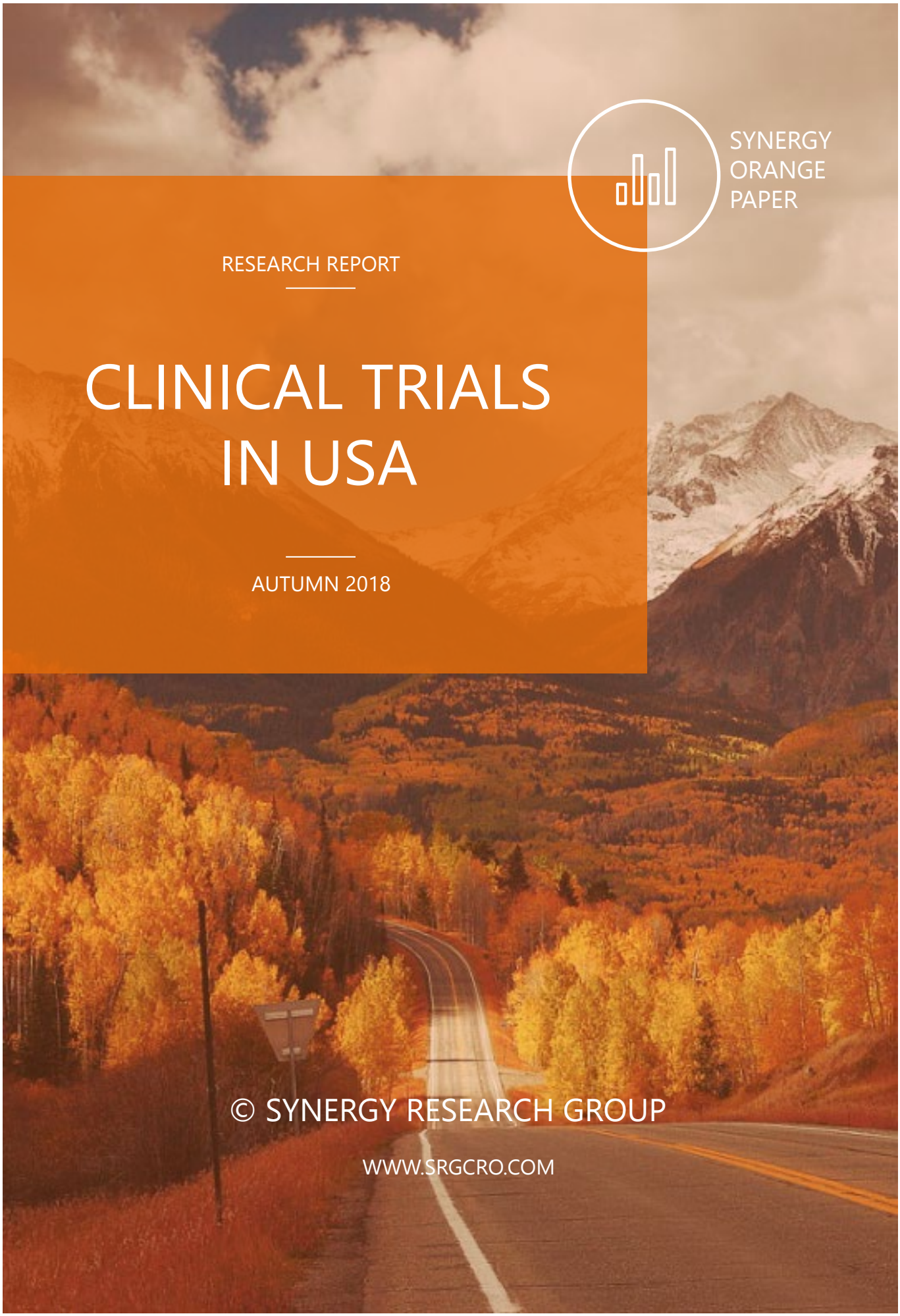

SYNERGY ORANGE PAPER

RESEARCH REPORT

CLINICAL TRIALS IN USA

AUTUMN 2018

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.

SYNERGY
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PAPER

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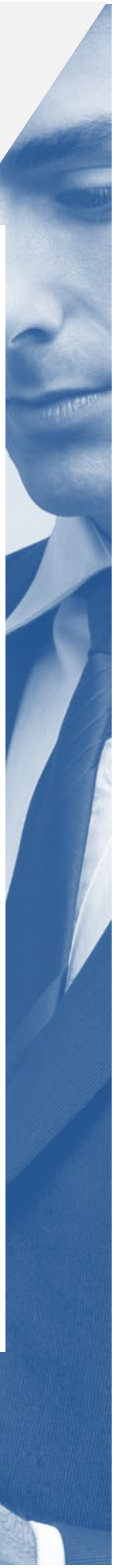
EXECUTIVE SUMMARY



During Q3 2018 the official FDA website showed approvals for initiation of 6,396 new clinical trials of all types worldwide, including local and bioequivalence studies. There were 2,076 studies approved in USA and 1,615 trials were approved in 17 leading European countries. This translates to worldwide overall year on year growth rates of 19% worldwide, 8% in USA and a 23% decline in 17 leading European countries by number of studies (we set a threshold of as minimum 20 Clinical trials conducted in Q3 2018 as including criteria for European countries).

Interventional clinical trials are the dominant type of research with 82% market share worldwide, 90% in USA and 82% in Europe. The most prevalent phase of clinical trials conducted worldwide by number of studies was Phase II.

In the USA the top-ten sponsors account for only 7% of total number of studies conducted in USA during this quarter although they account for 23% of all patients enrolled in these trials. In comparison, in Russia the ten largest pharmaceutical companies combined account for 29% of all clinical trials by number of studies and 49% of patients enrolled in these studies.

During Q3 2018 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) evaluated 21 new drugs. One drug was withdrawn, 20 drugs received positive opinions and were approved for marketing.

In the same quarter, the Center for Drug Evaluation and Research (CDER) of the FDA approved 13 new drugs; four of them were new molecular entities (NME); various improvements in existing pharmaceutical products.

Three top tech trends in the Pharmaceuticals industry in Q3 2018 were:

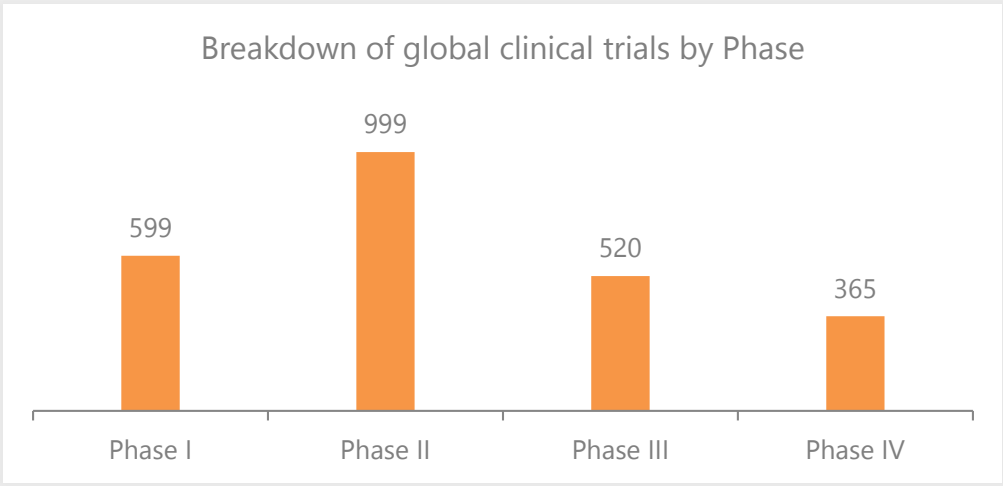
- Improving quality of Patient Relationship with patient-faced services like Medication Adherence apps, Telemedicine services and In-Home Diagnostic devices;
- Improving quality, speed and cost-efficiency in clinical trials with Risk Management solutions, Study Data Analysis tools and Study Compliance systems;
- Improving speed and cost-efficiency in Clinical Practice of Healthcare Providers with AI-powered automated Diagnostic tools and voice-powered Physician's Assistant tools.

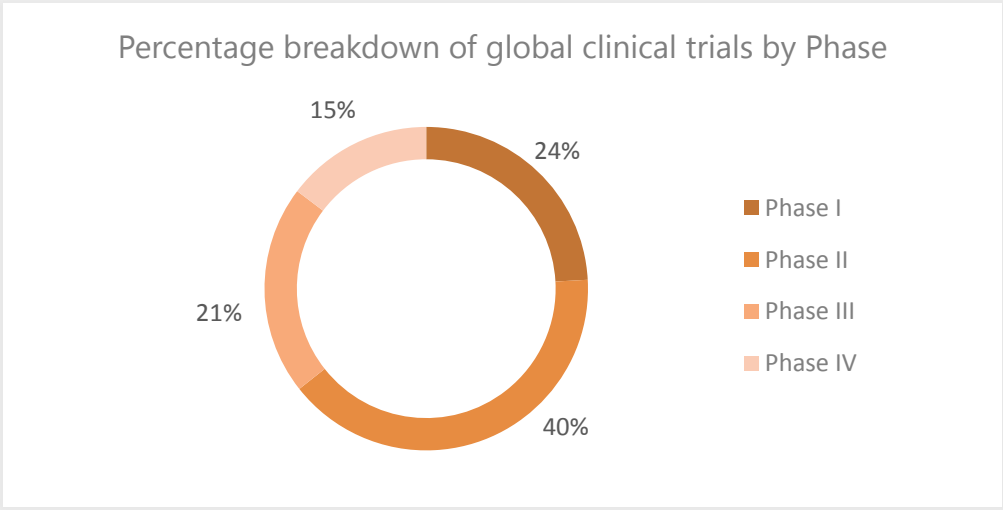
WORLDWIDE CLINICAL TRIALS

Trial Data

During Q3 2018 the official FDA website showed approvals for initiation of 6,396 new clinical trials of all types worldwide, including local and bioequivalence studies with an overall year on year growth rate of 19% driven in large by an increasing number of trials in developing countries.

Interventional study types identified as Phase (I- IV) were confirmed for 2,483 clinical trials. The most prevalent phase of clinical trials on a global scale was Phase II. The combined market share of USA and European countries reached 57% by the number of initiated studies; Russia accounts for only 3% of the global clinical trials market. Interventional clinical trials are the dominant type of research with 82% market share.

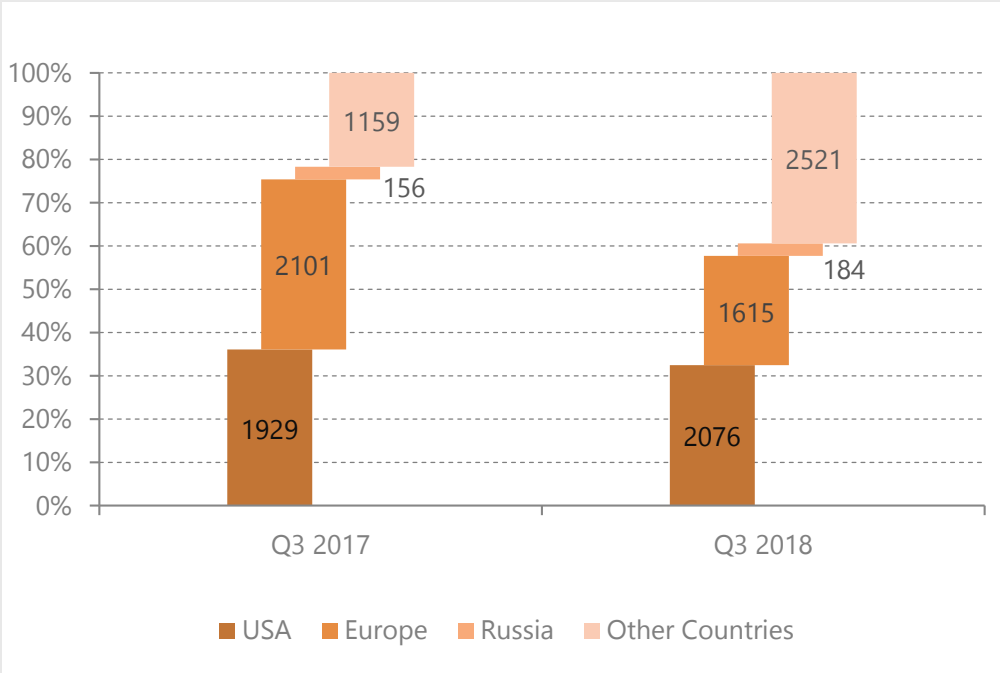


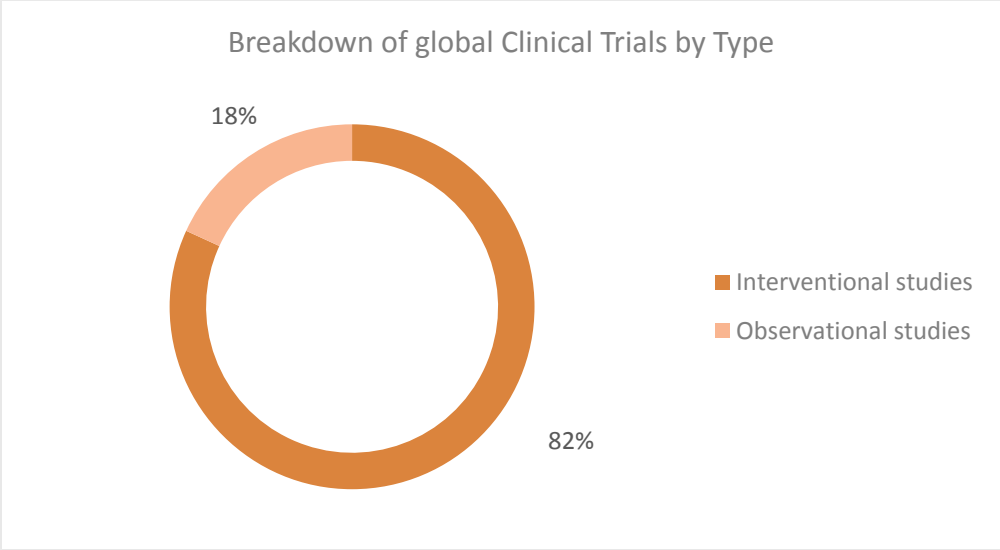


Breakdown by region of origin

The proportions between different regions (USA, Europe, Russia, Other Countries) for trials conducted in Q3 2018 changed in comparison to Q3 2017.

The share of Clinical Trials conducted in Russia stayed at 3% in comparison with Q3 2017.

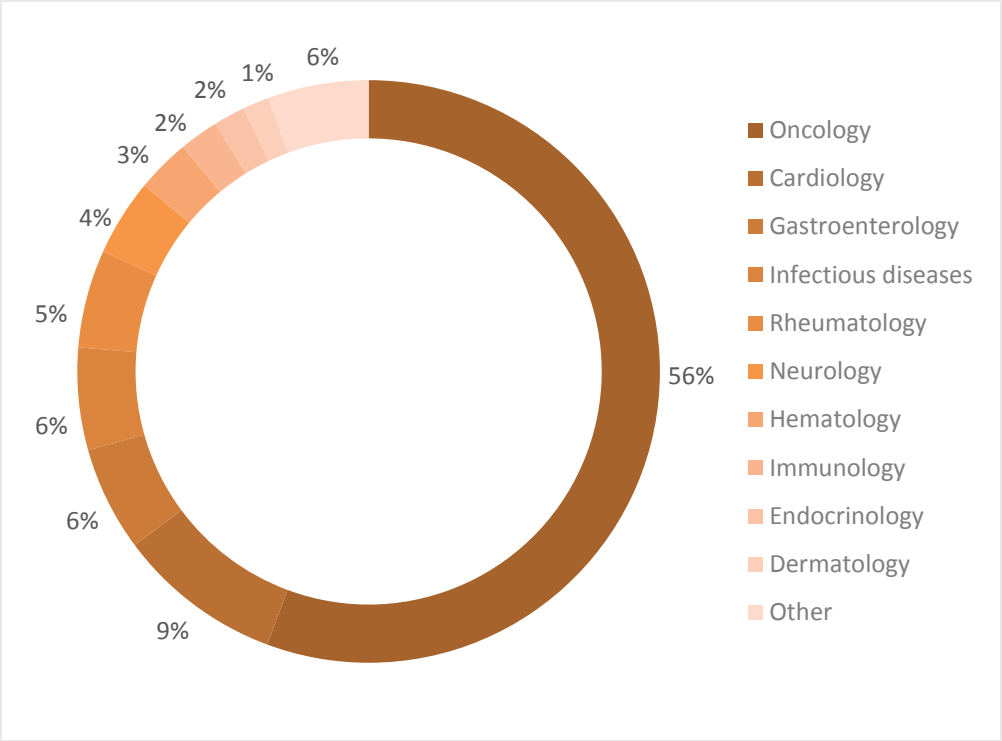




Therapeutic areas of clinical trials worldwide

The largest number of studies were initiated in Oncology (1382 studies), Cardiology (228 studies), Gastroenterology (144), Infectious diseases (141) and Rheumatology (135 studies).

More than one therapeutic area could be assigned to a trial. BE studies were not included in any therapeutic area group.



WORLDWIDE CLINICAL TRIALS

Sponsor Data

"Team members" comprising the TOP-TEN global sponsors of clinical trials worldwide has remained static for the past 5 years – this fact may be explained by the substantial and continuously rising amounts of investments required for research and development of new drugs.

It's remarkable that the combined market power of these leading pharmaceutical corporations is about 10% of the patient population engaged in interventional clinical trials where a study phase has been identified.

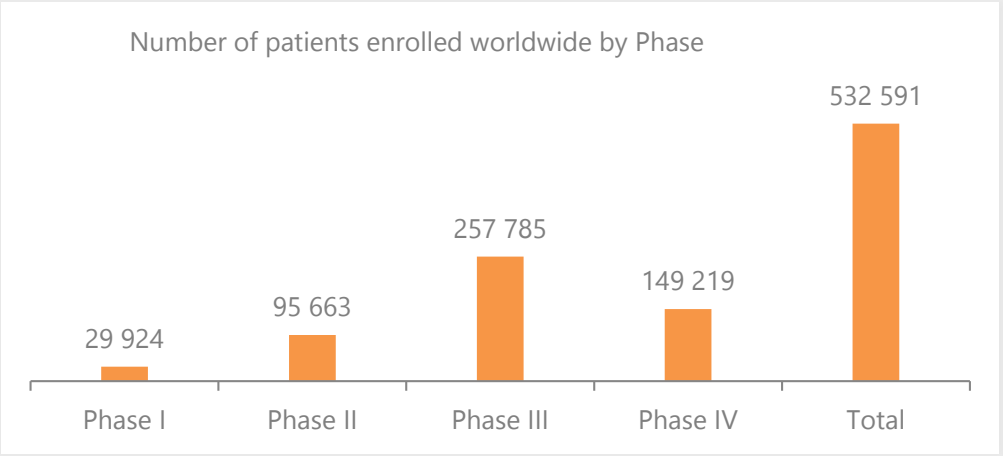
№	Company Name	No. studies	No. patients
1	Novartis	32	7 033
2	Pfizer	23	3 302
3	Hoffman-La Roche	21	15 129
4	Abbvie	16	4 765
5	Merck	14	8 998
6	GlaxoSmithKline	14	13 045
7	Janssen	12	1 010
8	Eli Lilly	11	3 164
9	Boehringer Ingelheim	11	654
10	AstraZeneca	11	6 032
Combined market share of top-10 companies		**3%**	**10%**

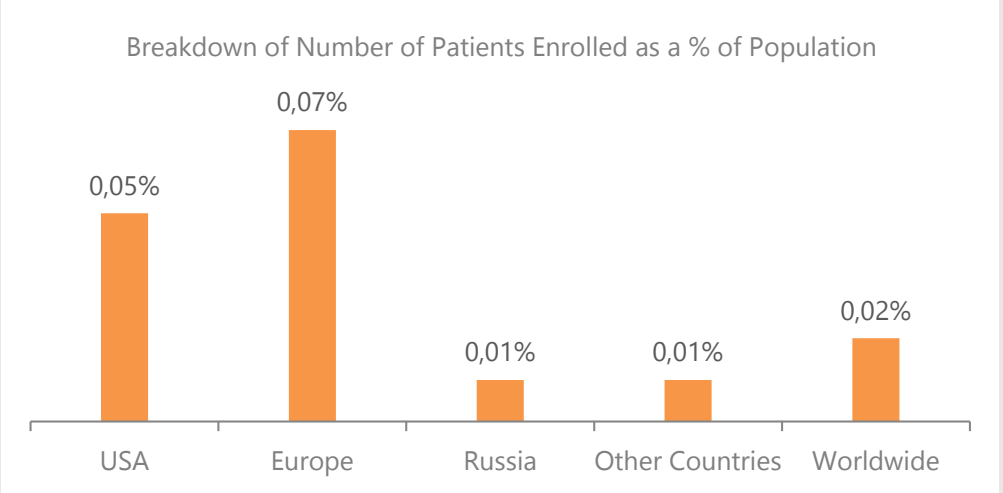
WORLDWIDE CLINICAL TRIALS

Patient Data

The worldwide population of patients enrolled in clinical trials of all types in Q3 2018 reached 1.2 million people. Six hundred thousand of these patients are enrolled in interventional trials with an identified study phase (I – IV). The majority of patients are enrolled in Phase III trials, with the largest growth in global patient population being in Europe.

However, the share of patients participating in clinical trials remains extremely low in comparison with the overall size of population – approximately 0,02% Worldwide and 0,01% in Russia. The prevalent therapeutic areas of clinical trials worldwide are Oncology and Cardiology.



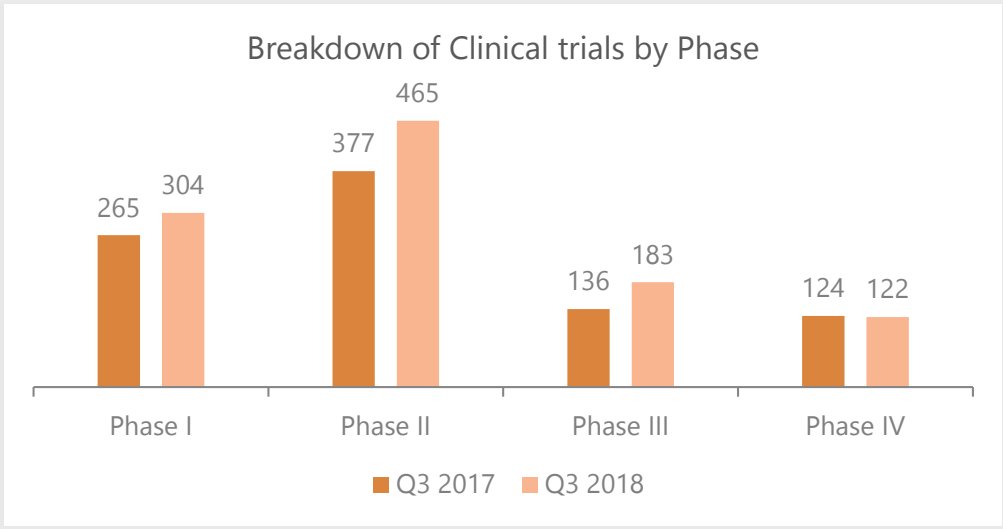


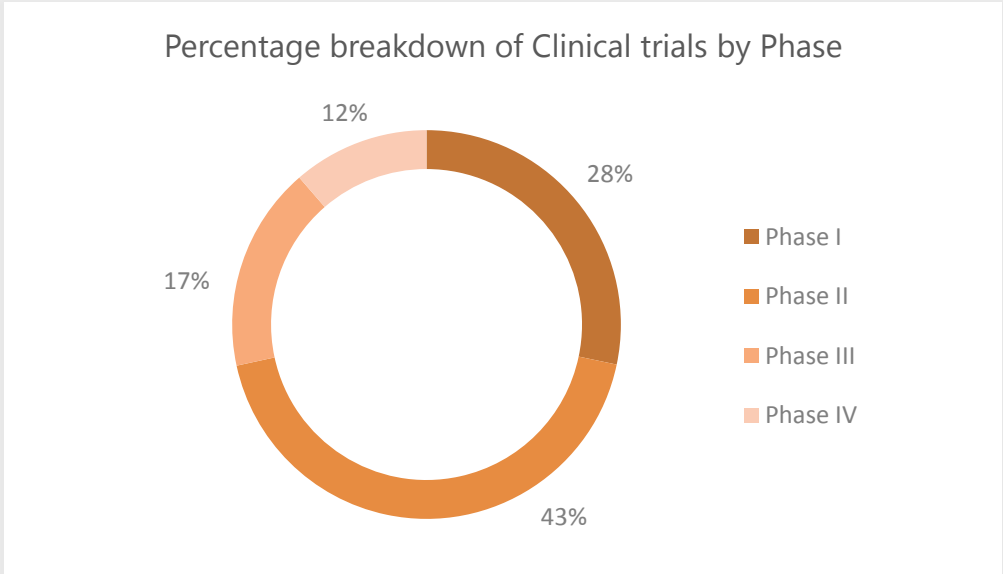
CLINICAL TRIALS IN USA

Trial Data

During Q3 2018 the FDA approved the initiation of 2,076 new clinical trials of all types in the USA, including local and bioequivalence studies with an overall year on year growth rate of 8%. The most prevalent type of clinical trials conducted in US sites were interventional studies with a 90% market share.

The most frequent phase of clinical trials conducted across US sites by number of studies was Phase II.

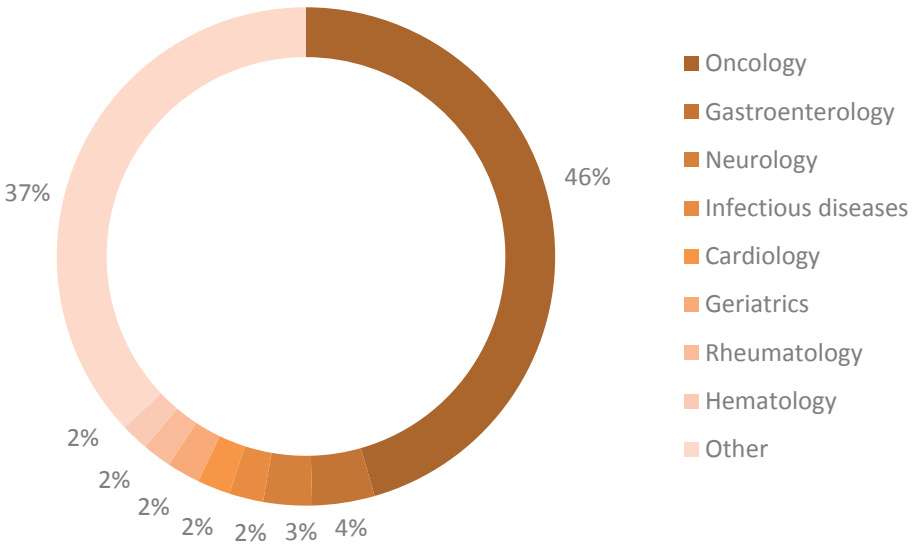




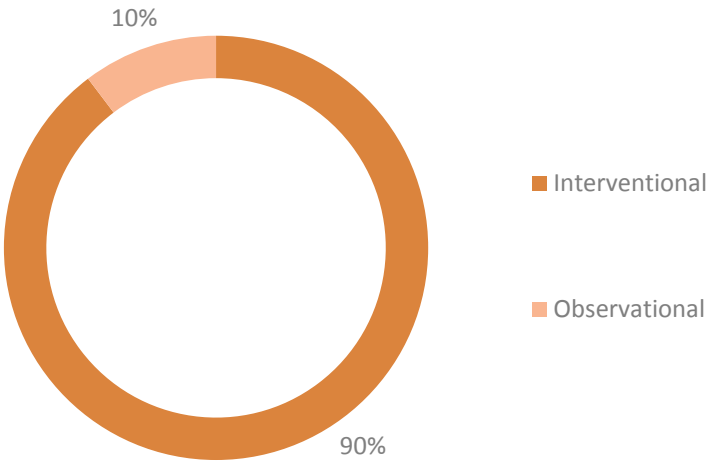
The largest number of clinical trials initiated in the USA in Q3 2018 were related to Oncology (867 studies), Gastroenterology (77 studies), Neurology (60 studies), Infectious diseases (42 studies), Cardiology and Geriatrics (42 studies each).

The majority of Clinical trials conducted in the USA in Q3 2018 were Interventional.

Therapeutic areas of Clinical trials in USA in Q3 2018



Percentage breakdown of Interventional vs. observational trials



CLINICAL TRIALS IN USA

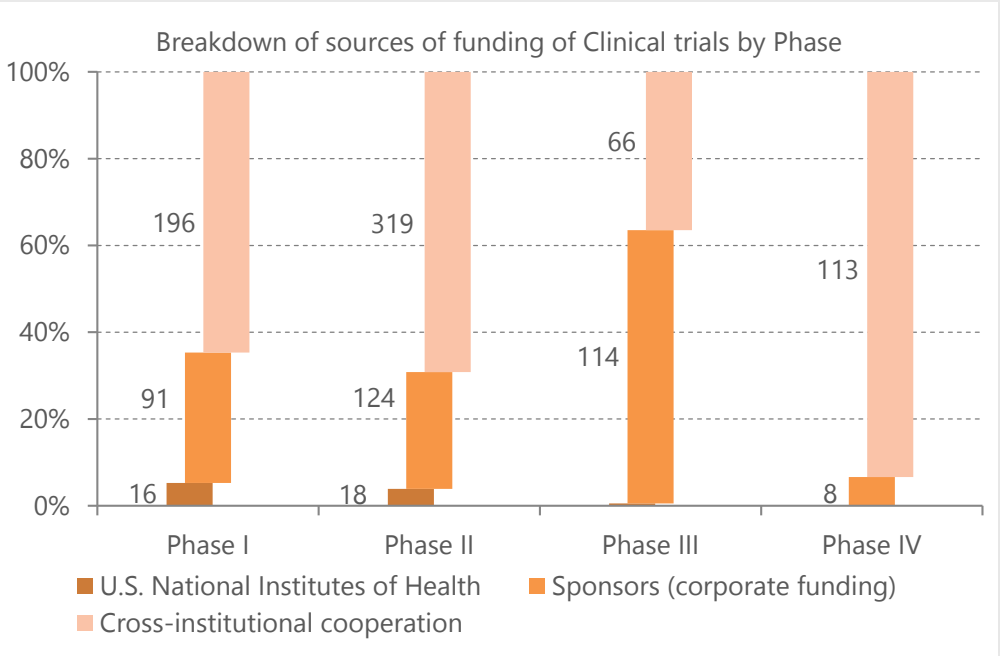
Sponsor Data

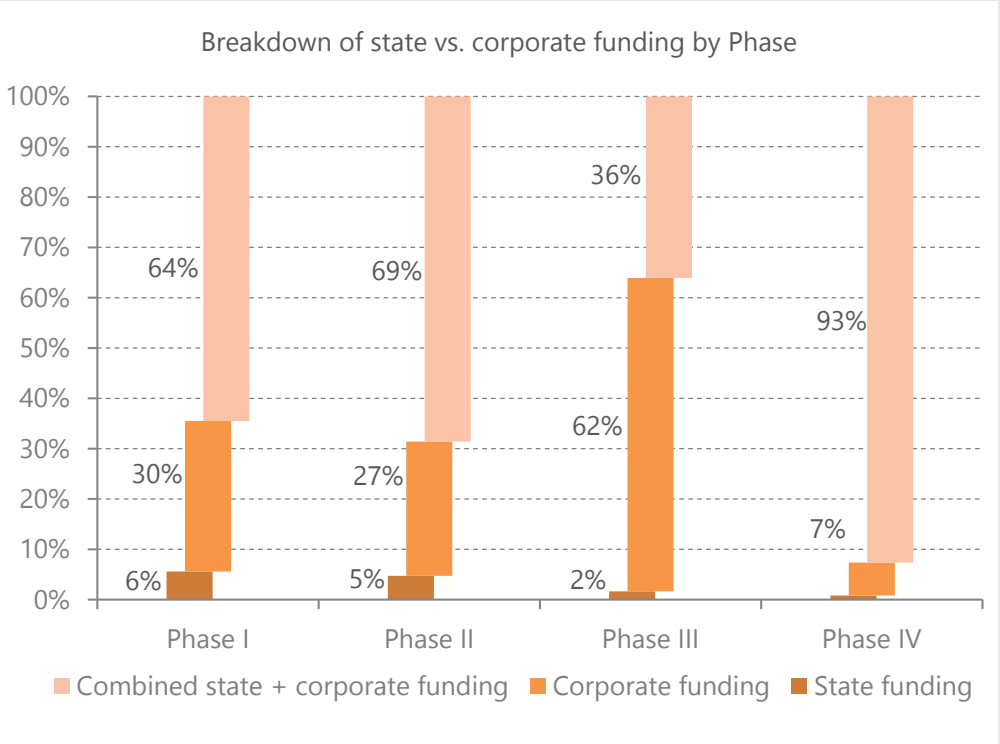
The most prevalent country of origin of pharmaceutical companies sponsoring clinical trials initiated in the USA in Q3 2018 was the USA. The headquarters of the most active foreign companies sponsoring clinical trials initiated in the US are located primarily in Europe - in Switzerland (Hoffmann-La Roche), UK (AstraZeneca) and Denmark (Novo Nordisk).

Studies initiated by the top-10 companies accounted for 3% of all studies initiated in the USA in Q3 2018, and for 10% of all patients enrolled across those studies.

№	Company Name	No. studies	No. patients
1	AbbVie	12	4 503
2	Hoffman-La Roche	11	11 163
3	Merck	10	6 668
4	Pfizer	9	2 618
5	Janssen	8	828
6	Bristol-Myers Squibb	7	2 834
7	AstraZeneca	6	5 762
8	Eli Lilly	6	2 834
9	Incyte Corporation	6	379
10	Novo Nordisk	5	3 062
Combined market share of top-10 companies		**3%**	**10%**

It's quite remarkable that the largest amount of investments in clinical trials of new drugs in the USA is a result of cross-institutional partnerships between the pharma business and state institutions (e.g. National Institute of Health, U.S. Federal agencies, etc.)

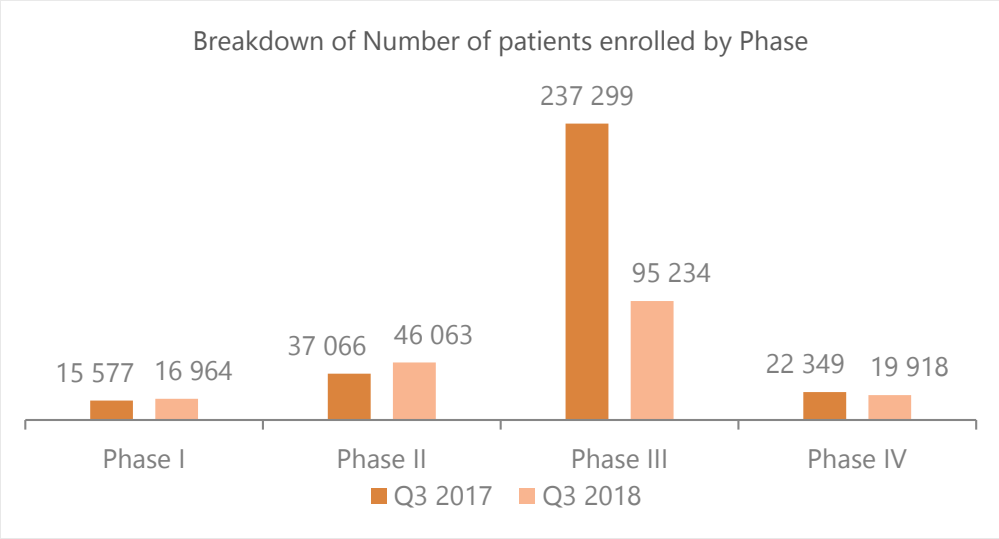


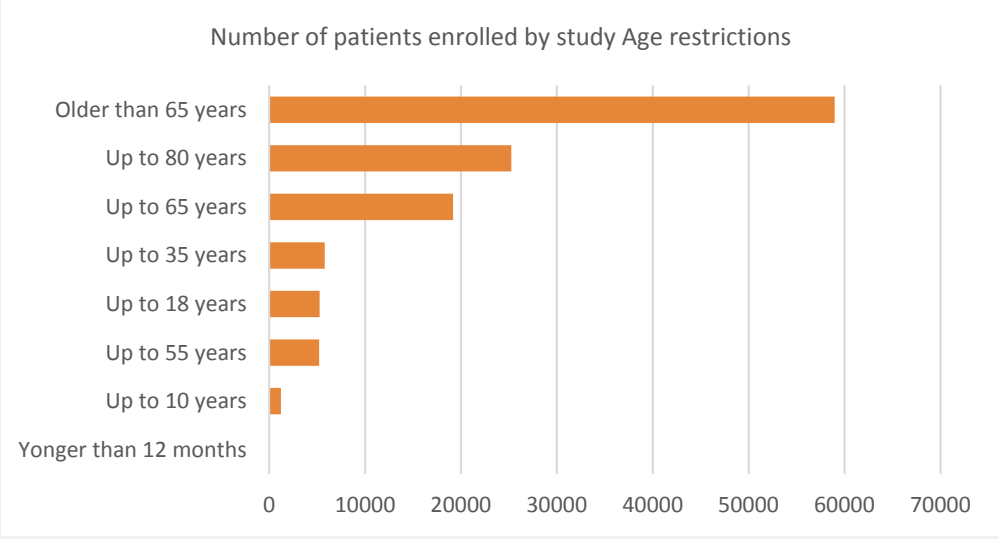


CLINICAL TRIALS IN USA

Patient Data

The overall number of patients involved in clinical trials initiated in the USA in Q3 2018 reached 178,179 people however, this remains extremely low in comparison with the size of the US population – approximately 0,05% of the population in the USA participate in clinical trials with an identified study Phase (I-IV). The most prevalent phase of clinical trials by number of participating patients is Phase II. The largest patients' cohorts by age were "older than 65 years" and "up to 80 years".





Regulatory Data

During Q3 2018 the Center for Drug Evaluation and Research (CDER) of the FDA approved 13 new drugs as new molecular entities (NME); other approvals concerned various improvements in existing pharmaceutical products. Four of these 13 drugs were tested in clinical trials involving Russian sites.

Appr.date	Drug (active ingredient)	Company
07/13/2018	Tpoxxnda (Tecovirimat)	Siga Technologies
07/20/2018	Krintafelnda (Tafenoquine Succinate)	GlaxoSmithKline
07/20/2018	Tibsovonda (Ivosidenib)	Agios Pharms
07/23/2018	Orilissanda (Elagolix Sodium)	AbbVie
07/27/2018	Omegavennda (Fish Oil Triglycerides)	Fresenius Kabi
07/31/2018	Mulpletanda (Lusutrombopag)	Shionogi
08/10/2018	Galafoldnda (Migalastat Hydrochloride)	Amicus Theraps
08/10/2018	Annoveranda (Ethinyl Estradiol; Segesterone Acetate)	Population Council
08/10/2018	Onpattronda (Patisiran Sodium)	Alnylam Pharms
08/20/2018	Diacomitnda (Stiripentol)	Biocodex
08/27/2018	Xeravanda (Eravacycline Dihydrochloride)	Tetraphase Pharms
08/30/2018	Pifeltronda (Doravirine)	Merck

Inspection Data

According to official FDA website, 2 FDA inspections were conducted at U.S. investigative sites during Q3 - 2018. One inspection resulted in a No Action Indicated (NAI) outcome, and one inspection resulted in a Voluntary Action Indicated (VAI) outcome.

TECH TRENDS IN PHARMACEUTICALS AND HEALTHCARE INDUSTRIES

Patient Centricity

Streamlined tech disruption is occurring everywhere these days. The Pharmaceuticals and Healthcare industries are no exception from this global trend, but strong state authorities' regulations in these areas create a number of difficulties for tech startups trying to improve the efficiency of patient-to-service transaction processes. Nevertheless, beginning from early 2012, there have been a multitude of ambitious and innovative tech startups aiming to improve patient experience, diagnostics and treatment efficiency, exploring new insights in data analytics and reducing transactional costs for the Pharmaceutical and Healthcare industries.

The most promising areas of tech disruption in the Pharmaceuticals and Healthcare industries are Patient-faced services and new tech for clinical trials and healthcare providers.

Medication Adherence

Medication adherence app maker **Medisafe** has announced a partnership with **Boehringer Ingelheim** following a successful pilot program with their Pradaxa drug. A special version of Medisafe app incorporates Pradaxa-specific educational information which helps patients to comply with prescribed medication schedules.

Boehringer Ingelheim and adherence app maker **HealthPrize Technologies** announced that the digital adherence support program RespiPoints will be expanded to any patient who is taking certain Boehringer Ingelheim medications, including some available in the Respimat inhaler. This experience includes free reporting of daily adherence, verifying monthly medication refills, reading educational materials as well as completing quizzes and surveys.

Telemedicine

Leading UK telemedicine provider **Babylon Health** aims to double its London team of scientists and engineers by the end of this year, targeting to expand its capabilities and apply artificial intelligence to assist patients with the management of chronic diseases. The company proved that its AI had demonstrated the ability to provide health advice "on-par with practicing clinicians" in an MRCGP assessment in June. The MRCGP exam is the final test for trainee General Practitioners (GPs), set by the UK Royal College of General Practitioners (RCGP). Trainee GPs who pass this assessment have demonstrated their competence and clinical skills to a level which is sufficiently high enough for them to undertake independent practice.

U.S. telemedicine provider **Teladoc Health** now supports more than 20 languages in corporate services for multinational customers and become available in 24-7 mode. Physicians working at Teladoc will also be equipped with the cultural background and local health system know-how necessary when taking on non-emergency cases in various regions.

In-Home Diagnostic Devices

Inui Health, formerly Scanadu, announces an FDA-cleared home urine testing platform. The smartphone-connected system can perform five different tests (protein, glucose, ketone, leukocyte and nitrite concentration in urine) that could help diagnose UTIs, diabetes, and kidney diseases

Clinical Trials

Risk Management in Clinical Trials

Quanticate, a global data-focused CRO, has announced its partnership with risk-based monitoring software vendor **CluePoints** as part of its new Data Quality Oversight service. Quanticate's new service enables risk-based centralized statistical monitoring in response to the amendments to the ICH Good Clinical Practice (GCP) E6(R2) guidelines.

By partnering with CluePoints, Quanticate will offer customers the creation of statistical analytics reports on key risk indicators and comprehensive risk signals across all clinical and operational data which enable sponsors to interpret findings to assess the integrity of their trial sites and associated data.

Leading global CRO **Iqvia** is expanding its portfolio of its clinically-focused tech solutions to automate clinical trial processes and reduce patient burden with **Salesforce** machine learning solutions.

Study Data Analytics

U.S. National Institute of Health (NIH) deals with leading big data analysis platform **Palantir** to streamline health research with a $7M contract.

A 'subsidiary' of NIH, the National Center for Advancing Translational Sciences (NCAT) and its related groups aims to use the tech to automatically aggregate research data from public and private sources into a single interface for more streamlined analysis. This automatic platform will help the center's researchers interpret data that was previously disparate as part of a collective whole, and thereby achieve new insights.

Study Compliance

Deloitte acquires risk-based platform **QSpace** designed to manage the GxP validation life cycle of GxP and non-GxP computerized systems, manufacturing equipment, lab instruments and utility systems. It's Title 21 CFR Part 11 compliant E-signatures and configurable review workflows allow for an improved collaboration and accountability became the part of Deloitte services.

Healthcare Providers

AI Diagnostic Tools

Google DeepMind's AI can detect over 50 eye diseases as accurately as a doctor. The software is based on established principles of deep learning, which uses algorithms to identify common patterns in data and was trained on nearly 15,000 OCT scans from some 7,500 patients.

The system analyzes 3D scans of the retina, identifies dozens of common eye diseases from 3D scans and then recommends the patient for treatment. In a test where the AI's judgments were compared with diagnoses by a panel of eight doctors, the software made the same recommendation more than 94 percent of the time.

Digital pathology startup **Proscia** lands $8.3 M in a Series A funding round. The company develops digital pathology software and AI applications for cancer diagnosis.

The use of AI in diagnosis has been on the rise. In April the FDA granted **IDx** the first De Novo clearance for an AI-based software system for the autonomous detection of diabetic retinopathy in adults who have diabetes.

Physician's Assistants

Wearable, voice-powered doctor's assistant **Notable** raises $13.5M in a Series A funding to further develop its wearable AI voice assistant for physicians.

The platform combines AI and voice recognition technology to capture information from a doctor's visit. It can pick up on dictations and orders and can recommend the appropriate billing codes. Then the data from the visit is automatically entered into the EHR using secure robotic processing automation.

Voice-powered AI physician assistants are on the rise. In May, **Robin Healthcare**, another voice-enabled AI device designed to help doctors and clinicians write clinical notes, emerged from stealth mode. Additionally, voice-enabled doctor assistant **Suki** raised $20 million in the spring.

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.