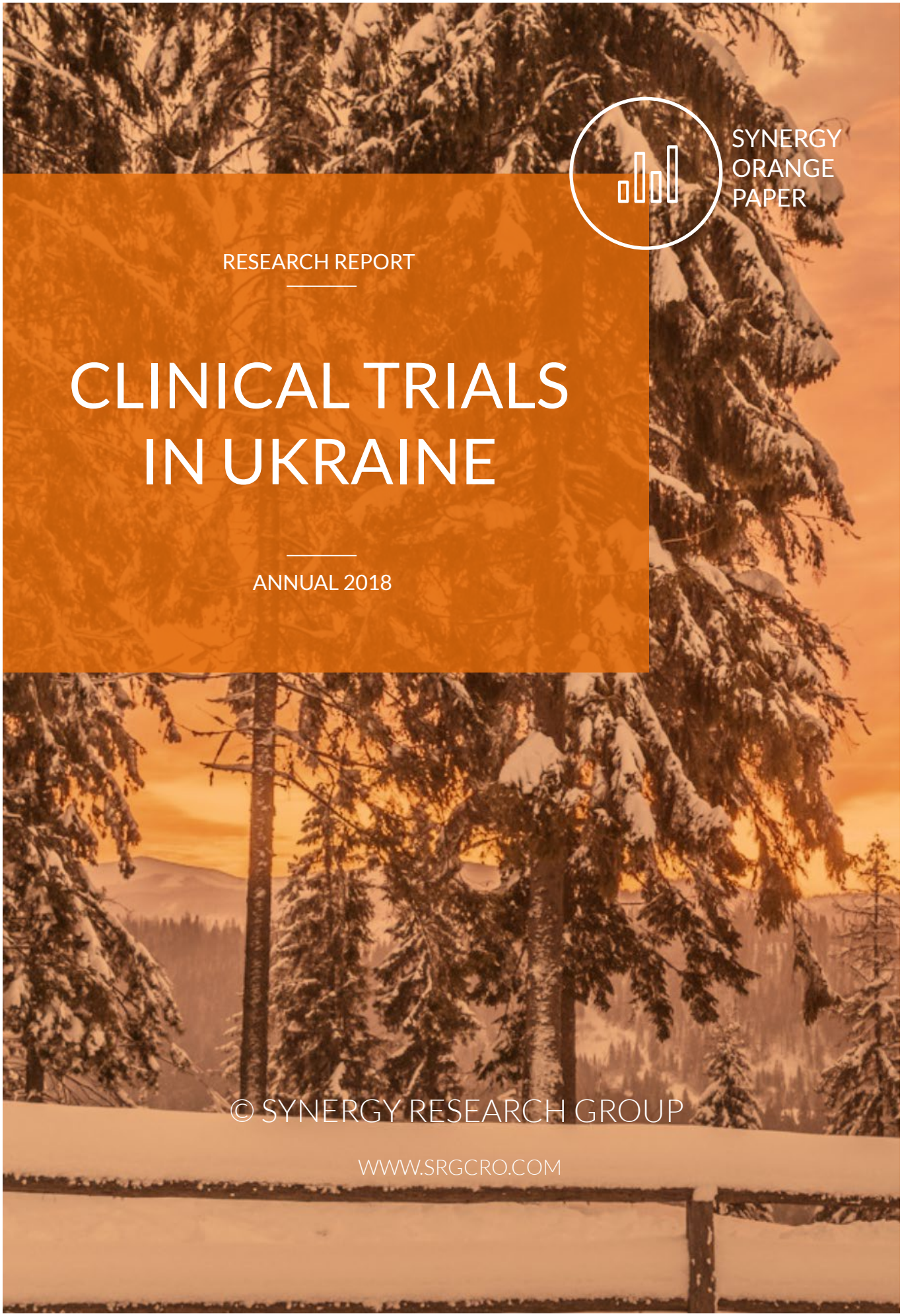

SYNERGY ORANGE PAPER

RESEARCH REPORT

CLINICAL TRIALS IN UKRAINE

ANNUAL 2018

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FOREWORD

The Orange Paper is a free publication produced by Synergy Research Group for the pharmaceutical industry since 2007. It pulls together data from numerous public sources into a single brief document to aid decision makers planning to conduct clinical trials. It is produced quarterly, with an annual summary at the close of each year.

SYNERGY ORANGE PAPER

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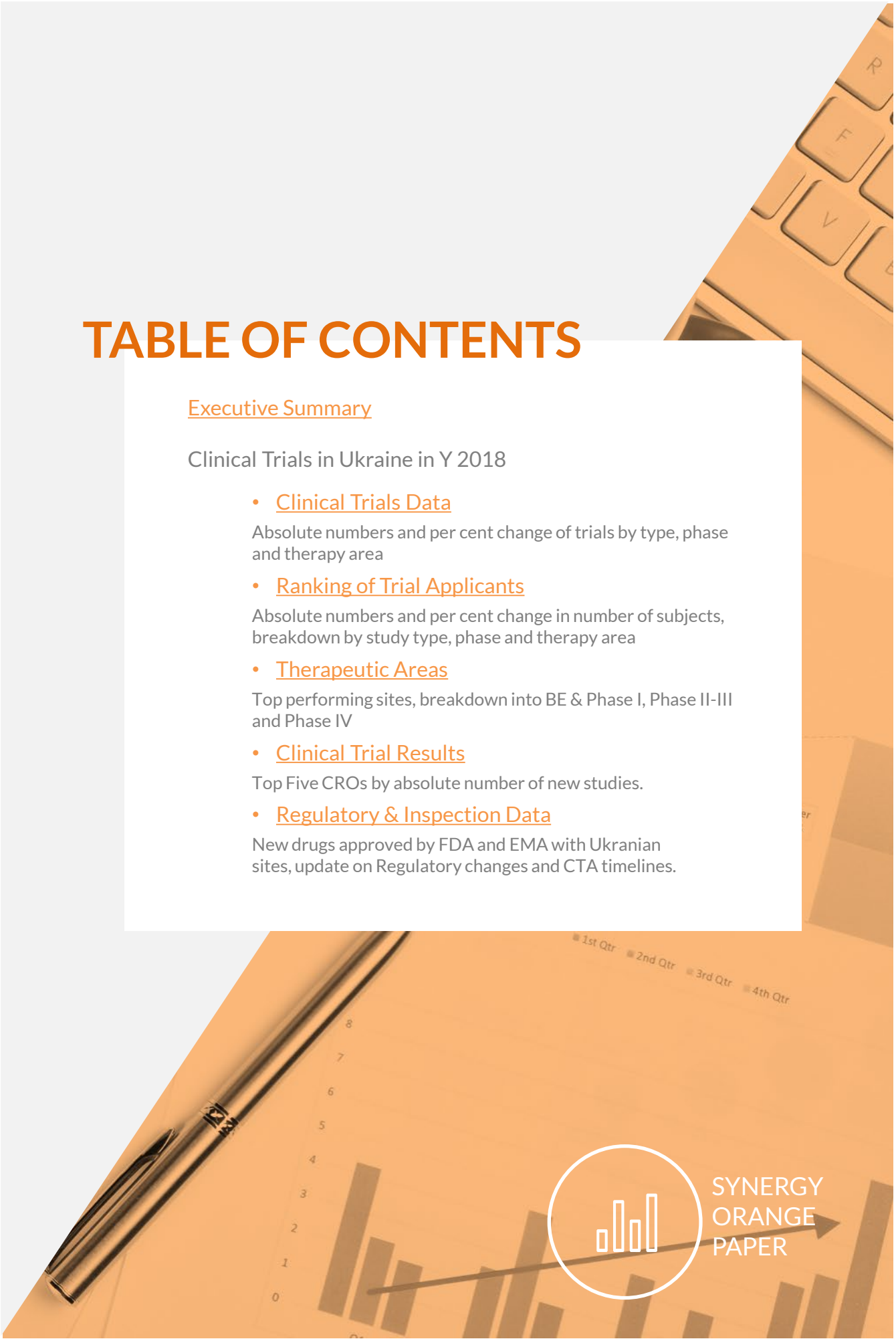


EXECUTIVE SUMMARY

In 2018 the MoH of Ukraine approved 208 new clinical trials representing a decline of approximately 10% in comparison to 2017.

The largest contribution to the total number of studies was made by multinational multi-center clinical trials (MMCT). The total number of MMCT studies decreased from 183 in 2017 to 178 in 2018 (representing a decline of approximately 3%). During the same period the number of bioequivalence studies (BE) rose in 2018 to 20 studies an increase of nine studies compared to 2017. The number of local clinical trials (LCT) however decreased from 36 to 10 clinical trials, (representing a decline of 72% compared to 2017).

In terms of international clinical trial applicants InnoPharm Ukraine (PPD) and MSD Ukraine, both hold 9% of the market share and were therefore in the top position in 2018. Second position was held by PSI Ukraine which had 8%. In third position were IQVIA Ukraine, INC Research Ukraine and ICON plc Ukraine each with 7%. The remaining companies had a combined total market share of 53%.

Among local clinical trial applicants (sponsors) the Ukrainian company PJSC “Farmak” held 25% of the market share and is number one among domestic pharmaceutical applicants in 2018. Second position was held by PrJSC “Darnitsa”, third place was held by PrJSC "Technolog.

The largest number of studies were initiated in Oncology (46), Psychiatry and Neurology (27), followed by Pulmonology (16), Rheumatology (9), Endocrinology (9), Cardiology (8) and Hematology (8).

During 2018, the State Expert Center of the MoH of Ukraine granted 25 positive permissions for MMCT to be conducted in pediatrics, one study less than in 2017 when 26 studies were approved and 19 more than 2016 when only six studies were approved.

The Center for Drug Evaluation and Research (CDER) of the US-FDA approved 162 new drugs during 2018; Forty Four of these were new molecular entities (NMEs); other approvals concerned new dosages, combinations or manufacturers. Fourteen of the 162 new drugs were (or are being) studied in clinical trials conducted (or being conducted) in Ukraine.

During the course of 2018, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 55 new drug applications , nine positive recommendations on new generic medicines, three for new hybrid medicines and 14 for new biosimilar medicines. A negative opinion was adopted for nine drugs. Forty nine new drugs which received positive opinions were tested in clinical trials in Ukraine.

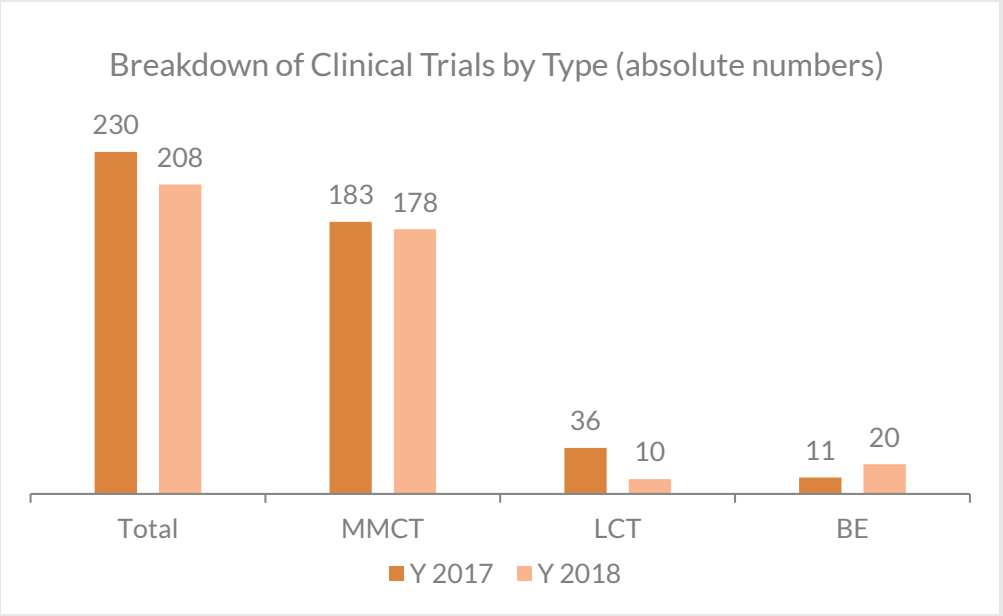
The State Expert Center of the MoH of Ukraine conducted 42 inspections (clinical audits) during 2018.

CLINICAL TRIALS IN UKRAINE

Trial Data

The MoH of Ukraine approved 208 new clinical trials of all types including MMCTs, LCTs and Bioequivalence (BE) studies during 2018, demonstrating a 10% decline in comparison to the previous year.

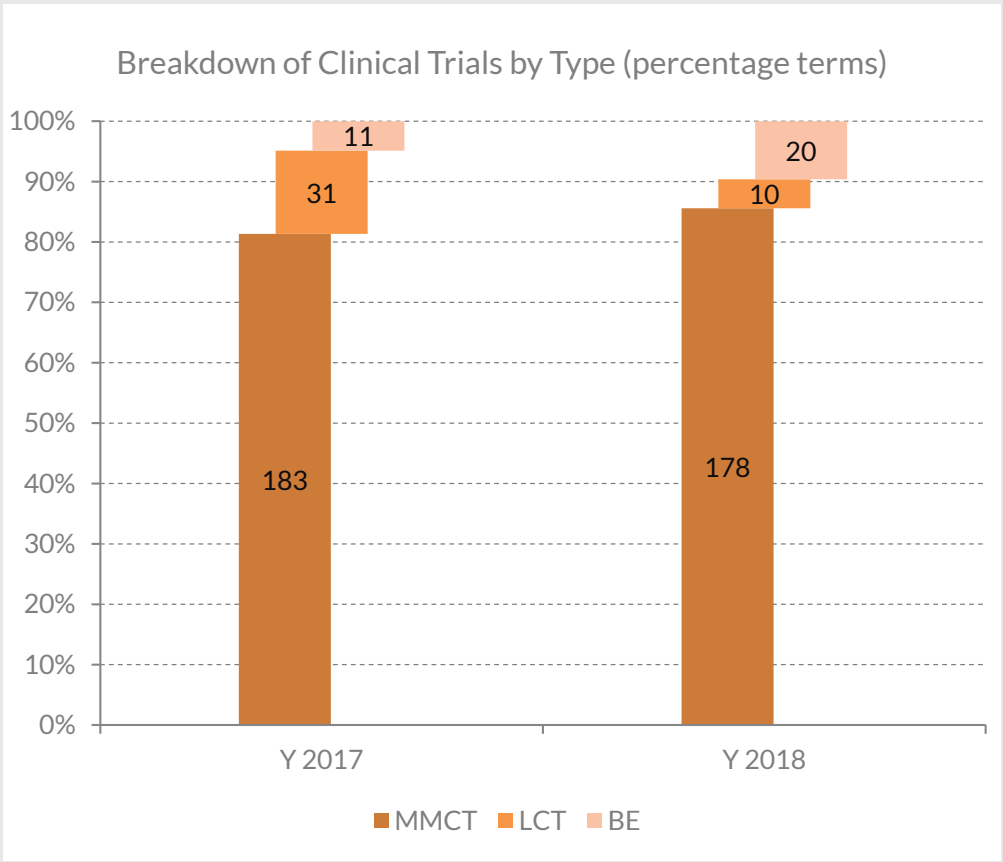
The main contribution to the total number of studies was made by multinational multi-center clinical trials (MMCTs), with the number of these studies decreasing from 183 studies in 2017 to 178 in 2018. The number of local clinical trials (LCT) decreased from 36 in 2017 to 10 clinical trials in 2018. The number of bioequivalence studies (BE) increased from 11 in 2017 to 20 clinical trials in 2018, an increase of 82% over last year's figure



The proportions between different study types (MMCTs, LCTs & BE's) changed noticeably from 2017 to 2018.

The share of bioequivalence studies increased from 5% in 2017 to 9% of the total number of clinical trials approved in 2018.

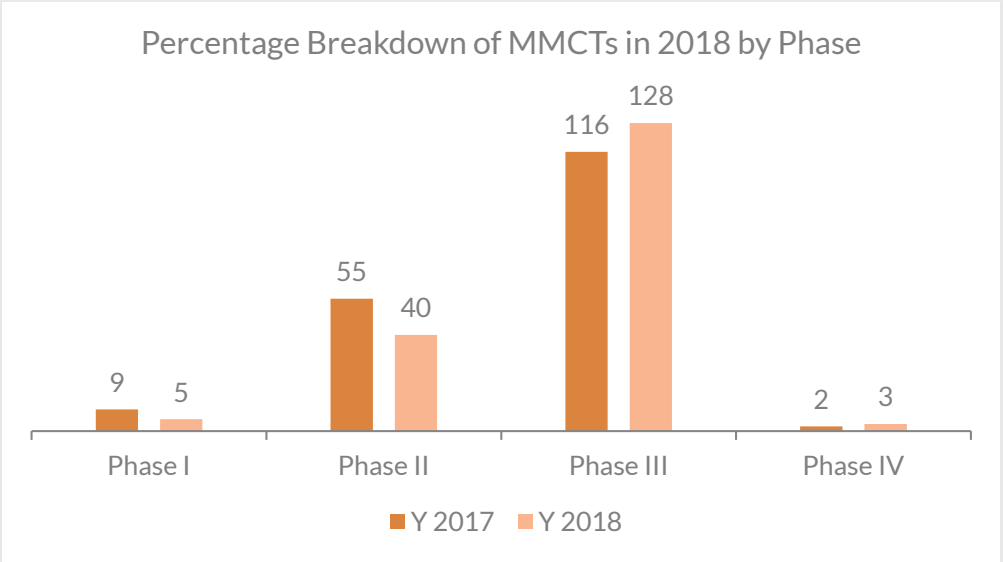
Of the total number of trials approved during 2018, the share of the LCTs decreased from 16% in 2017 to 5% in 2018 whilst the share of MMCTs increased from 79% in 2017 to 86% in 2018.

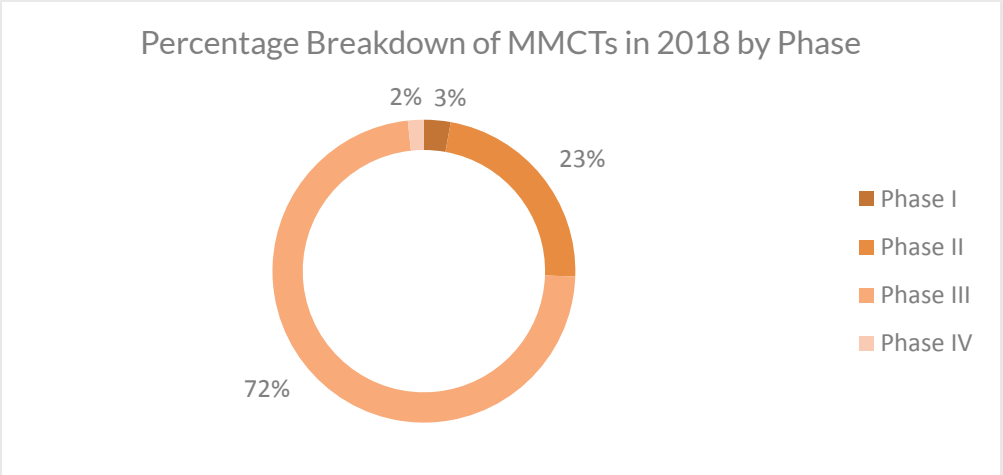


Multinational Multi-Center Clinical Trials (MMCTs) in Ukraine in 2018

2018 saw the approval of five new Phase I MMCTs a decrease of four studies compared to 2017. Phase IV trials increased from two studies in 2017 to three new studies in 2018.

Studies indicated by sponsors as phase I-II in the applications submitted to MoH, are shown in the phase II studies group; phase I-III, II-III and III-IV – are shown in the phase III studies group





Ranking of International Trial Applicants

Applicants of Multinational Multi-Center Clinical Trials in Ukraine in 2018

№	Company Name	Market Share
1	InnoPharm Ukraine (PPD)	9%
2	MSD Ukraine	9%
3	PSI Ukraine	8%
4	IQVIA Ukraine	7%
5	INC Research Ukraine	7%
6	ICON plc Ukraine	7%
7	Remaining Applicants	53%

Ranking of Ukrainian Trial Applicants

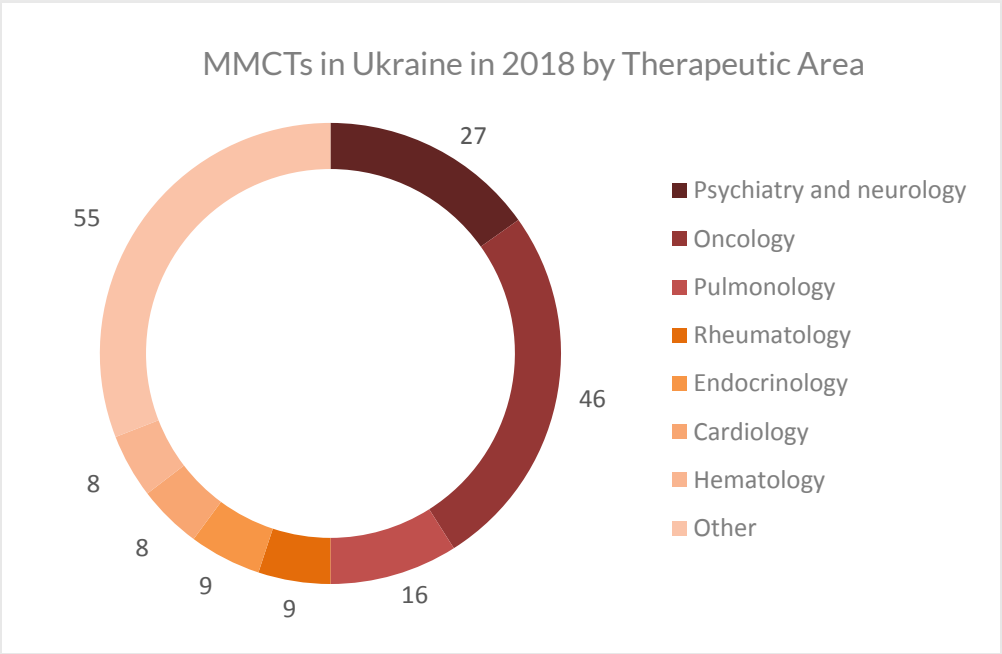
Applicants of Local Clinical Trials in Ukraine in 2018

№	Company Name	Market Share
1	PJSC “Farmak”	25%
2	PrJSC “Darnitsa”	16%
3	PrJSC "Technolog"	10%
4	“Microkhim” LTD	9%
5	LLC “Zdorovya”	9%
6	Remaining Applicants	31%

Therapeutic Areas of MMCTs in Ukraine in 2018

In 2018, the majority of MMCTs were initiated in seven leading therapeutic areas: the largest number of studies were initiated in Oncology (46), Psychiatry and Neurology (27), followed by Pulmonology (16), Rheumatology (9), Endocrinology (9); Cardiology (8) and Hematology (8).

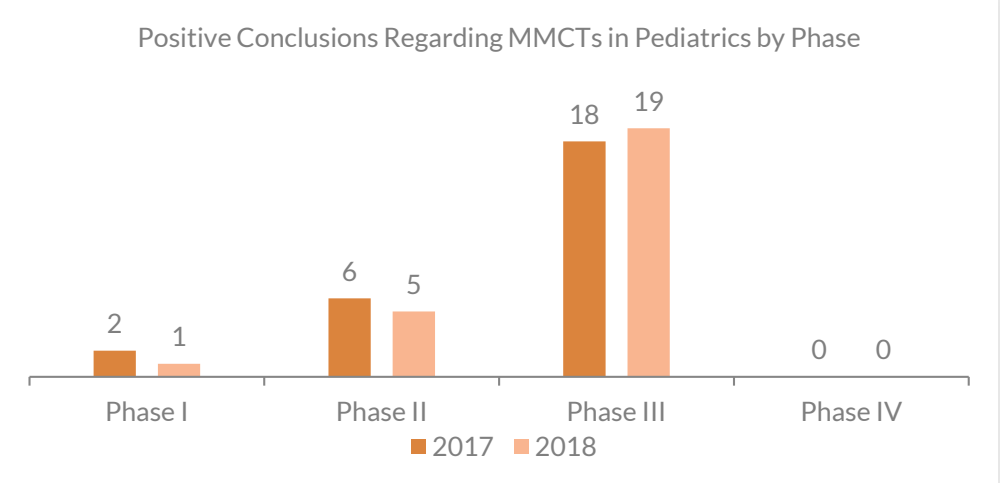
More than one therapeutic area could be assigned to a trial.



MMCTs in Pediatrics in Ukraine during 2018

During 2018, the State Expert Center of the MoH of Ukraine granted 25 positive permissions for MMCTs to be conducted in pediatrics, one study less than in 2017.

Phase I trials in pediatric patients approved in 2018 decreased from two studies in 2017 to one study in 2018. The number of pediatric Phase II trials decreased from six studies in 2017 to five 5 studies in 2018. Phase III pediatric trials increased from 18 (2017) to 19 (2018) respectively. Phase III trials in pediatric patients accounted for 76% of pediatric trials in 2018 compared with 69% in 2017.



Nosology	2017	2018
Psychiatry	0	8
Hematology	2	1
Infectious diseases	3	4
Endocrinology	3	1
Surgery	2	1
Neurology	1	0
Pulmonology	3	5
Oncology	1	0
Urology/Nephrology	1	1
Immunology	2	0
Gastroenterology	2	0
Dermatology	2	1
Cardiology	1	2
Rheumatology	1	1
Metabolic disorders	1	0
Allergology	1	0

CLINICAL TRIALS IN RUSSIA

Clinical Trial Results

The Center for Drug Evaluation and Research (CDER) of the US-FDA approved 162 new drugs during 2018; Forty Four of these were new molecular entities (NME); other approvals concerned new dosages, combinations or manufacturers. Fourteen of the 162 new drugs were (or are being) studied in clinical trials conducted (or being conducted) in Ukraine.

The table below shows the drugs which were approved by FDA in 2018 that were (or are being) tested in clinical trials in Ukraine.

APPROVAL DATE	DRUG (ACTIVE INGREDIENT)	COMPANY
16/02/2018	IMBRUVICA (IBRUTINIB)	PHARMACYCLICS INC
26/02/2018	VERZENIO (ABEMACICLIB)	ELI LILLY AND CO
20/03/2018	ILUMYA (TILDRAKIZUMAB-ASMN)	SUN PHARMA GLOBAL
24/05/2018	PROGRAF (TACROLIMUS)	ASTELLAS
31/05/2018	OLUMIANT (BARICITINIB)	ELI LILLY AND CO
27/06/2018	BRAFTOVI (ENCORAFENIB)	ARRAY BIOPHARMA INC
27/06/2018	MEKTOVI (BINIMETINIB)	ARRAY BIOPHARMA INC
28/06/2018	NUPLAZID (PIMAVANSERIN TARTRATE)	ACADIA PHARMS INC
29/06/2018	ARISTADA INITIO KIT (ARIPIPRAZOLE LAUROXIL)	ALKERMES INC
24/09/2018	COPIKTRA (DUVELISIB)	VERASTEM INC
28/09/2018	ARIKAYCE KIT (AMIKACIN SULFATE)	INSMED INC
02/10/2018	NUZYRA (OMADACYCLINE TOSYLATE)	PARATEK PHARMS INC
14/12/2018	HERZUMA (TRASTUZUMAB-PKRB)	CELLTRION INC
		Source: FDA

During the course of 2018, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 55 new drug applications , nine positive recommendations on new generic medicines, three for new hybrid medicines and 14 for new biosimilar medicines. A negative opinion was adopted for nine drugs. Forty Nine new drugs which received positive opinions were tested in clinical trials in Ukraine.

The table below shows the drugs which were approved by EMA in 2018 that were (or are being) tested in clinical trials in Ukraine

Approval date	Drug	Company
25/01/2018	SEGLUROMET	MERCK SHARP & DOHME LIMITED
25/01/2018	STEGLATRO	MERCK SHARP & DOHME LIMITED
25/01/2018	RELVAR ELLIPTA	GLAXO GROUP LTD
25/01/2018	REVINTY ELLIPTA	GLAXO GROUP LTD
22/02/2018	ALPIVAB	BIOCRYST UK LIMITED
22/02/2018	BOSULIF	PFIZER LIMITED
22/02/2018	LYNPARZA	ASTRAZENECA AB
22/02/2018	XGEVA	AMGEN EUROPE B.V.
22/03/2018	RUBRACA	CLOVIS ONCOLOGY UK LTD
22/03/2018	REPATHA	AMGEN EUROPE B.V.
26/04/2018	CIMZIA	UCB PHARMA SA
26/04/2018	PERJETA	ROCHE REGISTRATION GMBH
26/04/2018	PROLIA	AMGEN EUROPE B.V.
26/04/2018	TAGRISSO	ASTRAZENECA AB
26/04/2018	XELJANZ	PFIZER LIMITED
26/04/2018	XULTOPHY	NOVO NORDISK A/S
31/05/2018	RXULTI	OTSUKA PHARMACEUTICAL EUROPE LTD
31/05/2018	TRAZIMERA	PFIZER EUROPE MA EEIG
31/05/2018	BRIVIACT	UCB PHARMA S.A.
28/06/2018	NERLYNX	PUMA BIOTECHNOLOGY LIMITED
28/06/2018	LENVIMA	EISAI EUROPE LTD.

28/06/2018	ROACTEMRA	ROCHE REGISTRATION GMBH
26/07/2018	BRAFTOVI	PIERRE FABRE MEDICAMENT
26/07/2018	IMFINZI	ASTRAZENECA AB
26/07/2018	VERZENIOS	ELI LILLY NEDERLAND B.V.
26/07/2018	XERAVA	TETRAPHASE PHARMACEUTICALS IRELAND LIMITED
26/07/2018	HULIO	MYLAN S.A.S
26/07/2018	BINOCRIT	SANDOZ GMBH
26/07/2018	EPOETIN ALFA HEXAL	HEXAL AG
26/07/2018	KEYTRUDA	MERCK SHARP & DOHME B.V.
26/07/2018	MEKINIST	NOVARTIS EUROPHARM LIMITED
26/07/2018	NUCALA	GLAXOSMITHKLINE TRADING SERVICES LIMITED
26/07/2018	TAFINLAR	NOVARTIS EUROPHARM LIMITED
26/07/2018	XARELTO	BAYER AG
20/09/2018	APEALEA	OASMIA PHARMACEUTICAL AB
20/09/2018	VABOMERE	REMPEX LONDON LTD
20/09/2018	FULPHILA	MYLAN S.A.S
20/09/2018	ZIEXTENZO	SANDOZ GMBH
20/09/2018	ELEBRATO ELLIPTA	GLAXOSMITHKLINE TRADING SERVICES LIMITED
20/09/2018	GILENYA	NOVARTIS EUROPHARM LIMITED
20/09/2018	TRELEGY ELLIPTA	GLAXOSMITHKLINE TRADING SERVICES LIMITED
20/09/2018	VENCLYXTO	ABBVIE DEUTSCHLAND GMBH & CO. KG
20/09/2018	XTANDI	ASTELLAS PHARMA EUROPE B.V.
18/10/2018	BEVESPI AEROSPHERE	ASTRAZENECA AB
18/10/2018	OGIVRI	MYLAN S.A.S
15/11/2018	RAVICTI	HORIZON PHARMA IRELAND LIMITED
13/12/2018	ZIRABEV	PFIZER EUROPE MA EEIG
13/12/2018	SIMPONI	JANSSEN BIOLOGICS B.V.
13/12/2018	TRIMBOW	CHIESI FARMACEUTICI S.P.A.

Source: EMA

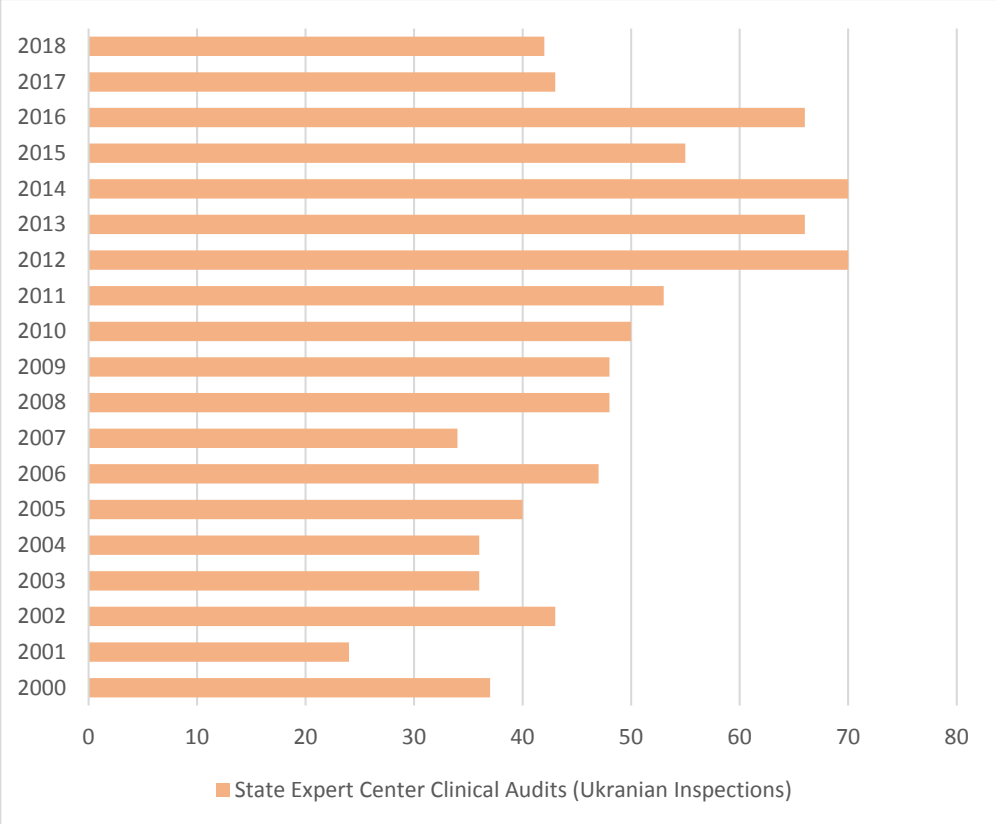
Regulatory & Inspection Data

FDA Inspections

In the period from 2012 to 2018 there were six US-FDA inspections conducted in Ukraine together with representatives of the State Expert Center of Ministry of Health of Ukraine; three inspections from the EMA, one from the Japanese PMDA (Pharmaceuticals and Medical Devices Agency) and one from State Medicines Control Agency of Lithuania.

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 inspectors from the State Expert Center. Forty two clinical audits were conducted in 2018, compared to 43 clinical audits in 2017, thus representing approximately 2% fewer clinical audits than in 2017.



Summary

According to the opinion of some clinical trials market experts 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 a country population of more than 42 million 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 the MoH of Ukraine, for providing full and detailed data on the statistics of clinical trials in Ukraine.

The 2019 Annual Summary of Clinical Trials in Ukraine Orange Paper is scheduled for April 2020

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.