portela & Cª, S.A.
21/04/2017	Besponsa	Pfizer Limited
21/04/2017	Kevzara	Sanofi-Aventis groupe
21/04/2017	Erelzi	Sandoz GmbH
21/04/2017	Rixathon	Sandoz GmbH
21/04/2017	Riximyo	Sandoz GmbH
21/04/2017	Avastin	Roche Registration Limited

Approval date	Drug	Company
18/05/2017	Reagila	Gedeon Richter
18/05/2017	Komboglyze	AstraZeneca AB
18/05/2017	Onglyza	AstraZeneca AB
22/06/2017	Mavenclad	Merck Serono Europe Limited
22/06/2017	Faslodex	AstraZeneca UK Ltd
22/06/2017	Mimpara	Amgen Europe B.V.
22/06/2017	Victoza	Novo Nordisk A/S
20/07/2017	Bavencio	Merck Serono Europe Ltd
20/07/2017	Dupixent	Sanofi-Aventis groupe
20/07/2017	Tecentriq	Roche Registration Ltd
20/07/2017	Fanaptum	Vanda Pharmaceuticals Ltd
20/07/2017	Bydureon	AstraZeneca AB
20/07/2017	Humira	AbbVie Ltd
20/07/2017	Keytruda	Merck Sharp & Dohme Ltd
20/07/2017	RoActemra	Roche Registration Ltd
20/07/2017	Vimpat	UCB Pharma S.A.
14/09/2017	Elebrato Ellipta	GlaxoSmithKline Trading Services
14/09/2017	Tremfya	Janssen-Cilag International N.V.
14/09/2017	Trelegy Ellipta	GlaxoSmithKline Trading Services
14/09/2017	Zejula	Tesaro UK Limited
14/09/2017	Cyltezo	Boehringer Ingelheim International GmbH
14/09/2017	Ontruzant	Samsung Bioepis UK Limited (SBUK)

REGULATORY DATA

Approval date	Drug	Company
14/09/2017	Adlumiz	Helsinn Birex Pharmaceuticals Ltd
14/09/2017	Benlysta	Glaxo Group Ltd
14/09/2017	Firazyr	Shire Orphan Therapies GmbH
12/10/2017	Alecensa	Roche Registration Limited
12/10/2017	Bydureon	AstraZeneca AB
12/10/2017	Faslodex	AstraZeneca UK Ltd
12/10/2017	Pegasys	Roche Registration Limited
09/11/2017	Fasenra	AstraZeneca AB
09/11/2017	Ocrevus	Roche Registration Limited
09/11/2017	Fanaptum	Vanda Pharmaceuticals Ltd
14/12/2017	Ozempic	Novo Nordisk A/S
14/12/2017	Herzuma	Celltrion Healthcare Hungary Kft.
14/12/2017	Taltz	Eli Lilly Nederland B.V.
		Source: EMA

REGULATORY UPDATE

In 2017, the Guideline 42-7.0: 2008 "Medicines. Good Clinical Practice" approved by the Order of the MoH of Ukraine #95 dated 16.02.2009 was amended and supplemented by the Order of the MoH of Ukraine #1169 dated 26.09.2017.

These amendments and supplements have been introduced in order to implement the new requirements for clinical trials, namely: Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 9 November 2016, after approval by all ICH member countries in October 2016.

Clinical Trials in Ukraine are conducted in accordance with Order #690 MoH of Ukraine dated 23.09.2009 with changes stated in Orders issued by MoH of Ukraine #523 dated 12.07.2012, #304 dated 06.05.2014, #966 dated 18.12.2014 and #639 dated 01.10.2015.

To date, a design version of the Register of Clinical Trials has been developed, and it is available on the State Expert Center official website in the test mode.
The purpose of the Register maintenance is to create a single database of clinical trials in Ukraine and to provide reliable information about status of clinical trials for all interested persons (patients, investigators, sponsors, applicants etc.)

INSPECTION DATA

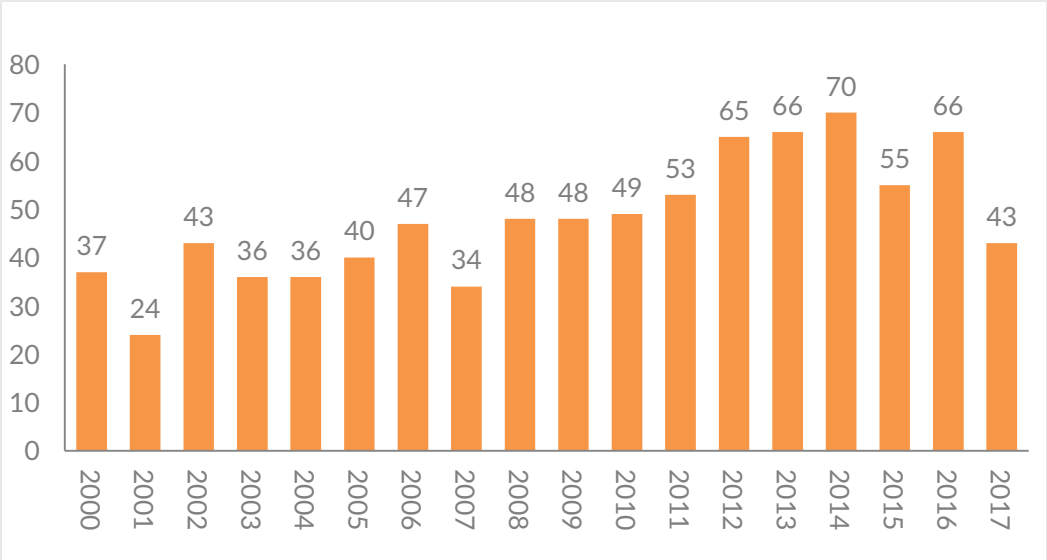
FDA INSPECTIONS

In the period from 2012 to 2017 there were 6 US-FDA inspections conducted in Ukraine together with representatives of the State Expert Center of Ministry of Health of Ukraine; 3 inspections of EMA and 1 from the Japanese PMDA (Pharmaceuticals and Medical Devices Agency).

STATE EXPERT CENTER CLINICAL AUDITS (INSPECTIONS)

One of the main components of quality assurance in clinical trials is the conduct of clinical audits, which are regularly held by the State Expert Center employees. 43 clinical audits were conducted in 2017, compared to 66 clinical audits in 2016, thus representing 23 audits (35%) fewer in 2016.

Two of 43 audits had no findings, 22 had non-significant findings and 18 of 43 audits found significant observations and 1 audit had critical findings.



AFTERWORD

According to the opinion of clinical trials market experts the Ukraine has only reached 10-15% of its total clinical trial capacity and an increase in the number of clinical trials to be conducted in the Ukraine is expected as a result of the step by step movement and harmonization of the Ukrainian health system with EU standards.

The current situation in Ukraine is favorable to conduct clinical trials. Contributing factors to this favorable environment include country population more than 42 million of inhabitants, a well-developed and structured system of healthcare, highly qualified staff and a growing number of experienced investigative sites that contribute to the rapid recruitment of patients.

Compliance with regulatory requirements and GCP standards, the availability of local Ethics committees, as well as a system for pharmacovigilance and control, ensure the quality of the data received from studies conducted in Ukraine.

We would like to express special gratitude to the employees of the State Expert Center of MoH of Ukraine, for providing full and detailed data on the statistics of clinical trials in Ukraine. The 2018 Annual Summary of Clinical Trials in Ukraine Orange Paper is scheduled for April 2019.

ABOUT SYNERGY

With its unique prevolutionary mind-set, Synergy is now the World's First Agile Risk Based CRO.

Prevolution is the implementation of thoughtful premeditated change resulting from the anticipation and analysis of future trends before they happen – in other words, being 'one step ahead of evolution'.

The high recruitment rates of the emerging markets combined with innovative technology allows our clients conduct faster, cost-effective studies without sacrificing quality. We replace outdated R&D strategies by novel, more efficient approaches to clinical research.