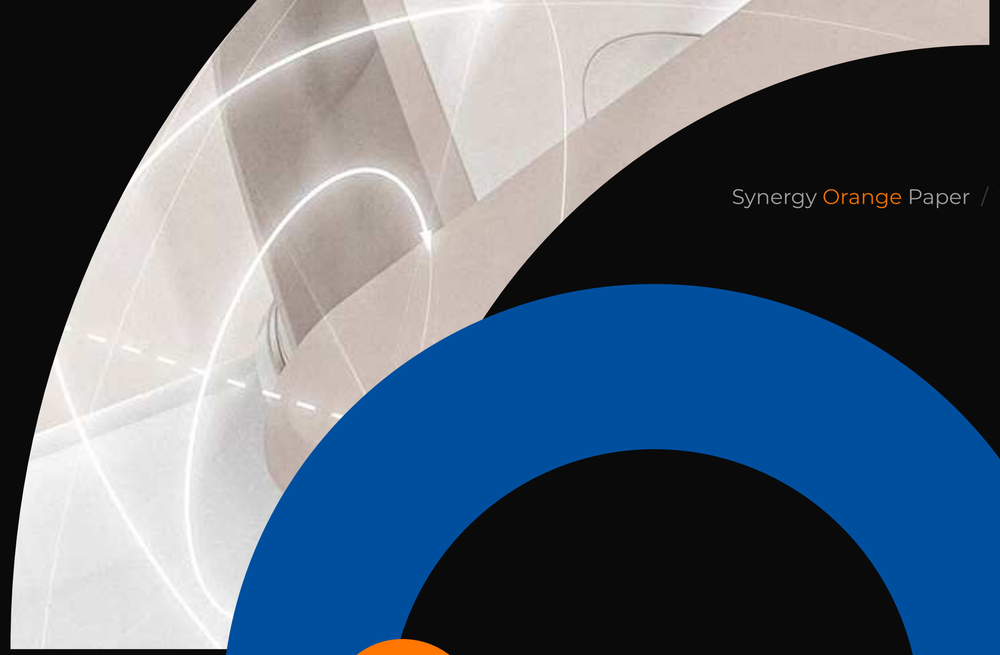
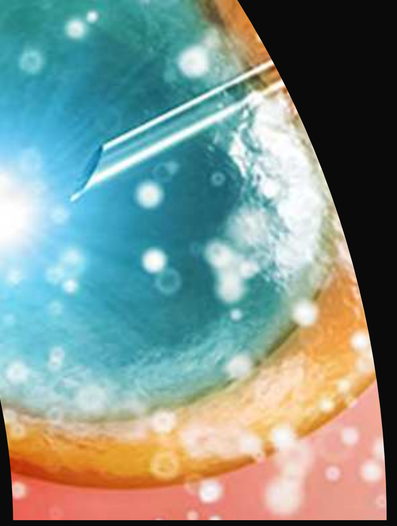




Synergy Orange Paper / 2019 Winter / Annual Report

srg

Clinical trials in Ukraine

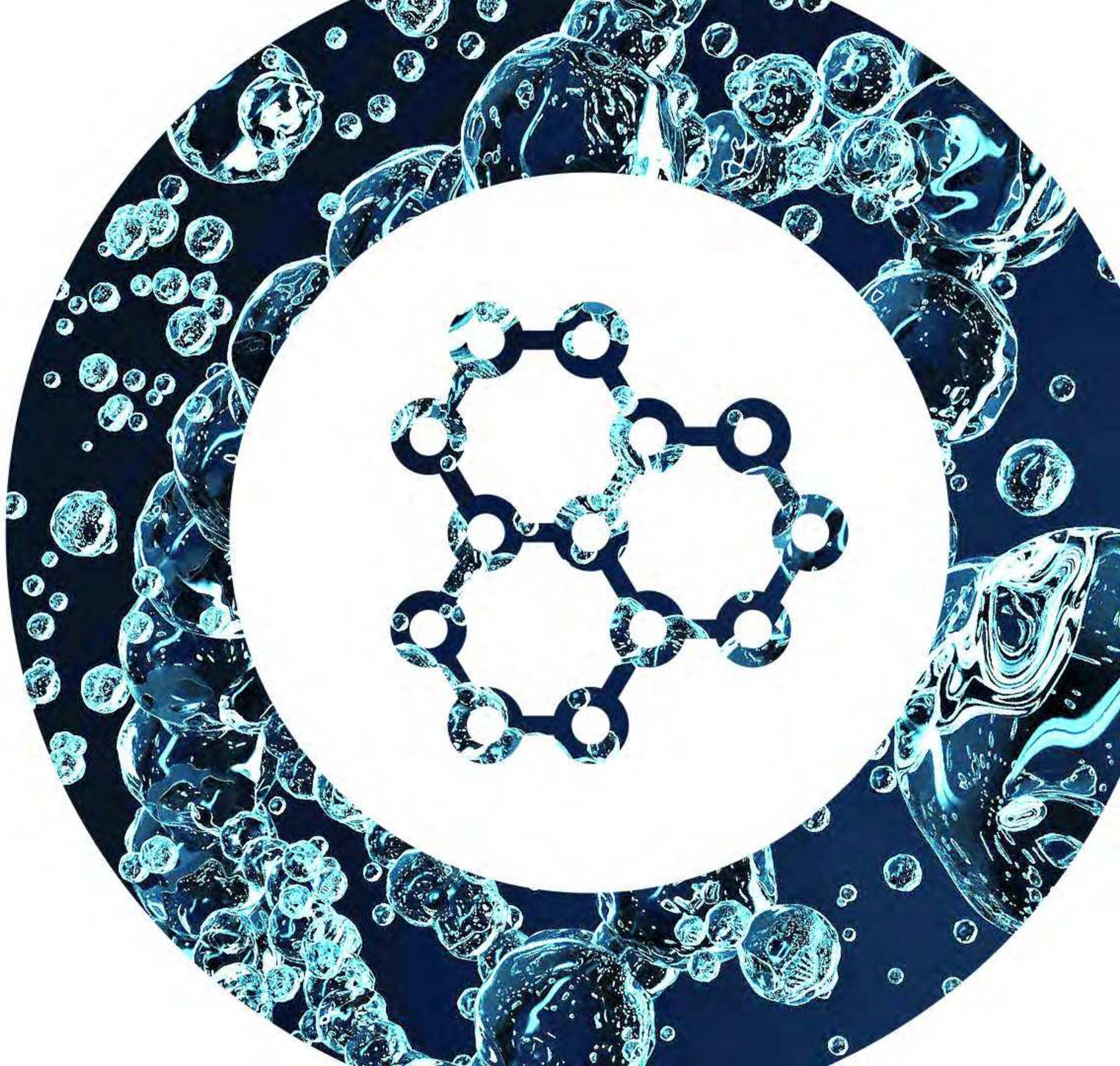
Research report

www.srgcro.com

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.

All of the data within this document are actual on date: 01/01/2020



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Executive Summary

According to statistical data obtained from the official websites of the State Expert Center of the Ministry of Health (MoH) of Ukraine, the U.S. FDA and the EMA there were 1,836 clinical trials approved for conduct in Ukraine from 2012 to 2019.

In 2019 the MoH of Ukraine approved 248 new clinical trials representing a growth of approximately 19% in comparison to 2018.

The largest contribution to the total number of studies was made by multinational multi-center clinical trials (MMCT). The total number of MMCT studies increased from 178 in 2018 to 210 in 2019 (representing a growth of approximately 18%). During the same period the number of bioequivalence studies (BE) rose in 2019 to 29 studies an increase of nine studies compared to 2018. The number of local clinical trials (LCT) decreased from 10 to 9 clinical trials, (representing a decline of 10% compared to 2018).

The share of MMCTs was 85% of the total number of clinical trials in 2019, whilst the share of bioequivalence studies amounted to 12% and local clinical trials 3% respectively.

The number of Phase I MMCTs increased from five studies in 2018 to ten new studies in 2019. The number of Phase II trials increased from 40 (2018) to 51 (2019), and the number of Phase III trials from 128 (2018) to 143 (2019) respectively. The number of Phase IV trials increased from four studies in 2018 to six studies in 2019

In terms of international clinical trial applicants, IQVIA RDC Ukraine held 13% of the market share and was therefore in the top position in 2019. Second position was held by INC Research Ukraine which had 8%. In third position were MSD Ukraine (7%), and in fourth Clinical research ICON Ukraine and PSI Ukraine each with 6%. The remaining companies had a combined total market share of 60%.

Executive Summary

Among local clinical trial applicants (Sponsors), the Ukrainian company JSC “Kyiv Vitamin Plant” held 17% of the market share and was ranked number one among domestic pharmaceutical applicants in 2019. Second and third positions were held by JSC “Pharmaceutical Firm Darnitsa” and “Microkhim” LTD with 14% each, whilst in fourth place was “Arterium LTD” with 11%. PJSC “Farmak” followed with 9%, and the remaining companies had a combined market share of 35%.

In 2019, the majority of MMCTs were initiated across seven leading therapeutic areas: the largest number of studies were initiated in Oncology (42), Psychiatry and Neurology (33), followed by Gastroenterology (27), Rheumatology (15), Hematology (15), Cardiology (14), and Endocrinology (12).

During 2019, the State Expert Center of the MoH of Ukraine granted 18 positive permissions for MMCT to be conducted in pediatrics, seven studies less than in 2018 when 25 studies were approved. In 2019 no Phase I trials in pediatric patients were approved, compared to one study in 2018. The number of Phase II pediatric trials increased from five studies in 2018 to six studies in 2019. Phase III pediatric trials decreased from 19 (2018) to 12 (2019) respectively. Phase III trials in pediatric patients accounted for 67% of pediatric trials in 2019 compared with 76% in 2018.

The Center for Drug Evaluation and Research (CDER) of the U.S. FDA approved 132 new drugs during 2019; thirty-seven of these drugs were new molecular entities (NME); other approvals concerned new dosages, combinations or manufacturers.

Eleven of these 132 new drugs were (or are being) studied in clinical trials conducted (or being conducted) in Ukraine.

During the course of 2019, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 73 new drug including 11 generics, 6 biosimilar and 9 orphan drugs. Eleven new drugs which received positive opinions were tested in clinical trials in Ukraine.

The State Expert Center of the MoH of Ukraine conducted 44 inspections (clinical audits) during 2019.

There were no significant Regulatory updates in Ukraine within 2019.

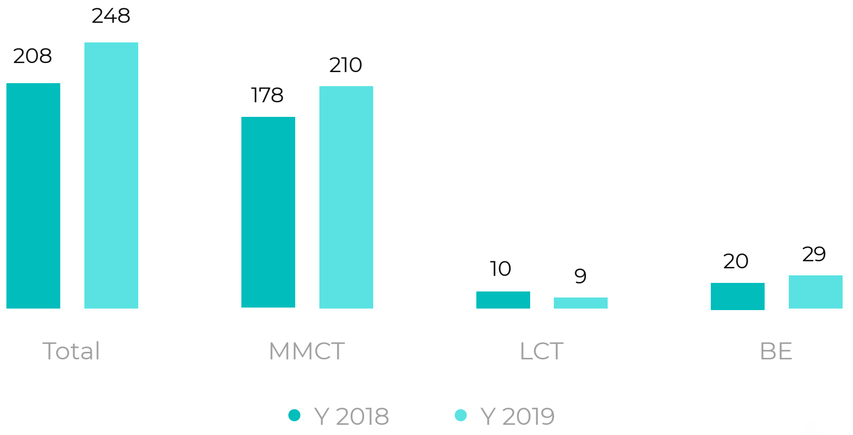
Trial Data

The MoH of Ukraine approved 248 new clinical trials of all types including MMCTs, LCTs and Bioequivalence (BE) studies during 2019 with a 19% growth 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 increasing from 178 studies in 2018 to 210 in 2019.

The number of local clinical trials (LCT) decreased from 10 in 2018 to 9 clinical trials in 2019. The number of bioequivalence studies (BE) increased from 20 in 2018 to 29 clinical trials in 2019, an increase of 45% over last year's figure.

Clinical Trials by Type 2018-2019 (Absolute Numbers)



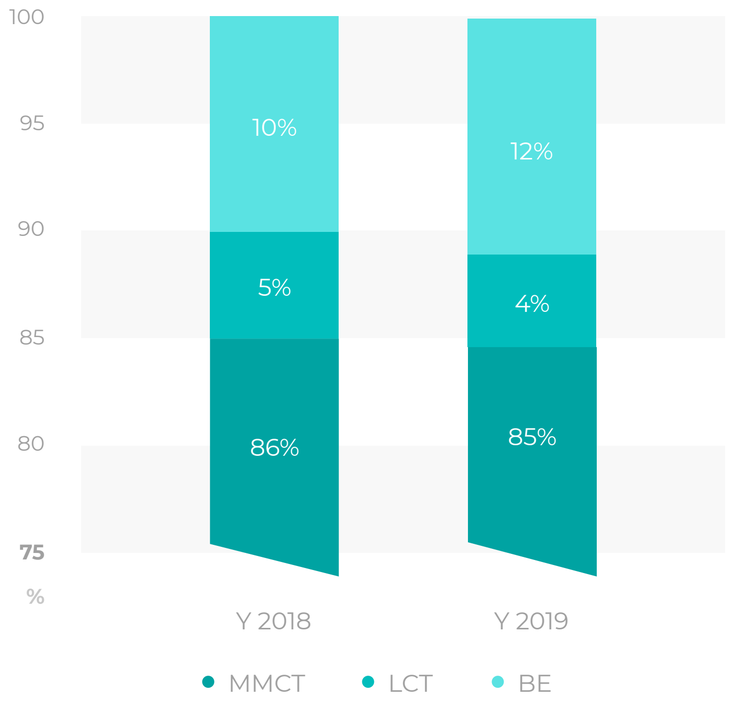
Trial Data

The proportions between different study types (MMCTs, LCTs & BE's) didn't changed noticeably from 2018 to 2019. The share of bioequivalence studies increased from 10% in 2018 to 12% of the total number of trials approved in 2019.

Of the total number of trials approved during 2019, the share of the LCTs decreased from 5% in 2018 to 4% in 2019 whilst the share of MMCTs decreased from 86% in 2018 to 85% in 2019.

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 2019, the Center issued 1,731 positive conclusions for MMCT amendments, representing approximately a 35% growth compared to 2018 (with 1,283 positive conclusions).

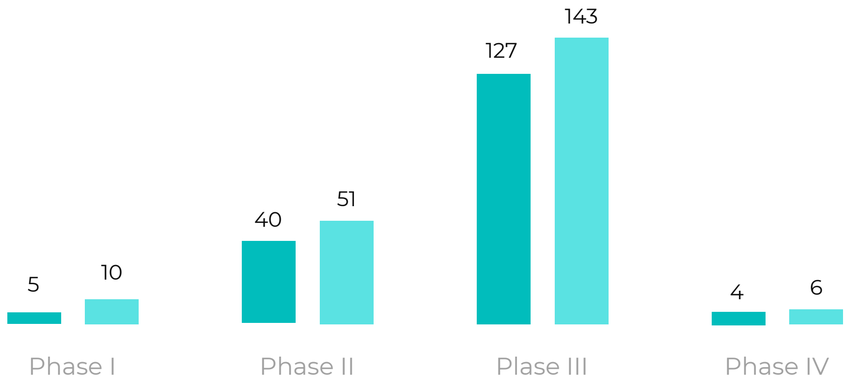
Clinical Trials by Type 2018-2019 (Percentage Terms)



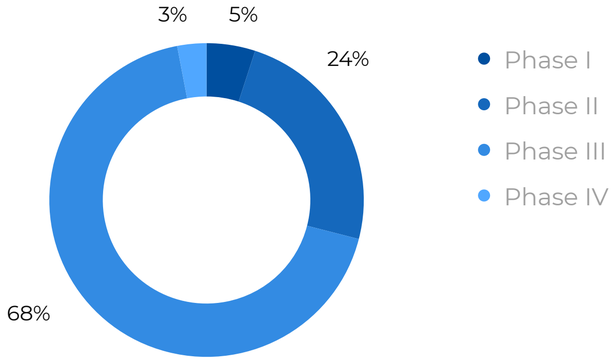
Trial Data

2019 saw the approval of ten new Phase I MMCTs a increase of five studies compared to 2018. Phase IV trials increased from four studies in 2018 to six new studies in 2019.

MMCTs by Phase 2018-2019 (Absolute Numbers)



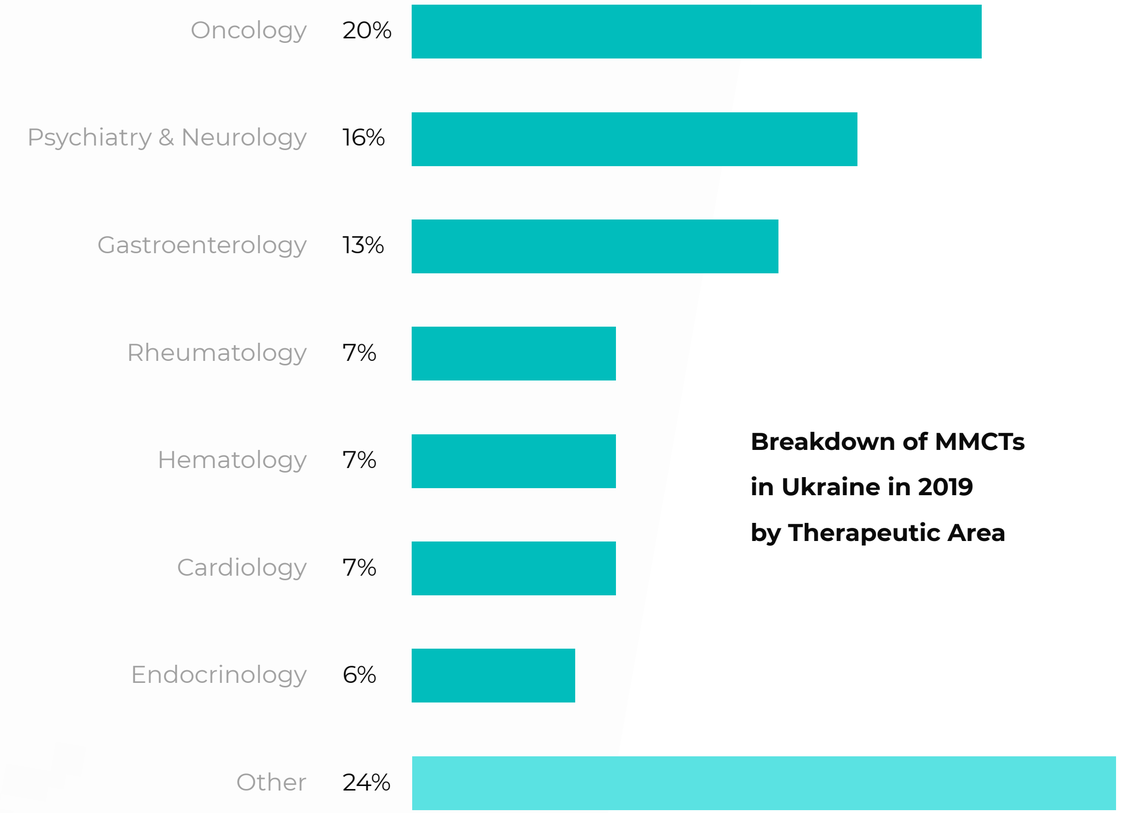
MMCTs in 2019 by Phase (Percentage Terms)



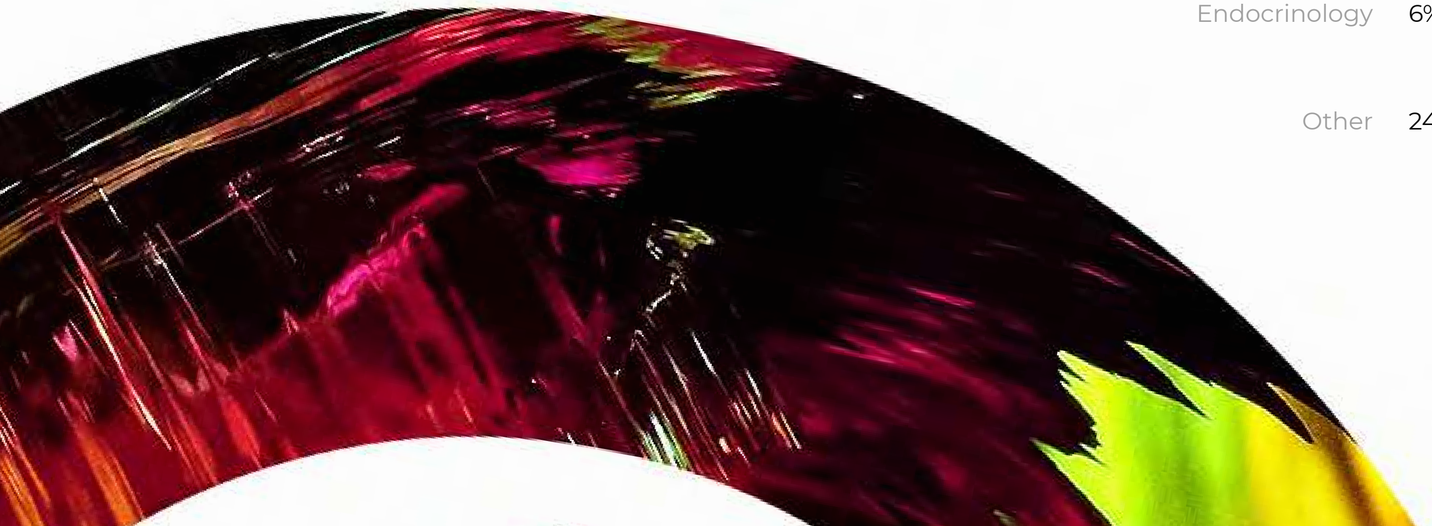
Studies indicated by sponsors as phase I-II in the applications submitted to MoH, are shown in the phase II studies group; phase I-III, II-III and III-IV – are shown in the phase III studies group.

Trial Data

In 2019, the majority of MMCTs were initiated in seven leading therapeutic areas: the largest number of studies were initiated in Oncology (42), Psychiatry and Neurology (33), followed by Gastroenterology (27), Rheumatology (15), Hematology (15), Cardiology (14), and Endocrinology (12).



Breakdown of MMCTs in Ukraine in 2019 by Therapeutic Area



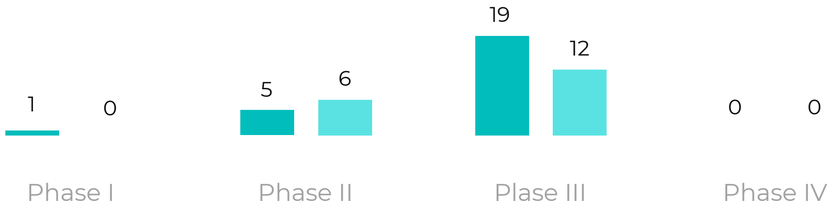
Trial Data

Multinational Multi-Center Clinical Trials in Pediatrics in Ukraine

During 2019, the State Expert Center of the MoH of Ukraine granted 18 positive permissions for MMCTs to be conducted in pediatrics, seven studies less than in 2018 when 25 studies were approved. The number of approved Phase I trials in pediatric patients decreased from one study in 2018 to none in 2019.

The number of pediatric Phase II trials increased from five studies in 2018 to six studies in 2019. The number of Phase III pediatric trials saw a decrease from 19 (2018) to 12 (2019). Phase III trials in pediatric patients accounted for 67% of pediatric trials in 2019 compared with 76% in 2018.

Positive Conclusions Regarding MMCTs in Pediatrics by Phase (2018 - 2019)



Therapeutic Areas of MMCTs in Pediatrics

Nosology	2018	2019
Psychiatry	8	2
Hematology	1	1
Infectious diseases	4	5
Endocrinology	1	3
Surgery	1	0
Neurology	0	1
Pulmonology	5	2
Oncology	0	0

Nosology	2018	2019
Urology/Nephrology	1	0
Immunology	0	0
Gastroenterology	0	0
Dermatology	1	1
Cardiology	2	1
Rheumatology	1	2
Metabolic disorders	0	0
Allergology	0	0

CRO Data

Applicants of Multinational Multi-Center Clinical Trials in Ukraine in 2019

№	Company Name	Market share
1	IQVIA RDC Ukraine	13%
2	INC Research Ukraine	8%
3	MSD Ukraine	7%
4	Clinical Research ICON, Ukraine	6%
5	PSI Ukraine	6%
6	Remaining Applicants	**60%**

Applicants of Local Clinical Trials in Ukraine in 2019

№	Company Name	Market share
1	JSC “Kyiv Vitamin Plant”	13%
2	JSC “Pharmaceutical Firm Darnitsa”	8%
3	“Microkhim” LTD	7%
4	“Arterium LTD”	6%
5	PJSC “Farmak”	6%
6	Remaining Applicants	**60%**

Regulatory & Inspection Data

Clinical Trial Results

The Center for Drug Evaluation and Research (CDER) of the U.S. FDA approved 132 new drugs during 2019; Thirty seven of these were new molecular entities (NME); other approvals concerned new dosages, combinations or manufacturers. Eleven of the 132 new drugs were (or are being) studied in clinical trials conducted (or being conducted) in Ukraine.

The following table shows the drugs which were approved by FDA in 2019 that were (or are being) tested in clinical trials in Ukraine.

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.

Drugs studied at Ukranian sites and approved by FDA in Y 2019

№	Appr. date	Drug (active ingredient)	Company
1	18/01/2019	Ontruzantbla (Trastuzumab-DTTB)	Samsung Bioepis
2	05/02/2019	Qternmet XRNDA (Dapagliflozin; Metformin Hydrochloride; Saxagliptin Hydrochloride)	AstraZeneca
3	12/04/2019	Balversanda (Erdafitinib)	Jannsen
4	23/04/2019	Skyrizibla (Risankizumab-RZAA)	Abbvie
5	16/07/2019	Recarbrionda (Cilastatin Sodium; Imipenem; Relebactam)	Merck
6	30/07/2019	Nubeqanda (Darolutamide)	Bayer
7	16/08/2019	Rinvoqnda (Upadacitinib)	Abbvie
8	20/09/2019	Rybelsusnda (Semaglutide)	Novo Nordisk
9	01/11/2019	Ibrancenda (Palbociclib)	Pfizer
10	08/11/2019	Reblozylbla (Luspatercept-AAMT)	Celgene
11	21/11/2019	Xcoprinda (Cenobamate)	SL Life Science

Source: FDA

Regulatory & Inspection Data

Clinical Trial Results

During the course of 2019, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 73 new drug including 11 generics, 6 biosimilar and 9 orphan drugs. Eleven new drugs which received positive opinions were tested in clinical trials in Ukraine.

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 four clinical audits were conducted in 2019, compared to 42 clinical audits in 2018, thus representing approximately 5% more clinical audits than in 2018. Three of 44 audits had no findings, 28 had non-significant findings and 9 of 44 audits found significant observations and four audits had critical findings.

Ukraine Regulatory Update

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. There were no significant Regulatory updates in Ukraine within 2019.

Drugs studied at Ukranian sites and approved by EMA in Y 2019

№	Appr. date	Drug (active ingredient)	Company
1	28/02/2019	Zynquista (Sotagliflozin)	Sanofi
2	26/04/2019	Libtayo (Cemiplimab)	Regeneron
3	27/06/2019	Lacosamide (Lacosamide)	UCB Pharma
4	25/07/2019	Lonsurf (Trifluridine; Tipiracil Hydrochloride)	Les Laboratoires Servier
5	25/07/2019	Tecentriq (Atezolizumab)	Roche
6	19/09/2019	Remsima (Infliximab)	Celltrion
7	19/09/2019	Dupixent (Dupilumab)	Sanofi-Aventis
8	19/09/2019	Qtrilmet (Metformin Hydrochloride; Saxagliptin; Dapagliflozin)	AstraZeneca
9	15/11/2019	Polivy (Polatuzumab Vedotin)	Roche
10	13/12/2019	Recarbrio (Imipenem; Cilastatin; Relebactam)	Merck
11	15/12/2019	Rinvoq (Upadacitinib)	AbbVie

Source: EMA

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 2020 Annual Summary of Clinical Trials in Ukraine Orange Paper is scheduled for April 2021.

About Synergy

Synergy Research Group is a contract research organization successfully operating in Russia, Kazakhstan, Ukraine and Canada since 2002.

From year to year our company is consistently in the TOP-10 of market leaders by the numbers of conducted clinical studies and enrolled patients.

The high recruitment rates of the emerging markets combined with innovative technology allows Synergy to conduct faster, more cost-effective studies without sacrificing quality for our clients.

We ensure the highest level of quality of SOPs and of final study data for all clinical studies conducted by our company. We're continuously working on improvements of our SOPs, study risk management and IT infrastructure – replacing outdated R&D strategies by novel, more efficient approaches to clinical research.