Meds
PIPELINE MONITOR 2022

NPDUIS
National Prescription Drug Utilization Information System

Patented Medicine Prices Review Board
Conseil d'examen du prix des médicaments brevetés

Canada

Published by the Patented Medicine Prices Review Board
June 2023

Meds Pipeline Monitor 2022 is available in electronic format on the PMPRB website.
Une traduction de ce document est également disponible en français sous le titre :
L'Observateur des médicaments émergents 2022.

Patented Medicine Prices Review Board
Standard Life Centre
Box L40
333 Laurier Avenue West
Suite 1400
Ottawa, ON K1P 1C1

Tel.: 1-877-861-2350
TTY 613-288-9654

Email: PMPRB.Information-Renseignements.CEPMB@pmprb-cepmb.gc.ca
Web: www.pmprb-cepmb.gc.ca

ISSN 2562-3834
Cat. No.: H79-5E-PDF

Suggested citation: Patented Medicine Prices Review Board. (2023). *Meds Pipeline Monitor, 2022*. Ottawa: PMPRB.

About the PMPRB

The Patented Medicine Prices Review Board (PMPRB) is an independent quasi-judicial body established by Parliament in 1987. The PMPRB has a dual regulatory and reporting mandate: to ensure that prices at which patentees sell their patented medicines in Canada are not excessive; and to report on pharmaceutical trends of all medicines and on research and development spending by patentees.

The NPDUIS Initiative

The National Prescription Drug Utilization Information System (NPDUIS) is a research initiative established by federal, provincial, and territorial Ministers of Health in September 2001. It is a partnership between the PMPRB and the Canadian Institute for Health Information (CIHI).

Pursuant to section 90 of the *Patent Act*, the PMPRB has the mandate to conduct analysis that provides decision makers with critical information and intelligence on price, utilization, and cost trends so that Canada's healthcare system has more comprehensive and accurate information on how medicines are being used and on sources of cost pressures.

The specific research priorities and methodologies for NPDUIS are established with the guidance of the NPDUIS Advisory Committee and reflect the priorities of the participating jurisdictions, as identified in the NPDUIS Research Agenda. The Advisory Committee is composed of representatives from public drug plans in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, Yukon, the Non-Insured Health Benefits Program (NIHB), and Health Canada. It also includes observers from CIHI, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Ministère de la Santé et des Services sociaux du Québec (MSSS), the pan-Canadian Pharmaceutical Alliance (pCPA) Office, and the Canadian Drug Agency Transition Office (CDATO).

Acknowledgements

This report was prepared by the Patented Medicine Prices Review Board (PMPRB) as part of the National Prescription Drug Utilization Information System (NPDUIS) initiative.

The PMPRB wishes to acknowledge the members of the NPDUIS Advisory Committee for their expert oversight and guidance in the preparation of this report. Please note that the statements and findings for this report do not necessarily reflect those of the members or their organizations.

We gratefully acknowledge Patricia Carruthers-Czyzewski, BScPhm, MSc, Sintera Inc. for providing pharmaceutical expertise and for her contribution to the scientific analysis.

Appreciation goes to Allison Carey for leading this project, and Tanya Potashnik and Kevin Pothier for their oversight in the development of the report. The PMPRB also wishes to acknowledge the contribution of the editorial staff, Shirin Paynter.

Disclaimer

NPDUIS operates independently of the regulatory activities of the Board of the PMPRB. The research priorities, data, statements, and opinions expressed or reflected in NPDUIS reports do not represent the position of the PMPRB with respect to any regulatory matter. NPDUIS reports do not contain information that is confidential or privileged under sections 87 and 88 of the *Patent Act*, and the mention of a medicine in an NPDUIS report is not and should not be understood as an admission or denial that the medicine is subject to filings under sections 80, 81, or 82 of the *Patent Act* or that its price is or is not excessive under section 85 of the *Patent Act*.

Although this information is based in part on data obtained under license from GlobalData and the MIDAS® Database proprietary to IQVIA Solutions Canada Inc. and/or its affiliates ("IQVIA"), the statements, findings, conclusions, views, and opinions expressed in this report are exclusively those of the PMPRB and are not attributable to either GlobalData or IQVIA.

EXECUTIVE SUMMARY

Meds Pipeline Monitor (MPM) is a horizon scanning report that features a selection of new medicines undergoing clinical evaluation or in pre-registration that may have an impact on future clinical practice and drug spending in Canada.

This edition expands the review for the selected medicine candidates in Phase III clinical trials or pre-registration to include information on other drugs in Phase II that share the same mechanism of action or indication. Having insight into other drugs under investigation (i.e., in Phase II) may provide additional information on the potential place in therapy for these pipeline candidates. Medicines in Phase III clinical trials or pre-registration are selected as candidates for the 'new medicines' list if they have the potential to address an unmet therapeutic need, offer a novel mechanism of action or therapeutic benefit over existing therapies, or treat a serious condition. The medicines in Phase II are also examined to identify other drugs that are in earlier phases of the pipeline that contain the same indication or mechanism of action as the selected medicine candidates.

The report collects data from two main sources: GlobalData's Healthcare database, which identifies medicines currently undergoing clinical evaluation, and Health Canada's Drug and Health Product Submissions Under Review Lists, which provide information on new medicines under review in Canada.

Highlights of the *Meds Pipeline Monitor 2022*

- In 2022, the pipeline contained over 9,000 new medicines in various stages of clinical development, compared to just under 8,500 the year before. The number of drugs in the pipeline is increasing by an average of 11% per year since 2018.
- Oncology continues to dominate the therapeutic mix in 2022, with cancer treatments representing almost one third (30%) of medicines in all phases of clinical trials. Treatments for infectious diseases held the second largest share of the pipeline, at 15%, due to the increased number of medicines for the treatment of COVID-19.
- Nearly one third (31%) of medicines in Phase III clinical trials or pre-registration had an early orphan designation approved through the US FDA or the EMA, which is consistent with the increasing trend in the prevalence of orphan-designated medicines entering the pharmaceutical market.
- Trends in the 2022 pipeline include a growing number of novel gene and cell therapies that are expanding to larger patient groups (e.g., Duchenne muscular dystrophy). The biosimilars pipeline is also expanding to therapeutic areas including asthma (omalizumab), bone health (denosumab), and myocardial infarction (tenecteplase).
- Twenty-eight new medicines including five new gene and cell therapies were selected for the 2022 MPM new medicines list based on their potential to impact the Canadian healthcare system. Nine of the medicines listed in this year's report have forecasted global annual revenues of over US $1 billion by 2028, one of which was approved by Health Canada in February 2023.
- Of the 42 new and retained medicines listed in the previous edition (MPM 2021), six received market authorization, 25 were retained on this year's list as they continued to satisfy the selection criteria, and 11 were removed as their clinical trials were discontinued or they no longer meet the selection criteria.
- As of September 2022, 550 vaccines and therapies were undergoing clinical evaluation globally for the prevention and treatment of COVID-19. Health Canada is reviewing 14 new and supplemental drug submissions for the prevention and treatment of COVID-19.

TABLE OF CONTENTS

LIST OF TERMS

For the purpose of this report, the following terms and associated definitions apply.

Cell therapy:
The transplantation of human cells to replace or repair damaged tissue and/or cells.

Clinical efficacy:
The maximum response achievable from a medicine in research settings and the capacity for sufficient therapeutic effect in clinical settings.[i]

Gene therapy:
A technique for the treatment of genetic disease in which a gene that is absent or defective is replaced by a healthy gene, as defined by Health Canada.[ii]

Market authorization:
The process of approval for a medicine to be marketed in a given country. In Canada, market approval is granted following a substantive scientific evaluation of a product's safety, efficacy, and quality, as required by the *Food and Drugs Act* and *Regulations*.[iii]

Medicinal ingredient:
A chemical or biological substance responsible for the claimed pharmacologic effect of a drug product. Sometimes referred to as a molecule, active substance, or active ingredient.[iv]

Medicine:
A broad term encompassing both the final drug product and medicinal ingredient(s); this encompasses chemically manufactured active substances and biologics, including gene therapies. Medicines are reported at the medicinal ingredient level and can refer to a single ingredient or a unique combination of ingredients.

Patent evergreening:
The acquisition of additional patents for minor modifications to an existing pharmaceutical product in order to extend the patent life of the medicine (e.g., new delivery systems, new dosages, new uses, new combinations or new forms).[v]

New medicine:
A medicinal ingredient that has not previously received market authorization by a regulator.[iv]

Orphan medicine:
A medicine used to treat a rare disease. For the purposes of this study, orphan medicines are defined as having an orphan designation granted by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for the relevant indication.

PHASES OF CLINICAL TRIALS

Phase I:
These trials test an experimental medicine on a small group of people for the first time. The purpose is to look at the medicine's safety, determine a safe dosage range, and monitor if there are any side effects.

Phase II:
In this phase, the medicine is given to a larger group of people (usually 100 or more) to gather data on how well the medicine works to treat a disease or condition, check its safety on a wider range of people, and determine the best dose.[vi]

Phase III:
These controlled or uncontrolled trials are conducted after preliminary evidence suggesting efficacy of the medicine has been demonstrated. They are intended to gather additional and confirmatory information about the clinical efficacy and safety of the medicine under the proposed conditions of use.[ii] Phase III trials are usually randomized with double-blind testing in several hundred to several thousand patients.

Pre-registration:
A medicine is in the pre-registration phase once all the necessary clinical trials have been completed and it is waiting for registration or approval for use by a governing body.[vii]

[i] Holford NHG, Sheiner LB. 1981. Understanding the dose-effect relationship: *Clinical application of pharmacokinetic-pharmacodynamic models.* Clin. Pharmacokinet. 6 (6): 429–453. doi: 10.2165/00003088-198106060-00002.
[ii] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/health-canada-clinical-trials-database/glossary.html
[iii] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products.html
[iv] http://www.pmprb-cepmb.gc.ca/en/npduis/view.asp?ccid=1310&lang=en
[v] https://academic.oup.com/jlb/article/5/3/590/5232981, https://pubmed.ncbi.nlm.nih.gov/35543377/
[vi] https://www.canada.ca/en/health-canada/services/clinical-trials.html
[vii] http://www.appliedclinicaltrialsonline.com/are-phase-labels-still-relevant

INTRODUCTION

This edition of the *Meds Pipeline Monitor* (MPM) features a selection of new medicines in Phase III clinical trials or pre-registration that have the potential to impact clinical practice and drug spending in Canada.

The methodology, which is detailed in the next section, uses a specific set of criteria to identify a list of new medicines in the pipeline from the GlobalData Healthcare database, as well as a list of medicines currently under review from Health Canada's Drug and Health Product Submissions Under Review (SUR) Lists. The new medicines listed in this report are selected based on a scientific review of the literature and clinical trial outcomes to determine if the medicine may impact the Canadian healthcare system by: addressing an unmet therapeutic need; offering a novel mechanism of action or therapeutic benefit over existing therapies; or treating a serious condition. Medicines reported in previous editions of the MPM are also reviewed and updated in this report. This report also provides an update on the medicines in last year's edition that have since received market authorization by either the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), or Health Canada. Likewise, the new medicines featured in this report will be monitored in future editions of the MPM to identify candidates that successfully enter the market.

To provide context for the selection of medicines, the MPM includes a snapshot of the number of drugs in each clinical phase of the pipeline year over year (2018-2022), and a breakdown of the various therapeutic areas for each phase of clinical development. This edition of the report also highlights select vaccines and other medicines undergoing clinical trials for the prevention and treatment of COVID-19, in global markets as well as in Canada. The medicines assessed for this portion of the analysis include new therapies as well as previously marketed treatments for other indications that have been repurposed for the treatment of COVID-19.

Meds Pipeline Monitor is a companion publication to *Meds Entry Watch*, which analyzes the market launch patterns of newly approved medicines in Canada and internationally. Together, these two PMPRB reports monitor the market continuum of late-stage pipeline medicines and new approvals, providing decision makers, researchers, patients, clinicians, and other stakeholders with information on the emerging medicines and evolving cost pressures.

METHODOLOGY

Snapshot of the Pipeline

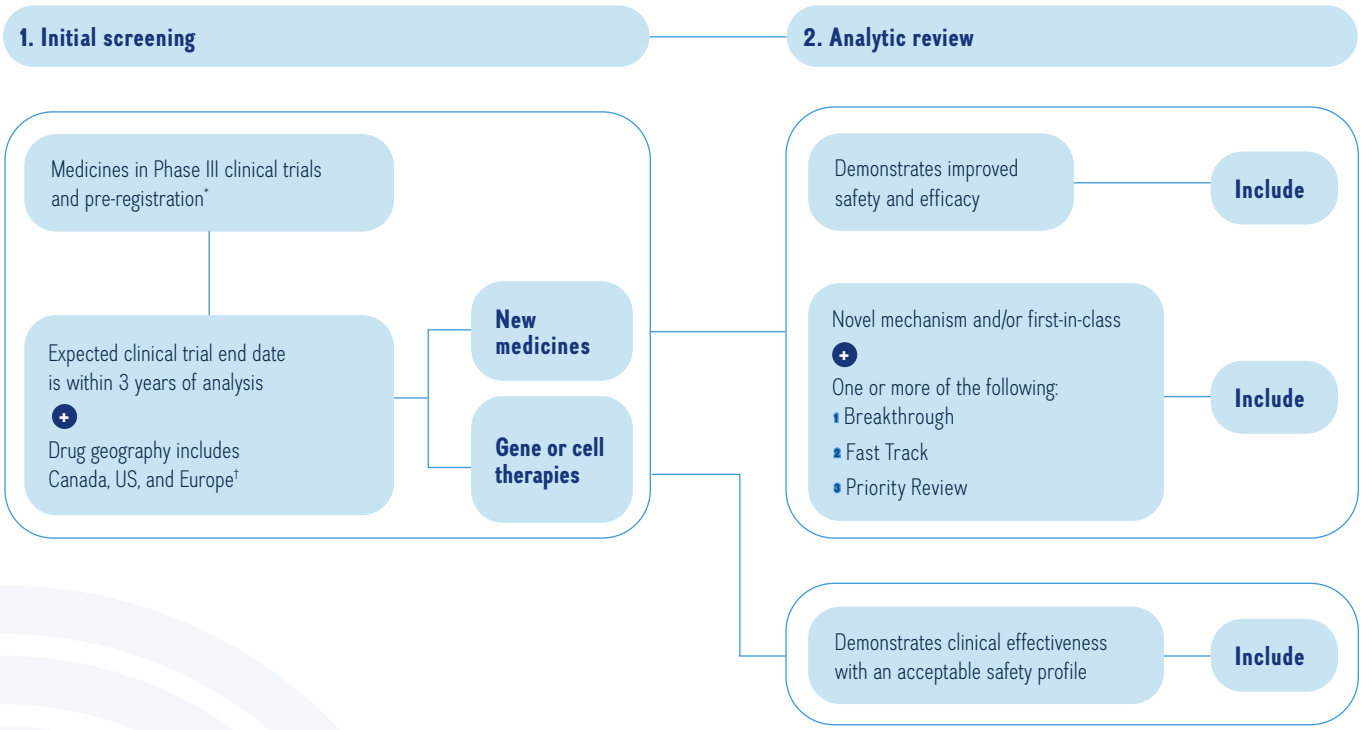
The snapshot of the 2022 pipeline identifies the composition of medicines in various phases of clinical development. For the purpose of this analysis, a full list of pipeline medicines was retrieved from GlobalData's Healthcare database in September 2022 and the selected medicine candidates for this year's report have been validated as of March 30, 2023.

New medicinal ingredients are identified as those with no prior approvals through the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), or Health Canada. The distribution of new medicines by therapeutic area corresponds to the indication under evaluation, as reported by GlobalData. Note that a single new medicine may be undergoing multiple clinical studies for separate indications.

Meds Pipeline Monitor

The MPM selects new medicines in Phase III clinical trials or pre-registration in Canada, the United States, and Europe. Many of the pipeline candidates are first-in-class or represent novel mechanisms for treatment in a specific therapeutic area. For this reason, this report includes additional review on other drugs undergoing Phase II clinical evaluation that share the same indication or mechanism of action. Pipeline medicines are selected for inclusion using a two-stage process (Figure 1). The initial screening stage selects medicines in the late phases of clinical evaluation, while the analytic review stage involves a more rigorous appraisal of each potential candidate to identify medicines that may have a significant clinical and budgetary impact.

FIGURE 1
Selection process for medicines featured in the MPM



* In pre-registration with the US Food and Drug Administration (FDA).

† Has Phase III clinical trials in Canada, the United States, or geographic Europe (excluding Russia and Turkey).

Stage 1: Initial screening

GlobalData's Healthcare database is used to identify a list of medicines undergoing Phase III clinical trials or in pre-registration. These medicines serve as the basis for the initial screening stage.

The drug geography, defined as the geographical region or country in which the medicine is either marketed or in pipeline development, is restricted to Canada and other countries with similar regulatory and approval processes: the US and geographic Europe (excluding Russia and Turkey). Only new medicinal ingredients that have adequate data that supports increased efficacy and safety from clinical trials are considered as candidates for inclusion.

Medicines approved or sold in Canada, the US, or Europe for any other indication or in any other strength or formulation are excluded during the selection process, as are medicines whose clinical trials are inactive, suspended, withdrawn, or terminated.

Stage 2: Analytic screening

Selection criteria

Following the initial screening, the second stage of the process considers a number of selection criteria to determine the final list of pipeline candidates. These criteria are detailed in Table 1.

Earlier phases of the pipeline (i.e., Phase II) are also examined to determine if there are other medicines with the same indication or mechanism of action as the selected candidates in Phase III and pre-registration. This provides additional information on the number of novel, first-in-class medicines that are undergoing clinical evaluation in Phase II that may influence the therapeutic significance of the selected candidates in Phase III and pre-registration.

TABLE 1
Selection criteria for the MPM

Selection Criteria	
	Improved safety and efficacy shown in clinical trials: a medicine that demonstrates increased safety, new outcome measures, or increased life expectancy or quality of life
	Novel mechanism / First-in-class: a medicine that uses a new mechanism of biochemical interaction to produce a medical effect, or a medicine that is the first in its therapeutic class In addition, **the medicine must fall into one or more of the three following FDA designations** for expedited development and review:
	Breakthrough – medicines intended to treat a serious condition and for which preliminary clinical evidence indicates that they may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)
	Fast Track – medicines used to treat serious conditions and fill an unmet medical need
	Priority Review – medicines that would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications
	Gene or cell therapy: a technique for the treatment of genetic disease in which a gene that is absent or defective is replaced by a healthy gene; or the transplantation of human cells to replace or repair damaged tissue and/or cells

Additional descriptive information

A profile of each successful pipeline candidate is provided, including the indication and mechanism of action, as well as a summary of the applicable published outcomes from clinical trials. Specific attributes that may influence the potential uptake or cost of each medicine are also identified. Table 2 provides a detailed description of these key attributes.

TABLE 2
Key attributes of new medicines selected for the MPM

Attribute		Relevance	Data sources
	**Clinical trials in Canada**	Medicines tested in Canada are likely to be of interest to Canadians	GlobalData Healthcare; Health Canada Clinical Trials Database; Health Canada Drug and Health Product Submissions Under Review; National Institutes of Health (NIH) Clinical Trial Registry
	**Rare or orphan designation**	Medicines used to treat rare diseases or conditions that generally have high treatment costs and may result in substantial spending	GlobalData Healthcare
	**Biologic medicine**	These complex molecules produced by living organisms are expected to have high costs, resulting in substantial spending	
	**Add-on therapy**	Medicines designed to be used in conjunction with existing medicines may increase the treatment cost and contribute to higher spending	
	**Potential evergreening**	Modified forms of the same product in order to extend the patent life. (e.g., new delivery systems, new dosages, new uses, new combinations or new forms)	GlobalData Healthcare

The profile also provides details of potential cost implications, if available, which includes the forecasted global revenues reported by GlobalData.

The indications and therapeutic areas of the featured medicines correspond to their Phase III clinical trial or pre-registration stage. A single clinical trial may assess multiple indications within the same therapeutic area. These medicines may also have additional indications at various phases of clinical evaluation that are not mentioned in this report. The scientific description and key attributes provided are focused on the specified indication(s) for the selected medicines.

Medicines reported for a given year are reassessed for each following edition of the MPM. They may be retained on the MPM list if they continue to meet the selection criteria. Medicines for which clinical trials have been discontinued or for which the selection criteria is no longer met are not reported in subsequent editions.

Spotlight on Canada

Health Canada's Drug and Health Product Submissions Under Review (SUR) Lists are assessed using a modified approach to the selection criteria to establish a list of medicines that may have the potential to impact Canadian drug spending or clinical practice.

Medicines listed in the SUR include new drug submissions containing medicinal ingredients that have not been approved in Canada for any indication, in any strength or form. Unlike the selection of medicines identified in the pipeline lists, these medicines may have previously received market authorization through the US FDA or the EMA.

Selection Criteria

Following this initial screening, the medicine must demonstrate at least one of three selection criteria to qualify for inclusion in the report. These criteria are listed in Table 3.

TABLE 3
Selection criteria for the list of medicines currently under review by Health Canada

Selection Criteria	
	**Improved safety and efficacy shown in clinical trials:** a medicine that demonstrates increased safety, new outcome measures, or increased life expectancy or quality of life
	**Novel mechanism or First-in-class:** a medicine that uses a new mechanism of biochemical interaction to produce a medical effect, or a medicine that is the first in its therapeutic class
	**Gene or cell therapy:** a technique for the treatment of genetic disease in which a gene that is absent or defective is replaced by a healthy gene; or the transplantation of human cells to replace or repair damaged tissue and/or cells

Additional descriptive information

The profile of each medicine under review includes the key attributes listed in Table 2, as well as the indication and mechanism of action, and a summary of the applicable published outcomes from clinical trials. Specific attributes that may influence the potential uptake or cost of each medicine are also identified, as well as potential cost implications, if available, which includes the forecasted global revenues reported by GlobalData.

Although FDA designations for expedited development or review are not a selection criteria for this list, relevant Breakthrough, Fast Track, and Priority Review designations are indicated where available. For a description of these designations, see Table 1.

Indications and therapeutic areas correspond to the information provided by GlobalData. The scientific description and key attributes provided are focused on the specified indication(s) for the selected medicine. For medicines under review for multiple indications, the primary indication is used.

Emerging COVID-19 Therapies

Vaccines and medicines under development globally with an indication for COVID-19 were extracted for this section of the report, based on a development stage of Phase I, II, and III clinical trials or pre-registration. All such medicines were assessed for this analysis, both new and existing. New medicines were identified as those that have not yet been marketed for any indication, while existing medicines include previously marketed therapies undergoing evaluation for new indications related to the prevention or treatment of COVID-19.

This section also highlights the COVID-19 medicines that have been approved as well as the medicines that are currently undergoing an expedited review process with Health Canada.

Data Sources

The GlobalData Healthcare database is the primary data source for the identification of pipeline medicines and their corresponding clinical information. GlobalData Healthcare tracks medicines from pre-clinical discovery, through clinical trials, to market launch and subsequent sales. The database is a comprehensive resource of medicines under various stages of clinical development. Search capabilities allow for controlled selection of specific attributes, including but not limited to the following: phase of clinical development, therapeutic area, molecule type, indication, drug geography, mechanism of action, and regulatory designations.

Health Canada's Drug and Health Product Submissions Under Review (SUR) Lists are used to determine the featured selection of new medicines currently undergoing review by Health Canada. The SUR is a publicly available set of lists that identify pharmaceutical and biologic drug submissions containing new medicinal ingredients not previously approved in Canada that have been accepted for review. This applies to submissions accepted on or after April 1, 2015.

As this selection is restricted to new medicines, additional sources of information are cross-referenced to confirm that the candidates have not previously been approved or sold. These include recorded sales data from the IQVIA MIDAS® Database (all rights reserved); regulatory approval records from the National Institutes of Health (NIH), US FDA, the EMA, and Health Canada; and information in Health Canada's Clinical Trials database and ClinicalTrials.org.

LIMITATIONS

This analysis captures a snapshot of the pipeline over a specific time period. Although it is assumed to be representative of the composition of medicines over the entire year, the pipeline is fairly dynamic and the share of medicines in any particular therapeutic area will vary.

This assessment is restricted to medicines under development for market in Canada and other countries with similar regulatory and approval processes: the US and Europe (excluding Russia and Turkey). Medicines that have not yet received market authorization in these countries were considered as potential pipeline candidates, even if they have been approved elsewhere in the world.

Some of the selected medicines may be undergoing clinical trials for additional indications; this analysis only reports on indications in the late stages of development—that is, in Phase III clinical trials or pre-registration with the US FDA—that satisfy the selection criteria set out in the methodology.

For each selected pipeline medicine, the primary manufacturer(s) and trade name, if available, are given along with the indication. In some cases, additional manufacturers, including subsidiaries, may also be involved in the development of the medicine with the primary companies, or other manufacturers may be developing the same medicine for other indications.

Although this report attempts to identify the most important pipeline medicines, the selection is not exhaustive and some medicines that are not included in this selection may have a significant impact on future clinical practice and drug spending in Canada.

Unless otherwise specified, the featured lists capture the composition of the pipeline as of September 2022 and are validated as of the end of March 2023. Due to the unpredictability and fast-moving nature of pipeline medicines entering the market, some of the medicines listed in this edition may have been approved or marketed in Canada, the US, or Europe following this date. Pipeline medicines that have not been included in this report due to the timing of the selection may presently meet the selection criteria; these, along with the rest of the drug pipeline, will be considered for the next edition of the report.

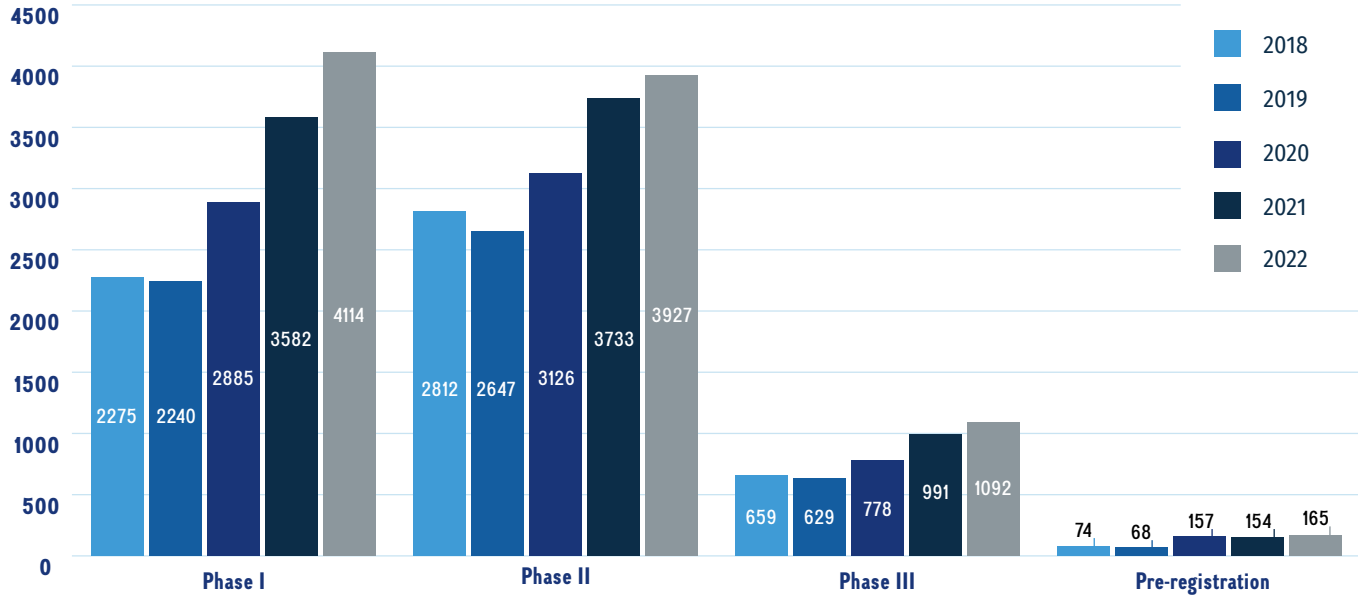
SNAPSHOT OF THE 2022 PIPELINE

The number of new pharmaceutical developments in the pipeline is increasing year over year. In 2022, over 9,000 new medicines were undergoing clinical evaluation, which has been increasing by an average of 11% per year since 2018.

Figure 2 provides a snapshot of the pipeline including the number of new medicinal ingredients in each phase of clinical development over the last 5 years.

FIGURE 2

Number of new medicines in each phase of clinical evaluation, 2018-2022



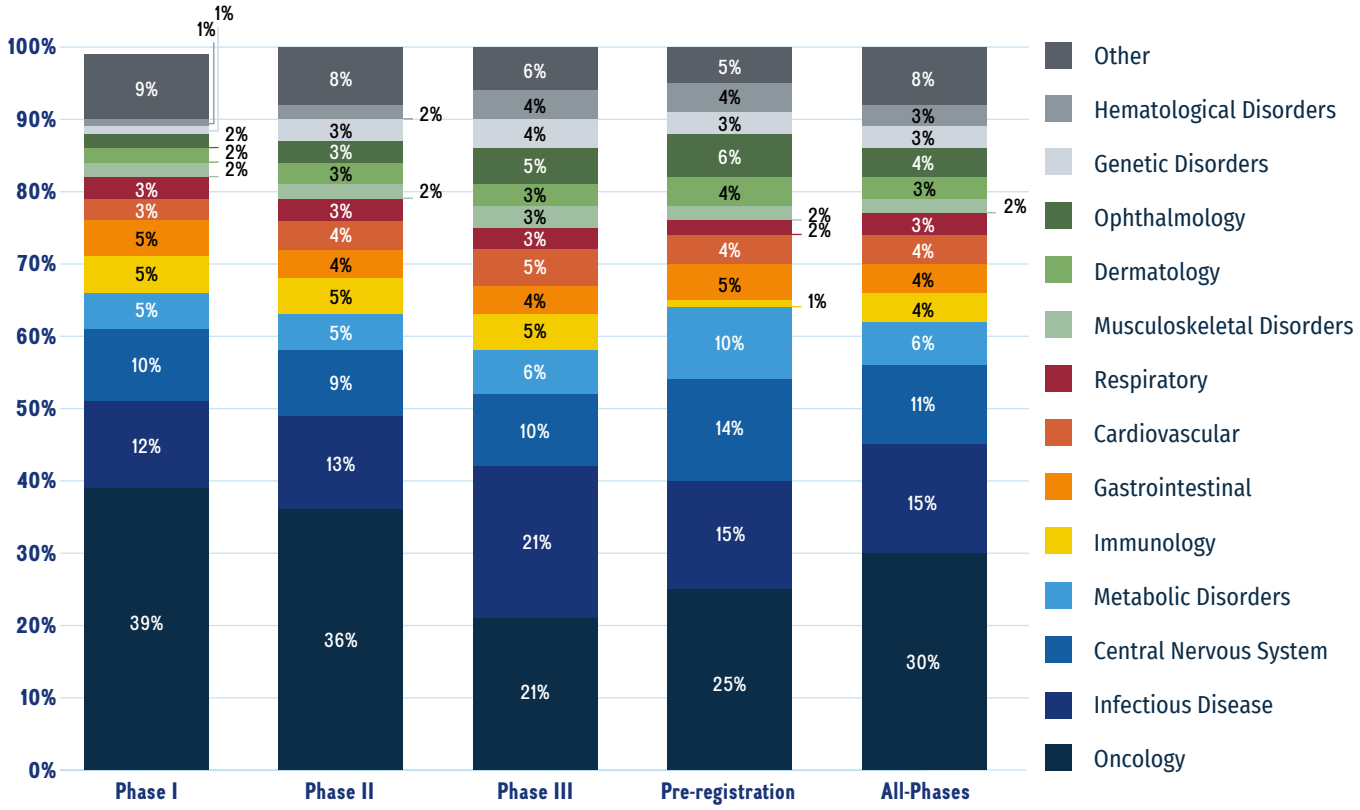
Data source: GlobalData Healthcare database (accessed September 2022); IQVIA MIDAS© Database.

Figure 3a illustrates the distribution of new medicines by therapeutic area from Phase I through to pre-registration. Although the findings show that pipeline medicines represented a wide range of therapeutic areas in 2022, cancer treatments dominated the therapeutic mix in each phase of the pipeline, accounting for nearly one third (30%) of medicines in all phases of clinical evaluation. Other important pipeline therapies include those for infectious diseases (such as COVID-19) and central nervous system therapies.

Figure 3b illustrates the top indications and number of medicines undergoing Phase II, Phase III or pre-registration in the major therapeutic areas in the pipeline in 2022

FIGURE 3A

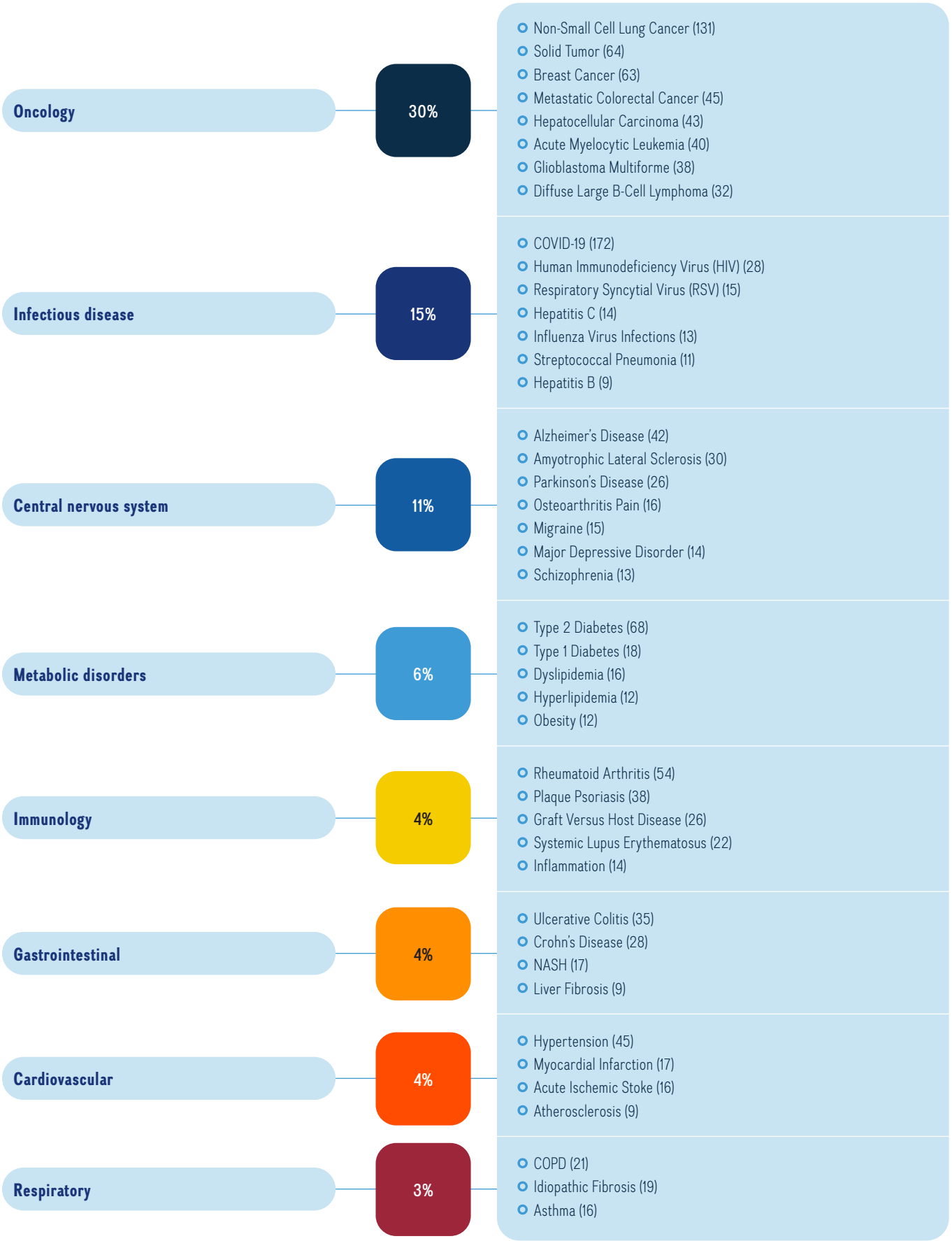
Therapeutic class distribution of pipeline medicines by phase of clinical evaluation, 2022



Data source: GlobalData Healthcare database (accessed September 2022).

FIGURE 3B

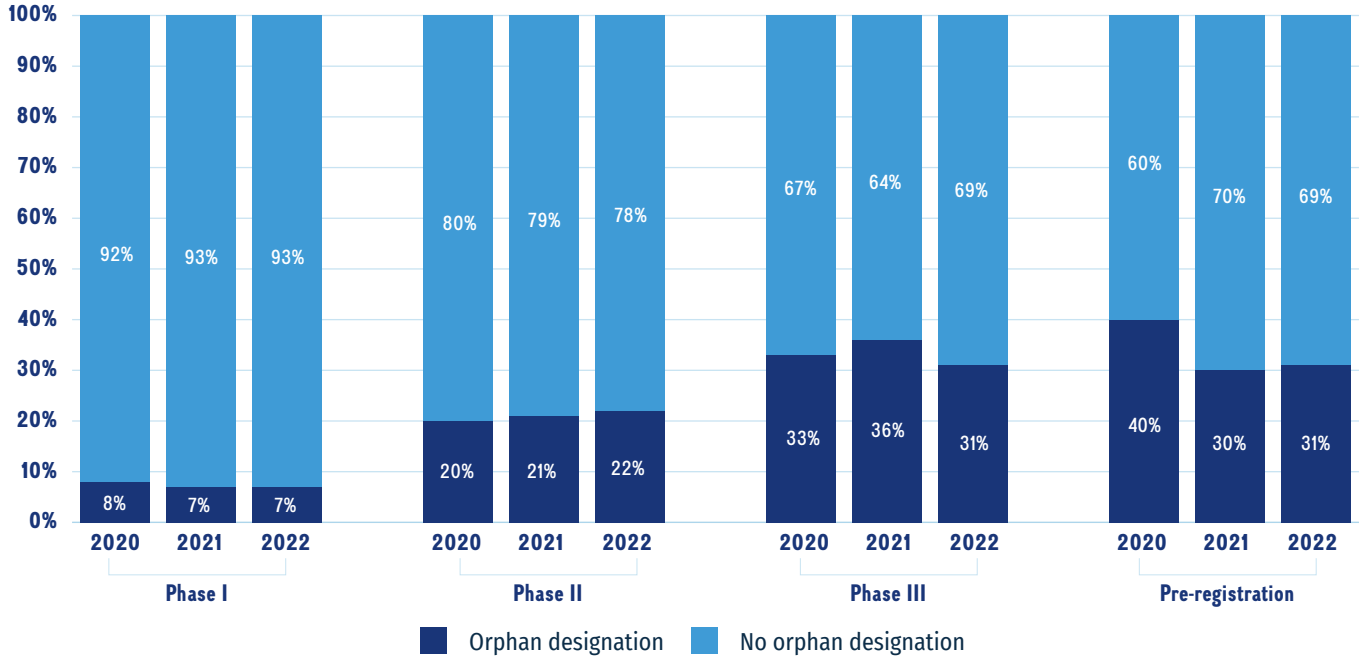
Top indications for major therapeutic areas in the pipeline, 2022



Orphan medicines, as designated by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA), accounted for a notable proportion of medicines in the 2022 pipeline. Figure 4 provides the shares of orphan designated medicines for all phases in the pipeline from 2020-2022. Orphan designated medicines make up a greater share in the later stages of the pipeline, increasing from 7% in Phase I to 31% in pre-registration in 2022. This has been a consistent trend since 2020.

FIGURE 4

Share of orphan medicines in the pipeline by highest phase of clinical evaluation, 2020-2022



Note: Includes all pipeline medicines with a highest development stage of Phase I to pre-registration that are being developed for market in Canada, the United States, or geographic Europe (excluding Russia and Turkey). Orphan medicines were defined as pipeline medicines that have been granted an orphan designation by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA).

Data source: GlobalData Healthcare database (accessed September 2022).

TREND WATCH 2022

The drug development landscape has been evolving over the last few years, from an earlier emphasis on blockbuster drugs developed in-house by large pharmaceutical companies, to niche markets and "personalized medicine"[viii] including various orphan drugs for rare disease, expanding therapeutic areas in gene and cell therapies, and the growing biosimilars pipeline.

Orphan drug approvals

Approvals for specialty medicines continue to increase, with orphan designated medicines accounting for 58% (29) of approved medicines in 2020 in Canada.[viii] This upward trend is ongoing: nearly half (49%) of the novel specialty medicines in the pipeline are indicated for orphan conditions. When including orphan cancer drugs, an estimated 80% of specialty drug development in 2022 was for orphan conditions.[xi] Aside from cancer drugs, another leading class of pipeline specialty drugs are novel anti-inflammatory therapeutics, including tumor necrosis factor inhibitors and targeted synthetic disease-modifying antirheumatic drugs (DMARDs).[xi]

Gene and cell therapies

The gene and cell therapy pipeline is growing rapidly, with more than 600 gene and cell therapies in various phases of development in 2022.[ix] According to market analysis forecasts from GlobalData, gene therapy will be a $25 billion per year market by 2034.[x] Among the many therapies undergoing clinical evaluation are novel therapies for Duchenne muscular dystrophy (6 drugs in Phase III and one in pre-registration), epidermolysis bullosa (3 drugs in preclinical evaluation, one in Phase II and one in pre-registration), and β thalassemia/sickle cell disease (10 drugs in preclinical evaluation and discovery).[xi]

Biosimilars pipeline

Biosimilars can provide patients and doctors with more affordable treatment options, which have the potential to provide savings and contribute to drug coverage sustainability. As of March 2023, 51 biosimilars of 16 innovator reference products have been approved in Canada. By comparison, there have been 40 approvals in the United States and 69 biosimilars approved by the European Medicines Agency.[xii] The global pipeline is growing with over 140 biosimilars in Phase III and pre-registration, including new therapeutic areas such as growth hormone, infertility, bone health, and immunosuppressants. As of March 2023, Health Canada is reviewing 8 biosimilars, two of which (eculizumab and ustekinumab) are the first biosimilar submissions for the reference product.

viii https://www.law.utoronto.ca/blog/faculty/pharmaceutical-industry-s-shift-towards-niche-markets-and-personalized-medicine-new
ix Meds Entry Watch report, 6th edition
x, ix GlobalData Healthcare database (accessed September 2022)
x, ix GlobalData Healthcare database (accessed September 2022)
xii https://www.ajmc.com/view/biosimilars-orphan-drugs-headline-market-trends-to-watch-in-specialty-drug-pipeline
xiii https://www.smartbiggar.ca/insights/publication/update-on-biosimilars-in-canada-june-2022

MEDS PIPELINE MONITOR 2022

The following tables include: selected new medicine candidates for 2022 (Table 4), retained medicines from previous editions of the *Meds Pipeline Monitor* (Table 5), and medicines from previous editions that have gained market authorization (Table 6).

Medicines in Phase III clinical trials or pre-registration are considered as candidates for the *Meds Pipeline Monitor* (MPM) if they have the potential to impact future clinical practice and drug spending in Canada (e.g., address an unmet therapeutic need, offer a novel mechanism of action or therapeutic benefit over existing therapies, or treat a serious condition).

Screening new medicine candidates

Of the 1,257 pipeline medicines in Phase III and pre-registration in 2022, twenty-eight (28) new medicines were selected for inclusion in the new medicines list (Table 4). Many of the pipeline candidates are first-in-class or represent novel mechanisms for the treatment of specific therapeutic areas. Having insight into other drugs under clinical evaluation (i.e., in Phase II) may provide additional information on the potential place in therapy of these pipeline candidates. The medicines in Phase II were examined to identify other drugs in the pipeline that have the same indication or mechanism of action as those listed in the 2022 new medicines list. The description for each new medicine listed in the 2022 new medicines list includes a statement indicating if there are any other drugs in Phase II development with the same indication or mechanism of action. Appendix A (Table A3) provides some further insights into the other drugs identified in Phase II for the indications targeted by the pipeline candidates. It is important to keep in mind that not all drugs in Phase II development will progress to Phase III. According to an industry analysis, Phase II clinical programs experience the lowest success rate of the development phases, with only 30.7% of developmental candidates advancing to Phase III.[1]

Of the new medicines featured in previous reports, 25 were retained as recent evidence continues to support promising clinical benefit and satisfies the selection criteria (Table 5). Six of the 2021 pipeline medicines have received market authorization in the US, Europe, or Canada as of March 30, 2023 (Table 6), while 11 were removed from the list as their clinical trials were discontinued or they no longer fulfill the selection criteria.

Screening biosimilars

Biosimilars differ from pipeline candidates in that their efficacy and safety is similar to originator biologics. However, their introduction can substantially impact drug spending in specific therapeutic areas. Of the 21 biosimilars identified in Phase III trials in 2022, 14 (67%) would be, if approved, the first biosimilars marketed for the originator biologic. Examples include: cetuximab (for specific cancers), denosumab (for post-menopausal osteoporosis), eculizumab (for paroxysmal nocturnal hemoglobinuria), ocrelizumab (for relapsing remitting multiple sclerosis), omalizumab (for urticaria), romiplostim (for idiopathic thrombocytopenic purpura), tenecteplase (for myocardial infarction), and ustekinumab (for plaque psoriasis).

The availability of these biosimilars could significantly impact costs in a wide range of therapeutic areas. Of note, as of March 30, 2023, a biosimilar for eculizumab and ustekinumab are under review by Health Canada.[2] Appendix A (Table A1) provides a list of the identified biosimilars in Phase III clinical trials and indicates whether a biosimilar currently exists for the originator biologic.

TABLE 4
Selected new medicines for 2022

Selection criteria		
Increased safety and efficacy	Novel mechanism	Gene or cell therapy
Breakthrough	Fast Track	Priority Review

Key attributes		
Clinical trials in Canada	Rare or orphan designation	Potential evergreening
Biologic medicine	Add-on therapy	

Medicine (Trade name) Company	Indication(s)	Description and key attributes
CARDIOVASCULAR		
Abelacimab Anthos Therapeutics Inc	Deep vein thrombosis (DVT); Pulmonary embolism; Atrial fibrillation	• A dual-acting, once-monthly, fully human monoclonal antibody targeting both Factor XI and Factor XIa with high affinity and selectivity.[3] • Administered through subcutaneous and intravenous routes. • A single intravenous dose after total knee arthroplasty was effective for the prevention of venous thromboembolism and was associated with a low risk of bleeding.[4] **Clinical trials** • Clinical trial data have shown that factor XI inhibitors like abelacimab are as effective as enoxaparin and apixaban in preventing DVT, but with a significantly lower incidence of bleeding. They can be administered daily or monthly; therefore, the monitoring interval can be longer.[5, 6] • Two Phase III trials in cancer-associated thrombosis are ongoing.[7, 8] • There are other drugs in Phase II development (n=1) but none with the same mechanism of action as abelacimab.[9] See Appendix A for additional information. **Forecasted revenue** • Forecasted annual global revenue unknown.

Medicine (Trade name) Company	Indication(s)	Description and key attributes
Aprocitentan Idorsia Pharmaceutical Ltd	Resistant hypertension	• A dual endothelin-receptor antagonist (ERA). It inhibits the binding of endothelin-1 to ETA and ETB receptors. By blocking the ERA receptor activation, it leads to inhibition of activity of endothelin-1 and causes vasodilation. • Administered orally. **Clinical trials** • It has demonstrated a "more favourable tolerability and safety profile in early clinical trials compared with other endothelin-receptor antagonists studied."[10] [Note: The endothelin pathway has been implicated in the pathogenesis of hypertension, but it is currently not targeted therapeutically.[11]] • Aprocitentan has a low potential for drug-drug interaction[12] and may expand the therapeutic options for resistant hypertension.[13] • An NDA has been submitted to US FDA.[14] • One Phase III trial was withdrawn,[15] and one has been completed.[16] • There are other drugs in Phase II development (n=3) but none with the same mechanism of action as Aprocitentan.[17] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $219 million by 2028.*
Etripamil Milestone Pharmaceuticals Inc Canada	Paroxysmal supraventricular tachycardia (PSVT)	• Novel administration intranasally as a nasal spray. • A short-acting calcium channel blocker. **Clinical trials** • Phase II trials in moderate to high doses demonstrated efficacy comparable to the standard of care (administered at a medical facility), and took an average of 3 minutes from drug administration to conversion to sinus rhythm.[18] • It addresses an unmet medical need since there are currently no products available for out-of-hospital treatment for patients with PSVT. The only currently available acute pharmacological therapy is IV treatment with adenosine or calcium channel blockers administered in a hospital or medically supervised environment. A self-administered product for PSVT would give patients the option to safely terminate acute episodes of PSVT without the need for a hospital visit and potential admission.[19] • An analysis pooling data from the RAPID trial and the NODE-301 study indicated that the nasal spray significantly reduced medical interventions and emergency department visits.[20] • It has the potential to improve quality of life, reduce health-care burden, and alter the current management paradigm for many patients with SVT.[21] • One Phase III trial has been completed[22] and others are ongoing,[23, 24, 25] including an open extension study by invitation.[26] • No other drug for this indication was identified in Phase II development at this time.[27] **Forecasted revenue** • Total global annual revenue forecasted to be $470 million by 2028.*

Medicine (Trade name) Company	Indication(s)	Description and key attributes
Obicetrapib NewAmsterdam Pharma BV	Dyslipidemia; Heterozygous familial hypercholesterolemia (heFH); Atherosclerosis	A cholesteryl ester transfer protein (CETP) inhibitor. It has HDL-raising and LDL-C lowering effects. Administered orally as a once-daily formulation. **Clinical trials** It has achieved significant reductions of LDL-C, up to 45%. It could become the first CETP inhibitor as add-on therapy for patients not reaching their guideline LDL-C targets.[28] It has the potential to be a simple, once-daily, low-dose treatment option for those who are currently struggling to achieve their lipid-lowering goals on traditional therapies.[29] The data to date provide evidence that it is differentiated from prior CETP inhibitors, with the potential to overcome the safety and efficacy challenges that have historically limited the potential of the drug class.[30] Several Phase III trials are ongoing.[31, 32, 33] Other CETP inhibitors (dalcetrapib, evacetrapib, and anacetrapib) have been studied for this condition but none are marketed in Canada, nor are they under review by Health Canada. There are other drugs in Phase II development (n=9) but none with the same mechanism of action as obicetrapib.[34] See Appendix A for additional information. **Forecasted revenue** Total global annual revenue forecasted to be $222 million by 2028.*
Sotatercept Acceleron Pharma Inc	Pulmonary arterial hypertension (PAH)	An activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein that increases hemoglobin levels and red blood cells.[35, 36] Administered subcutaneously and intravenously. **Clinical trials** In the Phase 3 STELLAR study, when added to background therapy, it showed a clinically significant effect on the primary efficacy outcome measure of improvement from baseline to 24 weeks in six-minute walk distance.[37] Despite some hurdles (such as low uptake since the initial five doses, administered subcutaneously every 21 days, require specialty infrastructure lacking in community centres), knowledge opinion experts say it could become a leading therapy for PAH due to strong efficacy and clinical data, and as the first disease-modifying therapy, a significant breakthrough for PAH patients.[38] Several Phase III trials are ongoing.[39, 40, 41, 42] There are other drugs in Phase II development (n=8) but none with the same mechanism of action as sotatercept.[43] See Appendix A for additional information. **Forecasted revenue** Total global annual revenue forecasted to be $1.8 billion by 2028.*

Medicine (Trade name) Company	Indication(s)	Description and key attributes
CENTRAL NERVOUS SYSTEM		
Evobrutinib Merck KGaA	Relapsing multiple sclerosis (RMS); Secondary progressive multiple sclerosis (SPMS)	 • A selective, central nervous system (CNS) penetrant immunomodulator that irreversibly blocks Bruton's tyrosine kinase (BTK) which suppresses the autoimmunity associated with the disease. • Administered orally. **Clinical trials** • No bleeding has been reported in clinical trials to date (in multiple sclerosis (MS)).[44] • There is evidence that it crosses the blood-brain barrier and may be superior to currently available disease-modifying therapies at dampening the chronic neuroinflammatory processes compartmentalized within the CNS that contribute to progressive worsening in people with MS.[45] • It has the potential to become a safe and highly efficacious treatment option for RMS by addressing both peripheral and central drivers of inflammation through inhibition of BTK. Its dual-faceted approach may offer better control of silent progression of the disease in between attacks on top of strong relapse control in people living with RMS.[46] • Two Phase III trials were terminated[47, 48] and two others are ongoing.[49, 50] • There are other drugs in Phase II development (n=9) but none with the same mechanism of action as evobrutinib.[51] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $798 million by 2028.*
Reldesemtiv Cytokinetics Inc	Amyotrophic lateral sclerosis (ALS)	 • A fast skeletal muscle troponin activator that slows the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibres, leading to an increase in skeletal muscle contractility.[52, 53] • Administered orally. **Clinical trials** • Although the primary efficacy analysis in a Phase II study did not demonstrate statistical significance, there were trends favouring reldesemtiv, with effect sizes generally regarded as clinically important.[54,55] • Additional analyses suggested that those with shorter disease duration and moderate-to-fast progression at study start may experience the greatest benefits.[56, 57] • Results suggest ALS patients receiving reldesemtiv may have a lower risk of and delayed need for durable medical equipment related to impaired mobility, breathing, swallowing, or speaking; this delay is consistent with other measures indicating delay in disease progression.[58] • Phase III trials are ongoing.[59, 60] • There are other drugs in Phase II development (n>10) but none with the same mechanism of action as reldesemtiv.[61] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $215 million by 2028.*

Medicine (Trade name) Company	Indication(s)	Description and key attributes
Soticlestat Takeda Pharmaceutical Co Ltd	Lennox-Gastaut syndrome; Dravet syndrome (severe myoclonic epilepsy of infancy)	 • It inhibits the activity of cholesterol 24-hydroxylase, one of several enzymes responsible for catabolism of cholesterol. Inhibition of the enzyme lowers the level of 24S-hydroxycholesterol, a brain-specific metabolite that modulates a wide variety of receptors and ion channels, including the N-methyl-D-aspartate receptor (NMDA) receptor.[62] • Administered orally. **Clinical trials** • It can ameliorate seizure symptoms through a mechanism distinct from conventional antiseizure medications.[63] • In a Phase II trial, treatment resulted in statistically significant, and clinically meaningful reductions from baseline in median seizure frequency and in convulsive seizure frequency.[64] • Phase III trials are ongoing.[65, 66, 67] • There are other drugs in Phase II development (n=2) but none with the same mechanism of action as soticlestat.[68] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $241 million by 2028.*
Ulotaront (SEP-363856) Sunovion Pharmaceuticals Inc	Schizophrenia	• A trace amine-associated receptor 1 (TAAR1) and serotonin 5-HT1A receptors agonist. • Administered orally. **Clinical trials** • In a Phase II study, it demonstrated sustained improvements in the negative symptoms of anhedonia and avolition in patients with schizophrenia between the ages of 18 and 40. Patients who took part in the 26-week, open-label extension study, showed a reduction in the total Positive and Negative Syndrome Scale (PANSS) score.[69] • It seems to lack the weight gain, metabolic issues, and extrapyramidal symptoms associated with traditional antipsychotics.[70] • It is not likely to pose a risk for recreational abuse and may have potential therapeutic utility as a treatment of substance use disorders.[71] • Several Phase III trials are ongoing.[72, 73, 74, 75, 76, 77, 78] • There are other drugs in Phase II development (n=9) with one having the same mechanism of action as ulotaront.[79] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $507 million by 2028.*

Medicine (Trade name) Company	Indication(s)	Description and key attributes
DERMATOLOGY		
Beremagene geperpavec Krystal Biotech Inc	Epidermolysis bullosa	 • A gene therapy consisting of a replication-defective, non-integrating viral vector, engineered to deliver functional human COL7A1 genes.[80] • It is administered as a topical gel. • There are no approved therapies for this serious condition. **Clinical trials** • The results of a Phase III study[81] showed that its use improved wound healing with good tolerability over six months, with 67% of treated wounds completely healed at six months, as compared with 22% of the wounds given a placebo gel.[82, 83] The study was limited by a relatively small sample size (n=31) and use of the agent in small wounds. It is also lacking in longer term information.[84] • An open-label study to assess long term safety is recruiting.[85] • No other drug for this indication was identified in Phase II development at this time. • There are no Canadian clinical trials currently listed in Health Canada's clinical trial database. **Forecasted revenue** • Total global annual revenue forecasted to be $613 million by 2028.*
GASTROINTESTINAL DISORDERS		
Resmetirom Madrigal Pharmaceuticals Inc	Non-alcoholic steatohepatitis (NASH); Non-alcoholic fatty liver disease (NAFLD)	 • It acts as a liver-directed thyroid hormone receptor (THR)-beta agonist. • Administered orally. • There are no approved therapies specifically for NASH/NAFLD.[86] Many agents are being investigated. **Clinical trials** • In a Phase II study, it was associated with greater improvements in physical functioning and Physical Component Summary (PCS) scores. Patients with improvement in NASH and fibrosis on liver biopsy also showed improvement in components of health-related quality of life (HRQL).[87] • The unpublished results of the Phase IIIb MAESTRO-NAFLD-1 trial demonstrated that it appears safe, well-tolerated and may provide statistically significant improvements in key measures of liver and cardiovascular health.[88] • Several Phase III trials are ongoing.[89, 90, 91, 92] • There are other drugs in Phase II development (n>10) with several having the same mechanism of action as resmetirom.[93] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $1.5 billion by 2028.*

Medicine (Trade name) Company	Indication(s)	Description and key attributes
Seladelpar lysine CymaBay Therapeutics Inc	Primary biliary cholangitis (primary biliary cirrhosis)	• A selective, peroxisomal proliferator-activated receptor delta (PPAR-delta) agonist. • Administered orally. **Clinical trials** • Treatment options for primary biliary cholangitis (PBC) are limited.[94] • Seladelpar treatment for 1 year led to consistent improvement in both symptom burden and biochemical response, suggesting its potential as a single agent to address key unmet needs in PBC patients.[95, 96] • It appeared safe and well tolerated and was not associated with any increase in pruritus.[97] • One Phase III trial was completed[98] and others are ongoing.[99, 100] • There are other drugs in Phase II development (n=6) at this time, but none with the same mechanism of action as seladelpar.[101] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $704 million by 2028.*
GENETIC DISORDERS		
Delandistrogene moxeparvovec Sarepta Therapeutics Inc	Duchenne muscular dystrophy	• It constitutes micro dystrophin gene carried through recombinant adeno-associated virus vector serotype 74 (AAV74). It acts by activating dystrophin.[102] • It is administered intramuscularly and intravenously. **Clinical trials** • In clinical results from more than 80 treated patients, it has demonstrated positive results at multiple time points, including one-, two- and up to four-years after treatment, in addition to demonstrating a consistent safety profile.[103] • A Phase III trial is ongoing.[104] • No other drug for this indication was identified in Phase II development at this time. • There are no Canadian clinical trials currently listed in Health Canada's clinical trial database. **Forecasted revenue** • Total global annual revenue forecasted to be $2.9 billion by 2028.*

Medicine (Trade name) Company	Indication(s)	Description and key attributes
REC-2282 Recursion Pharmaceuticals Inc	Neurofibromatosis type II (NF2)-mutated meningiomas	 • A pan-histone deacetylase (HDAC) inhibitor. It inhibits both histone and non-histone proteins. • Administered orally. **Clinical trials** • In studies to date, it appears to be well tolerated, including in patients dosed for multiple years.[105] • Its oral bioavailability, CNS penetrance, and potentially reduced cardiac toxicity would differentiate it from other HDAC inhibitors (e.g., vorinostat, romidepsin).[106] • If successful in the Phase III trials, it could be the first approved treatment for NF2-mutated meningiomas.[107] • A Phase II/III trial is ongoing.[108] • There is one other drug in Phase II development but not with the same mechanism as REC-2282.[109] See Appendix A for additional information. **Forecasted revenue** • Forecasted annual global revenue unknown.
IMMUNOLOGICAL DISORDERS		
Garadacimab CSL Ltd	Hereditary angioedema (HAE) (C1 esterase inhibitor [C1-INH] deficiency	 • A recombinant, fully human, immunoglobulin G4 monoclonal antibody that interferes with FXIIa-mediated coagulation. By targeting FXIIa, it inhibits the HAE cascade at its origin as compared with other HAE therapies that target downstream mediators. • Administered as a once-monthly subcutaneous injection and intravenously. **Clinical trials** • In a Phase III study, it reduced the number of attacks for up to six months and demonstrated favourable safety and tolerability.[110] • It has the potential to become a transformative first-in-class therapy for people living with HAE.[111] • One Phase III trial was completed[112] and another one is ongoing.[113] • There are other drugs in Phase II development at this time (n=3),[114] but none with the same mechanism as garadacimab. See Appendix A for additional information. **Forecasted revenue** • Forecasted annual global revenue unknown.

Medicine (Trade name) Company	Indication(s)	Description and key attributes
Omidubicel Gamida Cell Ltd	Hematopoietic stem cell transplantation	 • It is an ex vivo expanded hematopoietic progenitor cell and nonexpanded myeloid and lymphoid cell product derived from a single umbilical cord blood unit.[115] • It is administered as an infusion. **Clinical trials** • Transplantation with omidubicel results in faster hematopoietic recovery and reduces early transplant-related complications compared with standard umbilical cord blood transplantation (UCBT).[116, 117] • One-year post-transplant data showed sustained clinical benefits as demonstrated by significant reduction in infectious complications as well as reduced non-relapse mortality and no significant increase in relapse rates nor increases in graft-versus-host-disease rates.[118] • It has the potential to become the standard of care for adult patients eligible for UCBT.[119] • No other drug for this indication was identified in Phase II development at this time. • There are no Canadian clinical trials currently listed in Health Canada's clinical trial database. **Forecasted revenue** • Total global annual revenue forecasted to be $121 million by 2028.*
INFECTIOUS DISEASES		
Posoleucel AlloVir Inc	Herpesviridae infections	 • An allogeneic, off-the-shelf multi-virus specific T-cell therapy. • It is administered by intravenous injection and by infusion. **Clinical trials** • Currently, there are no approved therapies for most viral infections in the post-stem cell transplant setting, with the standard of care treatments having limited efficacy and associated with significant toxicity.[120] • Phase II data showed a substantial reduction in the expected rate of clinically significant viral infections or diseases in the high-risk patient population despite the expected high rates of viral reactivation.[121] • No other drug for this indication was identified in Phase II development at this time. • Phase III trials are ongoing.[122, 123, 124] **Forecasted revenue** • Total global annual revenue forecasted to be $1.4 billion by 2028.*
Zoliflodacin Entasis Therapeutics Holdings Inc	Uncomplicated cervical and urethral gonorrhea	• The first in a new class: the spiropyrimidinetriones. It is a DNA gyrase and topoisomerase IV inhibitor that leads to disruption of DNA synthesis and subsequently cell death. • Administered orally, as a single dose. **Clinical trials** • Its cardiac safety was evaluated and there were no clinically significant effects on heart rate, PR and QRS intervals, electrocardiogram morphology, or laboratory values, confirming that a single dose is safe and well tolerated.[125] • It has a unique mode of inhibition against bacterial type II topoisomerases with binding sites in bacterial gyrase that are distinct from those of the fluoroquinolones. It represents "a promising new oral therapy for drug-resistant infections caused by N. gonorrheae".[126] • A Phase III trial is ongoing.[127] • No other drug for this indication was identified in Phase II development at this time. **Forecasted revenue** • Forecasted annual global revenue unknown.

Medicine (Trade name) Company	Indication(s)	Description and key attributes
METABOLIC DISORDERS		
Insulin human, oral (ORMD-0801) Oramed Pharmaceuticals Inc	Type 2 Diabetes	 • An insulin receptor agonist. • Administered orally. **Clinical trials** • It has the potential to significantly impact therapy of type 2 diabetes. • Phase III trials are ongoing.[128, 129, 130] • There is an inhalational insulin human but are no other oral Insulins identified in Phase II development at this time. **Forecasted revenue** • Total global annual revenue forecasted to be $394 million by 2028.*
Insulin icodec Novo Nordisk AS	Type 1 diabetes (juvenile diabetes); Type 2 diabetes	 • A long-acting basal insulin analogue. • Administered subcutaneously once weekly. **Clinical trials** • In a Phase II clinical trial, once-weekly insulin icodec provided safe and efficacious glycemic control comparable to once-daily insulin glargine in type 2 diabetes patients.[131, 132] • A reduction in the frequency of basal insulin injections might facilitate treatment acceptance and adherence among patients with type 2 diabetes.[133] • Several Phase III trials have been completed[134, 135, 136, 137] and many are ongoing.[138, 139, 140, 141, 142] • There is no other once-weekly insulin identified in Phase II development at this time. **Forecasted revenue** • Total global annual revenue forecasted to be $973 million by 2028.*
ONCOLOGY		
Bemarituzumab Amgen Inc	Adenocarcinoma of the gastroesophageal junction; Gastric cancer; Bladder cancer; Gastroesophageal (GE) junction carcinomas	 • A targeted monoclonal antibody that is designed to block fibroblast growth factors (FGFs) from binding and activating fibroblast growth factor receptor 2b (FGFR2b), inhibiting several downstream pro-tumour signaling pathways and potentially slowing cancer progression. • Administered intravenously. **Clinical trials** • In the Phase II FIGHT trial, adding it to chemotherapy led to longer progression-free survival and overall survival in patients with advanced FGFR2b-positive gastric or gastroesophageal junction cancers. It was also associated with more side effects, including eye problems.[143] • Phase III trials are ongoing.[144, 145] • There are other drugs in Phase II development at this time (n>10),[146] including one drug with a similar mechanism of action to bemarituzumab. See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $639 million by 2028.*

Medicine (Trade name) Company	Indication(s)	Description and key attributes
Iberdomide hydrochloride Bristol-Myers Squibb Co	Refractory multiple myeloma; Relapsed multiple myeloma	 • An immunomodulatory imide drug that targets cereblon (CRBN) and inhibits CRBN ubiquitination and enhances T cell IL-2 production, but inhibits B-cell production of immunoglobulin. • Administered orally. **Clinical trials** • Iberdomide plus dexamethasone was generally safe and showed meaningful clinical activity in heavily pretreated patients with multiple myeloma, including in disease that was refractory to immunomodulatory drugs.[147] • Phase III trials are ongoing.[148, 149] • There are other drugs in Phase II development at this time (n>10),[150] including two drugs with a similar mechanism of action to iberdomide. See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $276 million by 2028.*
Imetelstat sodium Geron Corp	Myelodysplastic syndrome; Post-essential thrombocythemia myelofibrosis (post-ET MF); Post-polycythemia vera myelofibrosis (PPV-MF)	 • A lipid-conjugated oligonucleotide that binds directly with high affinity to the template region of the RNA component of human telomerase (hTR) and inhibits telomerase enzymatic activity. • Administered by intravenous infusion. **Clinical trials** • It demonstrated meaningful clinical benefit including a robust symptom response rate and potential overall survival benefit in IMbark, a Phase II study in intermediate-2 or high-risk myelofibrosis patients who have relapsed after or are refractory to Janus kinas inhibitors.[151, 152] • Phase III trials are ongoing.[153, 154] • There are other drugs in Phase II development at this time (n>10),[155] but none with the same mechanism as imetelstat. See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $945 million by 2028.*
Navitoclax dihydrochloride AbbVie Inc	Myelofibrosis	 • It acts as an antagonist of a subset of the B-cell leukemia 2 (Bcl-2) family of proteins. It selectively binds to apoptosis suppressor proteins Bcl-2, Bcl-w and Bcl-XL and prevents their binding to the apoptotic effectors Bax and Bak proteins, which may trigger apoptosis in tumour cells overexpressing Bcl-2 and Bcl-XL. • Administered orally. **Clinical trials** • The clinical data to date, especially in synergistic combination with traditional Janus kinas 2 (JAK2) inhibitors, have been promising for those with refractory or relapsing disease on prior therapies.[156] • Its addition to ruxolitinib in patients with persistent or progressive myelofibrosis resulted in durable spleen volume reduction, improved total symptom score, hemoglobin response, and bone marrow fibrosis.[157] • Phase III trials are ongoing.[158, 159] • There are other drugs in Phase II development at this time (n>10),[160] but none with the same mechanism as navitoclax. See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $611 million by 2028.*

Medicine (Trade name) Company	Indication(s)	Description and key attributes
Relacorilant Corcept Therapeutics Inc	Epithelial ovarian cancer	 • A selective glucocorticoid receptor antagonist that targets glucocorticoid receptor II (GR-II). • Administered orally. **Clinical trials** • Results of a Phase II study showed improvements in progression free survival, duration of response and overall survival without increased side effect burden.[161] • As there are no currently approved therapies or effective standard of care for heavily pretreated patients with ovarian cancer who have exhausted single-agent chemotherapy and/or bevacizumab, the combination of intermittently administered relacorilant and nab-paclitaxel may demonstrate a substantial improvement without increased toxicity compared with nab-paclitaxel.[162] • If the Phase III study confirms these results, "relacorilant plus nab-paclitaxel has the potential to become a new standard of care."[163] • The Phase III trial in ovarian cancer is ongoing.[164] • There are other drugs in Phase II development at this time (n>10),[165] but none with the same mechanism as relacorilant. See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $455 million by 2028.*
Rusfertide acetate Protagonist Therapeutics Inc	Polycythemia vera (PV)	 • A synthetic mimetic of hepcidin, a natural hormone that regulates iron absorption, distribution, and storage, controlling the body's production of red blood cells. • Administered weekly as a subcutaneous injection. • It has been suggested to offer 'greater potency, stability, and solubility than with the natural hormone."[166] **Clinical trials** • In a Phase II study, its administration provided PV patients with an effective therapy that led to rapid and sustained hematocrit control, and potentially a better quality of life by keeping them essentially phlebotomy-free for up to 18 months.[167, 168] • It has the potential to provide a highly effective treatment option for patients with PV, providing an opportunity to fundamentally transform the management of this disease.[169, 170] • A Phase III trial is ongoing.[171] • There are no other drugs for this indication in Phase II development at this time.[172] **Forecasted revenue** • Forecasted annual global revenue unknown.

Medicine (Trade name) Company	Indication(s)	Description and key attributes
Zolbetuximab Astellas Pharma Inc	Adenocarcinoma of the gastroesophageal junction; Gastric cancer	 • A monoclonal antibody that targets and binds to claudin 18.2 (CLDN18.2, a transmembrane protein). • Administered as an intravenous infusion. **Clinical trials** • It yielded positive results with few high-grade adverse events; thus, it has the potential to be a novel and effective therapy.[173] • Claudin 18.2 (CLDN 18.2) is overexpressed in at least a third of esophagogastric adenocarcinomas. The combination of zolbetuximab and chemotherapy provides a survival benefit, correlated with the intensity of CLDN 18.2 expression.[174] • Results from one Phase III trial showed that both progression-free and overall survival were significantly improved with zolbetuximab plus mFOLFOX6 treatment.[175] • Phase III trials are ongoing.[176, 177] • There are other drugs in Phase II development at this time (n>10),[178] including two drugs with a similar mechanism of action to zolbetuximab. See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $622 million by 2028.*
OPHTHALMOLOGY		
Lenadogene nolparvovec GenSight Biologics SA	Leber's hereditary optic neuropathy (Leber optic atrophy)	 • A recombinant adeno-associated virus vector serotype 2 (AAV2) containing the human wild-type mitochondrial ND4 gene (rAAV2-ND4 vector). • It is administered intravitreally. **Clinical trials** • Leber hereditary optic neuropathy (LHON) remains a disease with a high unmet medical need.[179] • Its efficacy in improving visual acuity in LHON was confirmed in a large cohort of unilaterally-treated patients,[180, 181, 182] compared to the spontaneous natural history decline.[183, 184] • It has a good overall safety profile with excellent systemic tolerability, consistent with limited bio-dissemination.[185] • There is an unresolved question about whether bilateral injection could offer added benefits over unilateral injection. The FDA has requested that the company conduct an additional trial.[186] • There are no other drugs for this indication in Phase II development at this time. • There are no Canadian clinical trials currently listed in Health Canada's clinical trial database. **Forecasted revenue** • Forecasted annual global revenue unknown.

* Consensus forecasts for global revenue data were collected from GlobalData, Q4-2022, and are given in US dollars.

Data source: GlobalData Healthcare database.

TABLE 5

Update on pipeline medicines retained from the 2021 *Meds Pipeline Monitor*

Selection criteria		
Increased safety and efficacy	Novel mechanism	Gene or cell therapy
Breakthrough	Fast Track	Priority Review

Key attributes	
Clinical trials in Canada	Rare or orphan designation
Biologic medicine	Add-on therapy

Medicine (Trade name) Company	Indication(s)	Update
CARDIOVASCULAR		
Apabetalone Resverlogix Corp.	Coronary artery disease (CAD) (ischemic heart disease)	**Clinical trials** ○ Positive results from the Phase III have been published.[187] There is no information available at this time to confirm if an application has been submitted. **Forecasted revenue** ○ Forecasted annual global revenue unknown.
CSL112 CSL Ltd	Acute coronary syndrome (ACS)	**Clinical trials** ○ Phase III trial is still ongoing; targeted to be completed in December 2023.[188] ○ According to the Memorial Care Heart and Vascular Institute that is participating in the Phase III trial, "this infusion therapy is a game changer because we are able to administer this potentially lifesaving intravenous treatment directly into the bloodstream soon after the onset of a cardiac event, allowing us the potential to clear the blockages that cause heart attacks".[189] **Forecasted revenue** ○ Forecasted annual global revenue unknown.
CENTRAL NERVOUS SYSTEM		
Latozinemab (previously AL-001) Alector Inc	Frontotemporal dementia (FTD)	**Clinical trials** ○ The Phase III trial is still ongoing; targeted to be completed in December 2023.[190] **Forecasted revenue** ○ Total global annual revenue forecasted to be $333 million by 2028.*

Medicine (Trade name) Company	Indication(s)	Update
Valiltramiprosate (previously ALZ-801) Alzheon Inc	Alzheimer's disease (AD)	**Clinical trials** ○ The Phase III trial is still ongoing; targeted to be completed in July 2024.[191] **Forecasted revenue** ○ Forecasted annual global revenue unknown.
Midomafetamine (MDMA) Multidisciplinary Association for Psychedelic Sudies	Post-traumatic stress disorder (PTSD)	**Clinical trials** ○ A review article described MDMA-assisted psychotherapy as an effective therapy for patients with PTSD with a reasonable safety profile.[192] ○ Another Phase III trial has been completed;[193] the other is enrolling by invitation, until March 2023.[194] **Forecasted revenue** ○ Total global annual revenue forecasted to be $75 million by 2028.*
ND-0612 (levodopa/carbidopa for subcutaneous infusion) Mitsubishi Tanabe Pharma Corp	Parkinson's disease (PD)	**Clinical trials** ○ The Phase III trial is still ongoing; targeted to be completed in October 2023.[195] **Forecasted revenue** ○ Forecasted annual global revenue unknown.
GASTROINTESTINAL DISORDERS		
Brazikumab AstraZeneca Plc	Crohn's disease (regional enteritis)	**Clinical trials** ○ Phase III trials are still ongoing.[196, 197] **Forecasted revenue** ○ Total global annual revenue forecasted to be $377 million by 2028.*
RBX-2660 Rebiotix Inc	*Clostridium difficile* infections (*C. difficile* associated disease)	**Clinical trials** ○ A Phase III trial has been completed[198] and the results published.[199] It found that "RBX2660 is a safe and effective treatment to reduce recurrent *C. difficile* infection following standard-of-care antibiotics with a sustained response through 6 months. It is the first microbiota-based live biotherapeutic to demonstrate efficacy as early as first recurrence of *Clostridioides difficile (C. difficile)* infection."[200] ○ Another Phase III trial is still ongoing; targeted to be completed in September 2023.[201] **Forecasted revenue** ○ Forecasted annual global revenue unknown.

Medicine (Trade name) Company	Indication(s)	Update
GENITO URINARY SYSTEM AND SEX HORMONES		
Gepotidacin mesylate GlaxoSmithKline Plc	Cystitis; Urinary tract infections (UTI)	**Clinical trials** • The pivotal Phase III trials have stopped enrolment early for efficacy following a recommendation by the Independent Data Monitoring Committee.[202, 203] This decision was based on a pre-specified interim analysis of efficacy and safety data in over 3000 patients across the trials. The EAGLE-2 and 3 trials are now closed for recruitment, with final study visits and data collection anticipated during the first quarter of 2023.[204, 205] • The company expects to submit regulatory filings to the US FDA in the first half of 2023.[206] **Forecasted revenue** • Total global annual revenue forecasted to be $376 million by 2028.*
HEMATOLOGICAL DISORDERS		
Bentracimab PhaseBio Pharmaceuticals Inc	Bleeding and clotting disorders	**Clinical trials** • Interim Phase III results positive.[207] • The company plans to submit a BLA to the US FDA in late 2022.[208] **Forecasted revenue** • Total global annual revenue forecasted to be $436 million by 2028.*
Danicopan Alexion Pharmaceuticals Inc	Paroxysmal nocturnal hemoglobinuria (PNH)	**Clinical trials** • An interim analysis of the Phase III trial showed positive high-level results in patients with PNH who experience clinically significant extravascular haemolysis.[209] • The Phase III trial is ongoing; targeted to be completed in December 2023.[210] **Forecasted revenue** • Total global annual revenue forecasted to be $109 million by 2028.*
Fidanacogene elaparvovec Pfizer Inc	Hemophilia B (factor IX deficiency)	**Clinical trials** • The US FDA accepted a BLA in October 2022; a decision is expected by June 2023.[211] **Forecasted revenue** • Total global annual revenue forecasted to be $364 million by 2028.*
Fitusiran Sanofi	Hemophilia A; Hemophilia B	**Clinical trials** • Results from a Phase III trial are positive.[212] Further investigation under an amended protocol with lower doses and a less frequent dosing regimen (every other month) is underway.[213] • A Phase III long-term study, until October 2026, is ongoing.[214] **Forecasted revenue** • Total global annual revenue forecasted to be $415 million by 2028.*

Medicine (Trade name) Company	Indication(s)	Update
HORMONAL DISORDERS		
Palopegteriparatide (TransCon PTH) Ascendis Pharma AS	Hypoparathyroidism	**Clinical trials** ○ Results from the Phase III trial have been published.[215] ○ A NDA has been submitted to the US FDA and was granted Priority review.[216] **Forecasted revenue** ○ Total global annual revenue forecasted to be $1.1 billion by 2028.*
INFECTIOUS DISEASES		
V-7 Immunitor Inc	Tuberculosis (TB)	**Clinical trials** ○ No further updates. ○ It is one of many in the tuberculosis pipeline.[217] **Forecasted revenue** ○ Forecasted annual global revenue unknown.
MALE HEALTH		
Fexapotide triflutate Nymox Pharmaceutical Corp	Benign prostatic hyperplasia (BPH)	**Clinical trials** ○ An NDA has been submitted to the US FDA.[218] **Forecasted revenue** ○ Forecasted annual global revenue unknown.
METABOLIC DISORDERS		
Birtamimab Prothena Corp Plc	Primary systemic amyloidosis	**Clinical trials** ○ Results from the Phase III (AFFIRM-AL) trial will be presented.[219] ○ The Phase III trial is ongoing; targeted to be completed in June 2024.[220] **Forecasted revenue** ○ Total global annual revenue forecasted to be $193 million by 2028.*
Donislecel (Lantidra) CellTrans Inc	Type 1 diabetes (T1D; juvenile diabetes)	**Clinical trials** ○ A BLA has been submitted to the US FDA. The FDA Advisory Committee voted 12 yes / 4 no (one abstention) that donislecel delivered by intraportal administration has an overall favorable benefit-risk profile for some patients with type 1 diabetes.[221] **Forecasted revenue** ○ Forecasted annual global revenue unknown.

Medicine (Trade name) Company	Indication(s)	Update
Pegunigalsidase alfa Chiesi Farmaceutici SpA	Fabry disease (FD)	**Clinical trials** ○ Company met with the US FDA to discuss issues from previous application[222] and resubmitted their data.[223] It is also being reviewed by the EMA.[224] **Forecasted revenue** ○ Forecasted annual global revenue unknown.
ONCOLOGY		
Arfolitixorin Isofol Medical AB	Metastatic colorectal cancer	**Clinical trials** ○ The Phase III trial is still ongoing; targeted to be completed in January 2023.[225] **Forecasted revenue** ○ Forecasted annual global revenue unknown.
SGX-301 (synthetic hypericin) (HyBryte) Soligenix Inc	Cutaneous T-cell lymphoma (CTCL)	**Clinical trials** ○ The Phase III trial is completed [226] and results have been published.[227] ○ The company has filed an NDA; the US FDA issued a refusal letter on the basis that it was insufficient to allow for substantive review.[228] The company plans to meet with the US FDA. **Forecasted revenue** ○ Total global annual revenue forecasted to be $8 million by 2028.*
Ipatasertib Genentech, Inc	Metastatic hormone refractory (castration resistant, androgen independent) prostate cancer	**Clinical trials** ○ A Phase III trial is still ongoing; targeted to be completed in October 2023.[229] **Forecasted revenue** ○ Total global annual revenue forecasted to be $424 million by 2028.*
Motixafortide (BL-8040; Aphexda) BioLineRx Ltd	Multiple myeloma (Kahler disease)	**Clinical trials** ○ The Phase III (GENESIS) trial is completed. Results showed that nearly 90% of patients collected an optimal number of cells for transplantation following a single administration and in only one apheresis session.[230] ○ An NDA has been submitted to the US FDA.[231] **Forecasted revenue** ○ Total global annual revenue forecasted to be $70 million by 2028.*

Medicine (Trade name) Company	Indication(s)	Update
OPHTHALMOLOGY		
Avacincaptad pegol sodium (Zimura) Iveric Bio Inc	Geographic atrophy (GA)	**Clinical trials** • Phase III trial is still ongoing; targeted to be completed in July 2023.[232] • The company has submitted an NDA to the US FDA and it has been accepted for review.[233] **Forecasted revenue** • Total global annual revenue forecasted to be $1.5 billion by 2028.*
WOMEN'S HEALTH		
Fezolinetant Astellas Pharma Inc	Vasomotor symptoms of menopause (hot flashes)	**Clinical trials** • An NDA has been submitted to the US FDA, with a target review date of February 22, 2023.[234] [Note: Results from a Phase III trial in Asia did not meet statistical significance.[235] This may impact the FDA review.] • The US FDA review, due February 22, 2023, has been extended by 3 months.[236] **Forecasted revenue** • Total global annual revenue forecasted to be $1.8 billion by 2028.*

* Consensus forecasts for global revenue data were collected from GlobalData, Q4-2022, and are given in US dollars.

Data source: GlobalData Healthcare database.

TABLE 6

Pipeline medicines from the 2021 *Meds Pipeline Monitor* that have gained market authorization

Selection criteria		
Increased safety and efficacy	Novel mechanism	Gene or cell therapy
Breakthrough	Fast Track	Priority Review

Key attributes	
Clinical trials in Canada	Rare or orphan designation
Biologic medicine	Add-on therapy

Medicine (Trade name) Company	Indication(s)	Approval status and key attributes
CENTRAL NERVOUS SYSTEM		
Lecanemab (Leqembi) Eisai Co Ltd	Alzheimer's disease (AD)	**Approval** ○ Approved by the US FDA (Leqembi; January 6, 2023).[237] **Forecasted revenue** ○ Total global annual revenue forecasted to be $4.7 billion by 2028.*
Ublituximab (Briumvi) TG Therapeutics, Inc.; LFB S.A.	Relapsing multiple sclerosis (RMS)	**Approval** ○ Approved by the US FDA (Briumvi; December 28, 2022).[238] **Forecasted revenue** ○ Total global annual revenue forecasted to be $826 million by 2028.*
HEMATOLOGICAL DISORDERS		
Etranacogene dezaparvovec (Hemgenix) CSL Ltd	Hemophilia B (factor IX deficiency)	**Approval** ○ Approved by the US FDA (Hemgenix; November 22, 2022).[239] **Forecasted revenue** ○ Total global annual revenue forecasted to be $386 million by 2028.*

Medicine (Trade name) Company	Indication(s)	Approval status and key attributes
INFECTIOUS DISEASE		
Oteseconazole (Vivjoa) Mycovia Pharmaceuticals Inc.	Recurrent vulvovaginal candidiasis (RVVC)	**Approval** Approved by the US FDA (Vivjoa; April 26, 2022)[240] **Forecasted revenue** Forecasted annual global revenue unknown.
METABOLIC DISORDERS		
Teplizumab (Tzield) Provention Bio Inc and Sanofi	Type 1 diabetes (T1D; juvenile diabetes)	**Approval** Approved by the US FDA (Tzield; November 17, 2022).[241] **Forecasted revenue** Total global annual revenue forecasted to be $604 million by 2028.*
ONCOLOGY		
Elacestrant (Orserdu) Stemline Therapeutics, Inc.	Human epidermal growth factor receptor 2 negative breast cancer (HER2- Breast Cancer); Metastatic breast cancer	**Approval** Approved by the US FDA (Orserdu; January 27, 2023).[242] [Note: US company is listed as Stemline Therapeutics, Inc] **Forecasted revenue** Total global annual revenue forecasted to be $57 million by 2028.*

* Consensus forecasts for global revenue data were collected from GlobalData, Q4-2022, and are given in US dollars.

Data source: GlobalData Healthcare database.

SPOTLIGHT ON CANADA

This section includes a list of select medicines currently under review by Health Canada that may have a significant impact on future clinical practice and drug spending. Medicines included on this list may be new to Canada but have been approved in other jurisdictions.

Health Canada's Drug and Health Product Submissions Under Review (SUR) Lists include biosimilars. Although they do not have improved safety and efficacy, their availability could have a potential impact on drug spending. The biosimilars under review, as of September 2022 are: aflibercept, bevacizumab, eculizumab, enoxaparin, pegfilgrastim, and trastuzumab. To date, there are no biosimilars for aflibercept or eculizumab. Their availability could have a potential impact on the costs set aside in drug budgets for the use of these therapies. Appendix A (Table A2) lists the biosimilars currently under review with Health Canada.

Table 7 highlights five new medicines currently on Health Canada's Drug and Health Product SUR Lists that have a novel mechanism of action or have demonstrated improved safety and efficacy in clinical trials. Of the four medicines reported in the 2021 edition, all have since received market authorization from Health Canada.

The SUR Lists are publicly available sources that identify pharmaceutical and biologic drug submissions with new medicinal ingredients that have been accepted for review in Canada.

TABLE 7
Selected new medicines currently under review by Health Canada, 2022

Selection criteria

Increased safety and efficacy	Novel mechanism	Gene or cell therapy

Key attributes

Breakthrough	Fast Track	Priority Review	Clinical trials in Canada	Rare or orphan designation	Biologic medicine	Add-on therapy

Medicine (Trade name) Company	Indication(s)†	Description and key attributes
CENTRAL NERVOUS SYSTEM		
Masitinib mesylate AB Science S.A.	Amyotrophic lateral sclerosis (ALS)	• A selective tyrosine kinase inhibitor. • Administered orally, in combination with riluzole. **Clinical trials** • In a survival analysis of patients previously randomized for a Phase III study, it was found to prolong survival by over 2 years as compared with placebo, in patients whose treatment started prior to severe impairment of functionality.[243] • An application has been filed with EMA for a conditional authorization.[244] [Note: In 2018, the EMA refused authorization for ALS (Alsitek; April 18, 2018[245]), but according to the manufacturer's information, issues identified by the EMA at that time have been addressed.] • There are other drugs in Phase II development for this indication but none with the same mechanism of action as Masitinib.[246] See Appendix A for additional information. **Forecasted revenue** • Forecasted annual global revenue unknown.

Medicine (Trade name) Company	Indication(s)†	Description and key attributes
HEMATOLOGICAL DISORDERS		
Concizumab Novo Nordisk Canada Inc	Haemophilia B	 • A monoclonal, humanized IgG4 antibody specific for the Kunitz-2 domain of Tissue Factor Pathway Inhibitor (TFPI).[247] • Administered once daily subcutaneously as prophylactic therapy (regular treatment to prevent prolonged and spontaneous bleeding) for hemophilia.[248] **Clinical trials** • Results of the Phase III trial showed an 86% reduction in treated spontaneous and traumatic bleeds when on concizumab prophylaxis, with an estimated mean annualized bleeding rate (ABR) of 1.7 compared to 11.8 with no prophylaxis.[249] • It offers the potential for everyday protection for people living with haemophilia and provides an important potential addition, especially in the haemophilia B with inhibitor population who currently have limited treatment options.[250] • There are other drugs in Phase II development for this indication but none with the same mechanism of action as concizumab.[251] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $177 million by 2028.*
IMMUNOLOGY		
Spesolimab Boehringer Ingelheim (Canada) Ltd	Generalized pustular psoriasis (GPP)	 • A humanized monoclonal antibody that acts as an interleukin (IL)-36 receptor antagonist. • It is administered intravenously. **Clinical trials** • In the 12-week pivotal clinical trial, it was rapidly effective in the majority of patients within one week of its first intravenous infusion for patients suffering from generalized pustular psoriasis.[252, 253] • Generalized pustular psoriasis (GPP) is a rare, life-threatening condition. There are no approved options to help manage GPP flares.[254, 255, 256] • Approved by the US FDA (SPEVIGO; September 1, 2022)[257] and conditionally by the EMA (Spevigo; October 13, 2022).[258] • No other therapy was identified in Phase II development at this time.[259] **Forecasted revenue** • Forecasted annual global revenue unknown.

Medicine (Trade name) Company	Indication(s)†	Description and key attributes
ONCOLOGY		
Ciltacabtagene autoleucel (Carvykti) Janssen Inc	Relapsed or refractory multiple myeloma	• Health Canada approved but not yet marketed as of February 9, 2023. • A chimeric antigen receptor (CAR) T-cell therapy that targets B-cell maturation antigen (BCMA) on the surface of cancer cells in B-cell malignancies, such as multiple myeloma.[260] • It is administered intravenously. **Clinical trials** • In a main study, a single infusion was effective at clearing cancer cells in patients with multiple myeloma that had returned and did not respond to three or more previous treatments. After one and a half years, about 84% of patients (95 out of 113) had a good response to the treatment and in 69% (78 out of 113) the signs of cancer had disappeared (complete response). It was not compared to another medicine in this study. These results were better than those seen in other studies of patients receiving standard treatments for multiple myeloma.[261] • It generally outperformed idecabtagene vicleucel (Abecma) in terms of efficacy in MM, but showed comparable adverse events.[262] • It showed superior efficacy compared with physician's choice of treatment, making it a promising new treatment option for patients with triple-class exposed relapsed or refractory multiple myeloma.[263] • Approved by the US FDA (Carvykti ; February 28, 2022)[264] and by the EMA (Carvykti; June 17, 2022).[265] • There are other gene therapies for this indication in Phase II development at this time.[266] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $4.8 billion by 2028.*
Glofitamab Hoffmann-La Roche Limited	Diffuse large B-cell lymphoma	• It is a full-length, IgG-like bispecific CD20-CD3 with a unique 2:1 configuration that provides an extended half-life and superior CD20 binding.[267] • It is administered intravenously. **Clinical trials** • Fixed-duration glofitamab (given for a fixed amount of time, and not taken until disease progression) generated a notable objective response rate and complete remission rate in patients with heavily pretreated, highly refractory large B-cell lymphoma.[268, 269] • It appears to be "a welcome addition to the treatment possibilities for patients with B-cell lymphomas who otherwise have limited therapeutic options."[270] • Under review by the EMA.[271] • There are other drugs in Phase II development for this indication but none with the same mechanism of action as glofitamab.[272] See Appendix A for additional information. **Forecasted revenue** • Total global annual revenue forecasted to be $634 million by 2028.*

* Consensus forecasts for global revenue data were collected from GlobalData, Q4-2022, and are given in US dollars.

† Health Canada's Drug and Health Product Submissions Under Review Lists provide the therapeutic area for the medicine under review but do not specify the indication. The indication listed in Table 7 is based on the information about the medicine in the literature and/or approvals in other jurisdictions. When there is an aligned review, in some cases the indication was confirmed by the CADTH Reimbursement Review report.

Data source: GlobalData Healthcare database.

EMERGING COVID-19 THERAPIES

This section of the Meds Pipeline Monitor includes an overview of new and existing pipeline medicines that are under clinical evaluation for indications related to the prevention and treatment of COVID-19. An analysis of global markets provides information on COVID-19 medicines in all phases of clinical trials and pre-registration.

Global markets

The COVID-19 drug pipeline has developed at unprecedented rates over the past 3 years. Published information confirming the safety and efficacy of the various treatments for COVID-19 is continuously evolving.

In addition to the wide variety of vaccines under development, many novel and repurposed medicines are currently being evaluated in clinical trials for their potential benefits in the treatment of COVID-19. These include antivirals, monoclonal antibodies, synthetic peptides and cell therapies.[273]

A breakdown of the COVID-19 pipeline vaccines and treatments by phase of clinical evaluation is shown in Figure 5. For this snapshot, data was extracted for medicines indicated for the treatment of COVID-19 with a development stage of Phase I, II, III, or pre-registration. These medicines are presented in three categories: vaccines, which are used to prevent infection of the novel coronavirus; treatments (new medicines), which are new medicines used for the prevention or reduction of some of the complications associated with COVID-19 (e.g., pneumonia or respiratory complications and hyperinflammation); and treatments (existing medicines), which are previously marketed medicines that have been repurposed to treat COVID-19 or its symptoms.

Brief Insights

The pipeline for COVID-19 medicines continues to grow with clinical investigations of novel and existing drugs. The following are some of the most significant advancements in 2022:

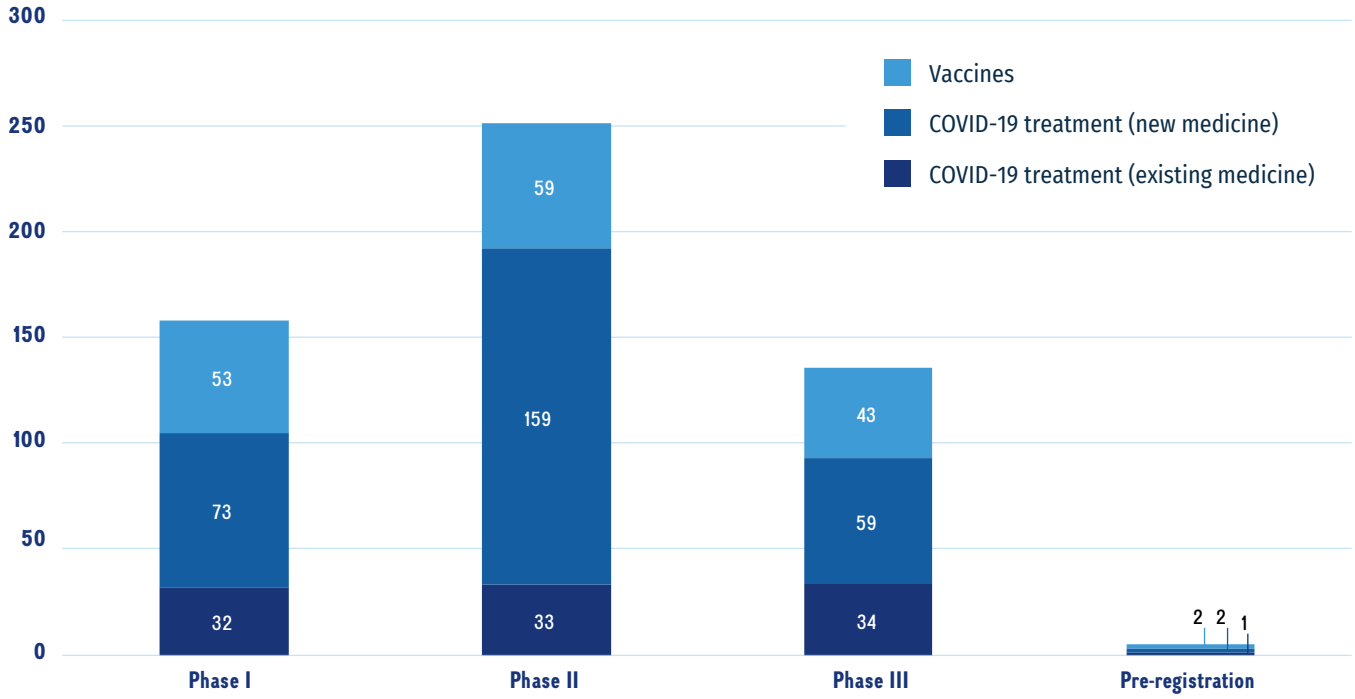
- In 2022, over 400 novel medicines were undergoing clinical evaluation for the treatment and prevention of COVID-19. This is a 10% increase from last year.
- Advances in vaccine technology have allowed for rapid updates and approvals for existing vaccines to protect against new strains of COVID-19.
- Bivalent vaccines that target the BA.4 and BA.5 subvariants of Omicron have been approved in many countries worldwide.
- Nasal vaccines are a growing alternative approach to preventing the infection of COVID-19. In 2022, there were 20 nasal vaccines in various phases of the pipeline. Currently there are two nasal or inhaled vaccines approved in China and India.
- More effective treatment options in the pipeline include oral antivirals and new monoclonal antibodies that have shown positive results in clinical trials.
- Stem cell therapy and stem cell-derived organoid models are a growing new treatment option and research method for COVID-19. As of February 2023, there were 53 cell therapies undergoing clinical evaluation in various phases of the pipeline.

Source: GlobalData Healthcare Database (February, 2023); Health Canada (February, 2023).

Figure 5 illustrates the number of clinical trials for COVID-19 treatments and vaccines by latest development phase as of September 2022. The majority of vaccines in the pipeline (97%) are new medicines intended to prevent COVID-19 infection. Antivirals are the most common therapy used to treat COVID-19 symptoms, with 74% new medicines in the pipeline. Other treatment options include monoclonal antibodies, cell therapies and synthetic peptides, that have a larger percentage of redirected and repurposed medicines in the pipeline.

FIGURE 5

Number of medicines undergoing clinical evaluation for the prevention and treatment of COVID-19 by phase of development, 2022

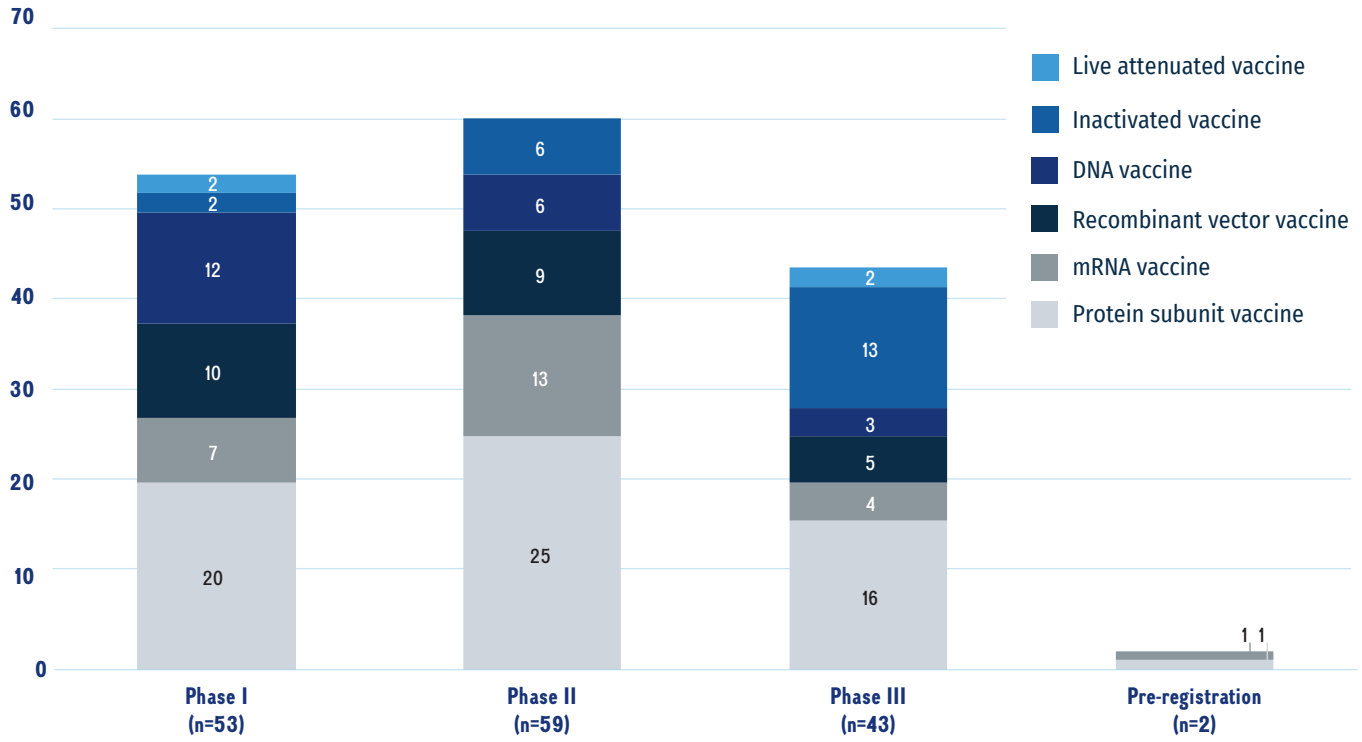


Data source: GlobalData (accessed September 2022).

Figure 6 breaks down the COVID-19 vaccines by mechanism of action and latest development phase.[xiv] Vaccines are categorized into various vaccine types based on their mechanism of action; for example, while live attenuated vaccines target the whole virus, protein subunit and recombinant vector vaccines target one specific part of the virus.

FIGURE 6

Distribution of COVID-19 vaccines by mechanism of action and phase of development, 2022



Data source: GlobalData (accessed September 2022).

Canada

COVID-19 continues to impact Canadians, with approximately 182,000 hospitalizations and over 52,000 deaths as of March 2023.[xv] Over 85% of Canadians have completed their primary series of vaccinations (two doses).[xvi] Health Canada's most recently approved vaccines are bivalent vaccines that target two different strains of the virus. The updated Moderna Spikevax and Pfizer-BioNTech Comirnaty vaccines target the original SARS-CoV-2 virus as well as the Omicron BA.4 and BA.5 subvariants, which were known to be resistant to previous versions of the vaccines. The vaccines are produced using the same methods as previous COVID-19 vaccines, except that they contain two mRNA components instead of one, which allows them to target more than one strain of the virus.

Health Canada is prioritizing reviews of all COVID-19 vaccine submissions. As of March 2023, Health Canada has approved 6 vaccines, including two mRNA vaccines (Comirnaty and Spikevax), two viral vector-based vaccines (Jcovden and Vaxzevria), one plant-based vaccine (Covifenz), and one protein-based vaccine (Nuvaxovid). Table 8 provides the number of medicines approved by Health Canada for the prevention and treatment of COVID-19, while Table 9 gives the number of COVID-19 medicines under review with Health Canada as of March 2023.

[xiv] Candidate vaccines in both clinical and preclinical evaluation are also reported by the World Health Organization. For a current list, visit their website: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

[xv] https://health-infobase.canada.ca/covid-19/current-situation.html

[xvi] https://www150.statcan.gc.ca/n1/pub/11-631-x/11-631-x2022001-eng.htm

TABLE 8
COVID-19 treatments and vaccines approved by Health Canada, 2022

Therapeutic area	Applicant	Medicinal ingredient(s)	Outcome of application	Date of decision/ outcome
Antivirals for systemic use	**Veklury** Gilead Sciences Canada Inc.	Remdesivir (solution for injection)	**Approved under:** *Food and Drug Regulations*; Notice of Compliance issued under the NOC/c Guidance **Expanded indication:** *Food and Drug Regulations*; authorized	27-Jul-20 22-Apr-22
Antivirals for systemic use	**Paxlovid** Pfizer Canada ULC	Nirmatrelvir and ritonavir (tablets for oral administration)	**Approved under:** *Food and Drug Regulations*; authorized with terms and conditions	17-Jan-22
Immune sera and immunoglobulins	**Evusheld** AstraZeneca Canada Inc.	Cilgavimab and tixagevimab solution for injection	**Approved under:** *Food and Drug Regulations*; authorized with terms and conditions **Expanded indication:** *Food and Drug Regulations*; authorized	14-Apr-22 18-Oct-22
Immune sera and immunoglobulins	**Casirivimab and imdevimab** Hoffmann-La Roche Ltd	Casirivimab and imdevimab (solution for injection)	**Approved under:** Interim order;* authorized with terms and conditions	09-Jun-21
Immune sera and immunoglobulins	**Bamlanivimab** Eli Lilly Canada Inc.	Bamlanivimab (solution for injection)	**Approved under:** Interim order;* authorized with terms and conditions	20-Nov-20
Immune sera and immunoglobulins	**Sotrovimab** GlaxoSmithKline Inc.	Sotrovimab (solution for injection)	**Approved under:** Interim order;* authorized with terms and conditions	30-Jul-21
Immune sera and immunoglobulins	**Actemra** Hoffmann-La Roche Ltd	Tocilizumab solution for injection	**Expanded indication:** *Food and Drug Regulations*; authorized	13-Oct-22
Vaccines	**Covifenz** Medicago Inc	Virus-like particles of SARS-CoV-2 spike protein	**Approved under:** *Food and Drug Regulations*; authorized with terms and conditions	24-Feb-22
Vaccines	**Nuvaxovid** Novavax Inc.	SARS-CoV-2 recombinant spike protein	**Approved under:** Adolescent dose (ages 12-17 years) *Food and Drug Regulations* First booster dose *Food and Drug Regulations*; authorized with terms and conditions *Food and Drug Regulations*; authorized with terms and conditions	06-Dec-22 17-Nov-22 17-Feb-22

Therapeutic area	Applicant	Medicinal ingredient(s)	Outcome of application	Date of decision/ outcome
Vaccines	**Vaxzevria** AstraZeneca Canada Inc.	ChAdOx1-S [recombinant] (solution for injection)	**Approved under:** *Food and Drug Regulations*; authorized with terms and conditions	19-Nov-21
			Interim order*	26-Feb-21
Vaccines	**Comirnaty** BioNTech Manufacturing GmbH	Tozinameran [mRNA vaccine, BNT162b2] (suspension for injection)	**Approved under:** Bivalent booster (ages 5-11 years) *Food and Drug Regulations*; authorized with terms and conditions	09-Dec-22
			Bivalent booster (ages 12 years and over) *Food and Drug Regulations*; authorized with terms and conditions	07-Oct-22
			Pediatric indication (ages 6 months-5 years) *Food and Drug Regulations*; authorized with terms and conditions	09-Sep-22
			First booster dose (ages 5-11 years) *Food and Drug Regulations*; authorized with terms and conditions	19-Aug-22
			First booster dose (ages 5-11 years) *Food and Drug Regulations*; authorized with terms and conditions	01-Jun-22
			First booster dose (ages 16-17 years) *Food and Drug Regulations*; authorized with terms and conditions	19-Nov-21
			Food and Drug Regulations; first booster dose	09-Nov-21
			Food and Drug Regulations; authorized with terms and conditions	16-Sept-21
			Interim order;* pediatric indication (ages 12-15)	05-May-21
			Interim order*	09-Dec-20

Therapeutic area	Applicant	Medicinal ingredient(s)	Outcome of application	Date of decision/ outcome
Vaccines	**Spikevax** Moderna TX, Inc.	Elasomeran (suspension for injection)	**Approved under:** First booster dose (ages 12-17 years) *Food and Drug Regulations*; authorized with terms and conditions	12-Jan-23
			Bivalent booster (ages 18 years and over) *Food and Drug Regulations*; authorized with terms and conditions	03-Nov-22
			Bivalent booster (ages 18 years and over) *Food and Drug Regulations*; authorized with terms and conditions	01-Sep-22
			Pediatric indication (ages 6 months-5 years) *Food and Drug Regulations*; authorized with terms and conditions	14-Jul-22
			Pediatric indication (ages 6-11 years) *Food and Drug Regulations*; authorized with terms and conditions	17-Mar-22
			First booster dose *Food and Drug Regulations*; authorized with terms and conditions	12-Nov-21
			Food and Drug Regulations; authorized with terms and conditions	16-Sept-21
			Interim order;* pediatric indication (ages 12-17)	27-Aug-21
			Interim order*	23-Dec-20
Vaccines	**Jcovden** Janssen Inc.	AD26.COV2.S [recombinant] (suspension for injection)	**Approved under:** First booster dose *Food and Drug Regulations*; authorized with terms and conditions	11-May-22
			Food and Drug Regulations; authorized with terms and conditions	23-Nov-21
			Interim order*	05-Mar-21
Vaccines	**Covishield** Verity Pharmaceuticals Inc/Serum Institute of India (in partnership with AstraZeneca Canada Inc)	ChAdOx1-S (recombinant)	**Approved under:** Interim order;* authorized with terms and conditions	26-Feb-2021 (expired 16-Sept-21)

* The *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19*, approved on May 23, 2020, introduced an alternate pathway to facilitate clinical trials for potential COVID-19 drugs and medicinal devices, while upholding strong patient safety requirements and validity of trial data.

Data source: Drug and vaccine authorizations for COVID-19: List of authorized drugs, vaccines and expanded indications (accessed March 2023):

https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/list-drugs.html

TABLE 9

COVID-19 treatments and vaccines under review by Health Canada, as of March 2023

Therapeutic area	Applicant	Medicinal ingredient(s)	Date submission accepted
Vaccines	Pfizer Canada ULC/ BioNTech SE	Tozinameran	Feb-22
Vaccines – Booster dose	AstraZeneca Canada Inc.	[ChAdOx1-S; [recombinant]	Dec-21
Vaccines – Booster dose	Janssen Inc.	Ad26.COV2.S	Dec-21
Vaccines – Pediatric dose (ages 6-11)	ModernaTX, Inc.	Elasomeran	Nov-21
Vaccines	Medicago Inc.	Coronavirus-like particle [CoVLP]	Aug-21
Vaccines	Novavax Inc.	NVX-CoV2373	Aug-21
Vaccines	Sanofi Pasteur Ltd	SARS-CoV-2 prefusion spike delta TM protein [recombinant]	Jul-21
Vaccines	Vaccigen Ltd	Whole virion inactivated coronavirus	Jul-21
Immune sera and immunoglobulins	AstraZeneca Canada Inc.	Cilgavimab, tixagevimab	Nov-21
Immune sera and immunoglobulins	Celltrion HealthCare Co. Ltd	Regdanvimab	May-21
Immune sera and immunoglobulins	Eli Lilly Canada Inc.	Bamlanivimab*	Jun-21
Immune sera and immunoglobulins	Hoffmann-La Roche Ltd	Casirivimab, imdevimab*	Sept-21
Immune sera and immunoglobulins	GlaxoSmithKline Inc.	Sotrovimab*	Oct-21
Immune sera and immunoglobulins	Eli Lilly Canada Inc.	Etesevimab	Sept-21
Immunosuppressants	Eli Lilly Canada Inc	Baricitinib	Sep-21
Antivirals for systemic use	Gilead Sciences Canada Inc	Remdesivir	Apr-21
Antivirals for systemic use	Dr Reddys Laboratories Ltd	Favipiravir	Sept-21
Antivirals for systemic use	Merck Canada Inc	Molnupiravir	Aug-21
CEASED REVIEWS			
Immune sera and immunoglobulins	CytoDyn Inc.	Leronlimab	Mar-21 (Expired)
Antigout preparations	Pendopharm Division of Pharmascience Inc	Colchicine	Jan-21 07-Jun-21 cancelled by sponsor
Other nervous system drugs	Sanotize Research & Development Corp.	Nitric oxide	Jun-21 01-Sep-21 cancelled by sponsor

* The applicant has filed a new drug submission under the Food and Drug Regulations to transition this product from the interim order. The product continues to be approved for sale in Canada during this transition period.

Data source: Drug and vaccine authorizations for COVID-19: List of applications received, Health Canada (accessed March 2023): https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/applications.html

APPENDIX A

TABLE A1
Biosimilars in Phase III (based on data extract from 2022-09)

Medicine	Reference product (manufacturer)	Other biosimilars (Y/N)	Manufacturers developing biosimilars	Indication(s)
Adalimumab	Humira (Abbvie Corp)	Y	Enzene Biosciences Ltd	Ankylosing spondylitis (Bekhterev's disease)
			Wuhan Institute of Biological Products Co Ltd	Plaque psoriasis (psoriasis vulgaris)
Aflibercept	Eylea (Bayer Inc)	N	Amgen Inc Alteogen Inc Alvotech SA Celltrion Inc Formycon AG Hexal AG Johnson & Johnson Sam Chun Dang Pharm Co Ltd Samsung Bioepis Co Ltd	Wet (neovascular/exudative) macular degeneration
Bevacizumab	Avastin (Hoffmann-La Roche Limited)	Y	Aurobindo Pharma Ltd Prestige BioPharma Ltd SinoCelltech Group Ltd	Non-small cell lung cancer
			Centrion†	N/A
Cetuximab	Erbitux	N	Ampo Biotechnology Inc Cinnagen Co Enzene Biosciences Ltd R-Pharm	Head and neck cancer squamous cell carcinoma; Lip cancer; Locally recurrent or locoregional solid malignancies; Oral cavity (mouth) cancer; Pharyngeal neoplasm; Metastatic colorectal cancer
Darbepoetin alfa	Aranesp (Amgen Canada Inc)	N	Biocad	Anemia in chronic kidney disease (renal anemia)
Denosumab	Prolia / Xgeva (Amgen Canada Inc)	N	Mabwell Shanghai Bioscience Co Ltd	Diabetes
			Celltrion Inc Eden Biologics Inc Fresenius Kabi SwissBioSim GmbH Gedeon Richter Plc Mabxience Holding SL Samsung Bioepis Co Ltd Sandoz International GmbH Teva Pharmaceutical Industries Ltd	Postmenopausal osteoporosis
			Sandoz International GmbH	Bone metastasis; Giant cell tumour of bone

Medicine	Reference product (manufacturer)	Other biosimilars (Y/N)	Manufacturers developing biosimilars	Indication(s)
Eculizumab	Soliris (Alexion Pharma GmbH)	N	Amgen Inc† Samsung Bioepis Co Ltd	Paroxysmal nocturnal hemoglobinuria
Enoxaparin	Lovenox (Sanofi-Aventis Canada Inc)	Y	Baxter Corporation† Fresenius Kabi Canada Ltd†	N/A
Etanercept	Enbrel (Immunex Corporation)	Y	Mycenax Biotech Inc	Rheumatoid arthritis
Follitropin alfa	Gonal-F / Pergoveris (EMD Serono, a division of EMD Inc., Canada)	N	Amega Biotech	Female infertility
Golimumab	Simponi (Janssen Inc)	N	Bio-Thera Solutions Ltd	Psoriatic arthritis
Liraglutide	Victoza / Saxenda (Novo Nordisk Canada Inc)	N	Shanghai Fosun Pharmaceutical (Group) Co Ltd	Obesity
Ocrelizumab	Ocrevus (Hoffmann-La Roche Limited)	N	Cinnagen Co	Relapsing remitting multiple sclerosis (RRMS)
Omalizumab	Xolair (Novartis Pharmaceuticals Canada Inc)	N	Synermore Biologics Co Ltd	Allergic asthma
			Celltrion Inc Synermore Biologics Co Ltd Teva Pharmaceutical Industries Ltd	Chronic urticaria or hives
			Synermore Biologics Co Ltd	Nasal polyps (nasal polyposis); Rhinosinusitis
Pegfilgrastim	Neulasta (Amgen Canada Inc)	Y	Lupin Pharma Canada Limited† Nora Pharma Inc†	Febrile neutropenia
Pertuzumab	Perjeta (Hoffmann-La Roche Limited)	N	Zydus Lifesciences Ltd	Human epidermal growth factor receptor 2-positive breast cancer (HER2+ breast cancer)
Ranibizumab	Lucentis (Novartis Pharmaceuticals Canada Inc)	Y*	Aurobindo Pharma Ltd Enzene Biosciences Ltd Generium Jecho Biopharmaceuticals Co Ltd Lupin Ltd PharmaResearch BIO Co Ltd	Wet (neovascular/exudative) macular degeneration
Romiplostim	Nplate (Amgen Canada Inc)	N	Generium	Idiopathic thrombocytopenic purpura (immune thrombocytopenic purpura)
Tenecteplase	TNKase (Hoffmann-La Roche Limited)	N	Hetero Drugs Ltd	Myocardial infarction

Medicine	Reference product (manufacturer)	Other biosimilars (Y/N)	Manufacturers developing biosimilars	Indication(s)
Trastuzumab	Herceptin (Hoffmann-La Roche Limited)	Y	Aprogen Inc Hetero Drugs Ltd Tanvex BioPharma Inc Prestige BioPharma Ltd. (HC)†	Human epidermal growth factor receptor 2-positive breast cancer (HER2+ Breast Cancer)
Ustekinumab	Stelara (Janssen Inc)	N	DM Bio Ltd Samsung Bioepis Co Ltd	Psoriatic arthritis
			Amgen Inc Alvotech SA Bio-Thera Solutions Ltd Celltrion Inc DM Bio Ltd Formycon AG Samsung Bioepis Co Ltd	Plaque psoriasis (psoriasis vulgaris)
			DM Bio Ltd	Crohn's disease (regional enteritis); Ulcerative colitis
			JiangSu Qyuns Therapeutics Co Ltd	Inflammatory bowel disease

* Approved but not marketed as of December 5, 2022.

† Biosimilar currently under review by Health Canada.

TABLE A2

New drug submissions under review by Health Canada (February 2023)

Medicinal ingredient	Therapeutic area	Manufacturer	Date submission accepted for review
Aflibercept	Ophthalmologicals	BGP Pharma ULC	2022-05
Bevacizumab	Antineoplastic agents	Celltrion Healthcare Co Ltd	2022-03
Eculizumab	Immunosuppressants	Amgen Canada Inc	2022-07
Enoxaparin sodium	Antithrombotic agents	Baxter Corporation	2022-09
Pegfilgrastim	Immunostimulants	Lupin Pharma Canada Limited	2022-05
Pegfilgrastim	Immunostimulants	Nora Pharma Inc	2022-05
Ranibizumab	Ophthalmologicals	Teva Canada Limited	2022-12
Trastuzumab	Antineoplastic agents	Prestige BioPharma Ltd.	2021-08

TABLE A3
Drugs in Phase II for indications targeted by pipeline candidates

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*
Abelacimab	Deep vein thrombosis (DVT); Pulmonary embolism	○ Undisclosed MOA (TF-0023, Zifa-01). There are no other drugs for this indication with the same MOA as abelacimab (a dual Factor XI and Factor Xia inhibitor) in Phase II development at this time.
Aprocitentan and **Firibastat**	Resistant hypertension	○ Angiotensinogen inhibitor (evazarsen, tonlamarsen); ○ Atrial natriuretic peptide receptor 1 agonist (PL-3994); ○ Cytochrome P450 11B2 mitochondrial inhibitor (baxdrostat). There are no other drugs for this indication with the same MOA as aprocitentan (a dual endothelin-receptor antagonist) or firibistat (a centrally-acting, aminopeptidase A inhibitor) in Phase II development at this time.

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*

Bemarituzumab and **Zolbetuximab**	Adenocarcinoma of the gastroesophageal junction; Gastric cancer; bladder cancer; Gastroesophageal (GE) junction carcinomas	• Angiopoietin 2 inhibitor (BI-836880);
		• C-C chemokine receptor Type 8 antagonist (BMS-986340, S-531011);
		• Cell therapy (RAPA-201);
		• Claudin-18 inhibitor (BNT-141, LM-302);
		• Cytotoxic to cells expressing:
		  ◦ Claudin-18 (CT-041, SOT-102);
		  ◦ Epidermal growth factor receptor (AFM-24I, cetuximab, MRG-003);
		  ◦ Intercellular adhesion molecule 1 (gebasaxturev);
		  ◦ Receptor tyrosine protein kinase ERBB 2 (cinrebafusp alfa, DP-303c);
		  ◦ Stabilin 1 (bexmarilimab);
		  ◦ Telomerase reverse transcriptase (suratadenoturev);
		• Delta like protein 4 inhibitor (navicixizumab);
		• Deoxyuridine 5' triphosphate nucleotidohydrolase mitochondrial inhibitor (TAS-114);
		• Dickkopf related protein 1 inhibitor (DKN-01);
		• DNA synthesis inhibitor (doxorubicin);
		• DNA topoisomerase i inhibitor (irinotecan);
		• Epidermal growth factor receptor antagonist (GC-1118A, MCLA-129);
		• Fc fragment of IgG low affinity iii receptor agonist (CYNK-101);
		• Fibroblast growth factor receptor inhibitor (MAX-4);
		• Gremlin 1 inhibitor (UCB-6114);
		• Histone lysine N methyltransferase EZH2 inhibitor (CPI-0209);
		• Interleukin 2 receptor agonist (SAR-444245);
		• Interleukin 7 receptor subunit alpha agonist (efineptakin alfa);
		• Leukocyte immunoglobulin like receptor subfamily B member 1 antagonist (SAR-444881);
		• Leukocyte surface antigen CD47 inhibitors (AO-176, ligufalimab);
		• Low affinity immunoglobulin gamma Fc region receptor II-b antagonist (BI-1607);
		• Lymphocyte activation gene 3 protein inhibitor (miptenalimab);
		• Mitogen activated protein kinase 1 inhibitors (NMBS-2, ulixertinib);
		• Nuclear receptor ROR Gamma agonist (cintirorgon);
		• 5' nucleotidase inhibitor (uliledlimab);
		• Programmed cell death 1 ligand 1 inhibitor (ezabenlimab, HB-0036);
		• Serine/threonine protein kinase ATR inhibitor (ceralasertib);
		• Smoothened homolog antagonist (taladegib);
		• T cell immunoreceptor with Ig and ITIM domains antagonist (etigilimab);
		• Tumor necrosis factor receptor superfamily member 5 agonist (sotigalimab);
		• Tumor necrosis factor receptor superfamily member 18 agonist (ragifilimab);
		• Vaccines (IMU-131, ombipepimut-s);
		• Vascular endothelial growth factor inhibitor (KH-903);
		• Zinc transporter ZIP6 inhibitor (ladiratuzumab vedotin);
		• Others with undisclosed mechanism of action (ecubectedin, GEN-001, VE-800).
		
		There is another drug (MAX-4) with a similar MOA to bemarituzumab (a fibroblast growth factor receptor inhibitor) and others (BNT-141, LM-302) with a similar MOA to zolbetuximab (a claudin-18 inhibitor) in Phase II development at this time.

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*

Ciltacabtagene autoleucel* and **Iberdomide hydrochloride**	Refractory multiple myeloma; Relapsed multiple myeloma	• Activin receptor Type 1 antagonist (INCB-00928);
		• ADP ribosyl cyclase/cyclic ADP ribose hydrolase 1 inhibitors (BHV-1100, mezagitamab);
		• Arginase 1 inhibitor (numidargistat);
		• ATP dependent Clp protease proteolytic subunit mitochondrial activator (ONC-201);
		• B-cell lymphoma 2 inhibitor (APG-2575, BGB-11417);
		• CD3 agonist (ABBV-383, cevostamab, HPN-217, ISB-1342, linvoseltamab, REGN-5459, talquetamab);
		• Cell therapy (various, ACP- 001, Anti-BCMA/GPRC5D CAR-T, ARI-0002h, CAR-BCMA, ECT-001, GDA-201, NEXI-002, NK Cell Multiple Myeloma, RAPA-201, VAX-DC);
		• CREB binding protein inhibitor (inobrodib);
		• Cytotoxic to cells expressing:
		  ◦ ADP ribosyl cyclase/cyclic ADP ribose hydrolase 1 (GEN-3014, modakafusp alfa, STI-6129);
		  ◦ Carcinoembryonic antigen related cell adhesion molecule 8 (TLX-66);
		  ◦ Kappa myeloma antigen (MDX-1097);
		  ◦ Membrane cofactor protein (oncolytic virus);
		  ◦ Tumor necrosis factor receptor superfamily member 17 (ALLO-605, CC-99712, HDP-101);
		• Dickkopf related protein 1 inhibitor (BHQ-880);
		• DNA repair protein RAD51 homolog 1 inhibitor (CYT-0851);
		• DNA synthesis inhibitor (doxorubicin);
		• Dual specificity mitogen activated protein kinase kinase 1 inhibitor (trametinib dimethyl sulfoxide + uprosertib);
		• Exportin 1 inhibitor (eltanexor);
		• Fibroblast growth factor receptor 1 inhibitor (ABSK-091);
		• Gene-modified cell therapy (various, Descartes-08, Descartes-11, Descartes-25, GDT-002, KJC-2111, letetresgene autoleucel, OPC-415, orvacabtagene autoleucel, PBCAR-269A, PHE-885, SENL-302, zevorcabtagene autoleucel);
		• Heparanase inhibitor (roneparstat);
		• Hepatocyte growth factor inhibitor (MP-0250);
		• Histone deacetylase 6 inhibitor (ricolinostat);
		• Interleukin 2 receptor subunit alpha agonist (ANV-419);
		• Interleukin 15 receptor subunit alpha agonist (NKTR-255);
		• Interleukin 18 inhibitor (AVTX-007);
		• Killer cell immunoglobulin like receptor 2DL1 Antagonist (lirilumab);
		• Leukocyte surface antigen CD47 inhibitor (AO-176, PF-07901801);
		• Phosphatidylinositol 4,5 bisphosphate 3 kinase catalytic subunit beta isoform inhibitor (GSK-2636771);
		• Programmed cell death protein 1 antagonist (pidilizumab);
		• 20s proteasome inhibitor (CX-13608);
		• Protein cereblon activator (CFT-7455, mezigdomide);
		• Protein S100 A9 inhibitor (tasquinimod);
		• RAC alpha serine/threonine protein kinase inhibitor (uprosertib);
		• Small ubiquitin related modifier 2 inhibitor (subasumstat);
		• T cell immunoreceptor with Ig and ITIM domains antagonists (belrestotug, BMS-986207);
		• TGF beta receptor Type 1 inhibitor (vactosertib);
		• Vaccines (biropepimut-S, GVAX Multiple Myeloma Vaccine, ImMucin, IO-103, PVX-410);
		• Wee1 like protein kinase inhibitor (adavosertib);
		• Others with undisclosed MOA (CB-103 , imifoplatin, iopofosine i-131, KES-0001).
		
		There are other drugs (CFT-7455, mezigdomide) for this indication with a similar MOA to Iberdomide (a protein cereblon activator) and other gene therapies like ciltacabtagene in Phase II development at this time.

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*
Concizumab*	Haemophilia B	○ Coagulation factor VII replacement (OPK-88005); ○ Coagulation factor IX activator (lanacogene vosiparvovec, verbrinacogene setparvovec); ○ Coagulation factor IX replacement (dalcinonacog alfa LA); ○ Coagulation factor X activator (STSP-0601); ○ Vitamin K dependent protein C inhibitor (SerpinPC). There are no other drugs for this indication with the same MOA as concizumab (a tissue factor pathway inhibitor) in Phase II development at this time.
Evobrutinib	Relapsing multiple sclerosis (RMS); Secondary progressive multiple sclerosis (SPMS)	○ ACE inhibitor (lisinopril); ○ CD40 ligand inhibitor (SAR-441344); ○ Cell therapy (ATA-188, ATA-190, CLS-12311, NG-1); ○ Combination (ASA and dimethyl fumarate); integrin alpha 4 inhibitor (ATL-1102); ○ Lysine specific histone demethylase 1A inhibitor (vafidemstat); repulsive guidance molecule A inhibitor (elezanumab); ○ Serine/threonine protein kinase Sgk2 activator (OCS-05); ○ Sphingosine 1-phosphate receptor 1 antagonist (amiselimod); ○ T cell surface glycoprotein CD3 Epsilon chain antagonist (foralumab); ○ Other with an undisclosed MOA (IB-MS, IMCY-0141, MP-101, RNS-60, smderpept, temelimab, WP-1303). There are no other drugs for this indication with the same MOA as evobrutinib (a selective, CNS penetrant immunomodulator that irreversibly blocks BTK) in Phase II development at this time.
FCR001	Kidney transplant rejection	○ Antibody (LIS-1); ○ CD40 ligand inhibitor (tegoprubart); ○ Cell therapies (MDR-102, MIC-Lx, TX-200); ○ T cell specific surface glycoprotein CD28 antagonists (FR-104, lulizumab pegol); ○ T cell surface antigen CD2 inhibitor (siplizumab); ○ T lymphocyte activation antigen CD80 inhibitor (belatacept). There are other cell therapies like FCR001 for this indication in Phase II development at this time.
Firibastat		Refer to information under "aprocitentan"
Garadacimab	Hereditary angioedema (HAE) (C1 esterase inhibitor [C1-INH] deficiency	○ Complement C1s subcomponent inhibitor (C1 esterase inhibitor); ○ Gene therapy (BMN-331); ○ Plasma kallikrein inhibitor (KVD-824, NTLA-2002). There are no other drugs for this indication with the same MOA as garadacimab (an immunoglobulin G4 monoclonal antibody that interferes with FXIIa-mediated coagulation) in Phase II development at this time.

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*
Glofitamab	B-cell lymphomas	○ CTP synthase 1 inhibitor (STP-938); ○ Cyclin dependent kinase 2 inhibitor (fadraciclib); ○ Gene-modified cell therapy (CD19/70 Bi-specific CAR-T cell therapy ○ Glucocorticoid receptor agonist (dexamethasone); ○ 2 oxoglutarate dehydrogenase inhibitor (devimistat). There are no other drugs for this indication with the same MOA as glofitamab (a CD20xCD3 T-cell engaging bispecific antibody) in Phase II development at this time.
Iberdomide hydrochloride		Refer to information under "ciltacabtagene"
Imetelstat and **Navitoclax**	Myelodysplastic dyndrome; Post-rssential thrombocythemia myelofibrosis (post-ET MF); Post-polycythemia vera myelofibrosis (PPV-MF)	○ Activin receptor type 1 antagonist (INCB-00928); ○ Baculoviral IAP repeat containing protein 2 inhibitor (LCL-161); ○ Bromodomain containing protein 2 inhibitor (ABBV-744, BMS-986158); ○ E3 ubiquitin protein ligase Mdm2 inhibitor (siremadlin); ○ Glycogen synthase kinase 3 beta inhibitor (elraglusib); ○ Hemojuvelin inhibitor (DISC-0974); ○ Histone deacetylase 1 inhibitor (pracinostat); ○ Lysine specific histone demethylase 1A inhibitor (bomedemstat); ○ Lysyl oxidase homolog 2 inhibitor (GB-2064, PXS-5505A); ○ Serine/threonine protein kinase Pim 1 inhibitor (TP-3654); ○ Tyrosine protein kinase BTK inhibitor (TL-895); ○ Tyrosine protein kinase JAK2 inhibitor (ilginatinib); ○ Vaccine (Triplex); ○ Other with undisclosed MOA (INCB-57643). There are no other drugs for this indication with the same MOA as imetelstat (a telomerase inhibitor) or navitoclax (an antagonist of a subset of the B-cell leukemia 2 family of proteins) in Phase II development at this time.

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*
Masitinib* and **Reldesemtiv**	Amyotrophic Lateral Sclerosis (ALS)	• Anti-apoptosis Stressin-1 peptide (IPL-344); • Apoptosis regulator BAX inhibitor (GM-6); • Arachidonate 15 lipoxygenase inhibitor (PTC-857); • Ataxin 2 inhibitor (ION-541); • CD40 ligand inhibitor (tegoprubart); • Cell therapy (astrorx, COYA-101, NG-1, RAPA-501); • Coagulation factor V inhibitor (3K3A-APC); • Combinations (acamprosate + baclofen, celecoxib + ciprofloxacin, nicotinamide riboside + pterostilbene); • Fibroblast growth factor receptor 1 agonist (FGF-1); • Glial cell line derived neurotrophic factor activator (gene therapy); • Guanine nucleotide exchange c9orf72 inhibitor (WVE-004); • Ikappa B kinase inhibitor (OP-101); • Macrophage colony stimulating factor 1 receptor antagonist (sotuletinib); • 1-phosphatidylinositol-3-phosphate-5-kinase inhibitor (apilimod); • Receptor interacting serine/threonine protein kinase 1 inhibitor (DNL-788); • Reverse transcriptase inhibitor (censavudine); • Reversible redox cofactor (EPI-589); • Superoxide dismutase activator (AP-101); • Other with an undisclosed MOA (MP-101, NP-001, RNS-60, TM-700). There are no other drugs for this indication with the same MOA as masitinib (a selective tyrosine kinase inhibitor) or reldesemtiv (a fast skeletal muscle troponin activator) or in Phase II development at this time.
Navitoclax dihydrochloride		Refer to information under "imetelstat"
Obicetrapib	Dyslipidemia; Heterozygous familial hypercholesterolemia (heFH); Atherosclerosis	• Angiopoietin related protein inhibitor (AROANG-3, LY-3561774); • Apolipoprotein A inhibitor (olpasiran); • Dual inhibitor of cholesterol and triglyceride synthesis (gemcabene); • Geranylgeranyl pyrophosphate synthase inhibitor (antroquinonol); • Low density lipoprotein receptor agonist (AEM-28); • Proprotein convertase subtilisin/kexin type 9 inhibitor (AZD-8233, cepadacursen, MK-0616, NN-6434); • Thyroid hormone receptor beta agonist (VK-2809); • Toll like receptor 2 and 4 antagonist (VB-201); • Other with an undisclosed MOA (DWJ-1506, DWJ-1507, PC-mab). There are no other drugs for this indication with the same MOA as obicetrapib (a CETP inhibitor) in Phase II development at this time.
Pegcetacoplan*	Paroxysmal Nocturnal Hemoglobinuria	• Complement C5 inhibitor (tesidolumab); • Complement factor D inhibitor (ALXN-2050, BCX-9930). There are no other drugs for this indication with the same MOA as pegcetacoplan (a complement C3 and fragment C3b inhibitor) in Phase II development at this time.

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*

Relacorilant	Epithelial ovarian cancer	• Arginase 1 inhibitor (numidargistat);
		• Bromodomain containing protein inhibitor (ff-21101);
		• Cd3 agonist (hpn-536, ubamatamab);
		• Cell membrane disruptor (at-101);
		• Cell therapy (avova-1);
		• Cellular tumor antigen p53 activator (kevetrin);
		• Cyclin dependent kinase 2 inhibitor (ebvaciclib, pf-07104091);
		• Cytotoxic to cells expressing:
		  ◦ Cd40 ligand (load-703);
		  ◦ Folate receptor alpha (farletuzumab ecteribulin);
		  ◦ Membrane cofactor protein (oncolytic virus to target cd46 and slc5a5 for oncology);
		  ◦ Mucin 16 (regn-5668);
		  ◦ Receptor tyrosine protein kinase erbb 2 (dp-303c);
		  ◦ Trophoblast glycoprotein (naptumomab estafenatox);
		• Delta like protein 4 inhibitor (navicixizumab);
		• Dickkopf related protein 1 inhibitor (dkn-01);
		• Dna topoisomerase i inhibitor (nlg-207);
		• Epidermal growth factor receptor antagonist (fmab-2
		• Focal adhesion kinase inhibitor (defactinib, in-10018);
		• Gene-modified cell therapy (various);
		• Granulocyte macrophage colony stimulating factor receptor subunit alpha agonist (oncos-102);
		• Heat shock protein 90 inhibitor (ganetespib);
		• Interleukin 12 subunit alpha activator (gen-1);
		• Leukocyte surface antigen cd47 inhibitor (ao-176, ligufalimab, pf-07901801);
		• Mitogen activated protein kinase 14 inhibitor (ralimetinib mesylate);
		• 5' nucleotidase inhibitor (ulileclimab);
		• 2'-5' oligoadenylate synthetase activator (poly-iclc);
		• Ornithine decarboxylase inhibitor (amxt-1501 + eflornithine);
		• Poly [adp ribose] polymerase 1 inhibitor (ceralasertib + olaparib);
		• Retinoic acid receptor agonist (fenretinide);
		• Serine/threonine protein kinase atr inhibitor (berzosertib);
		• Serine/threonine protein kinase chk1 inhibitor (esp-01);
		• Serine/threonine protein kinase mtor inhibitor (sapanisertib);
		• T cell immunoreceptor with ig and itim domains antagonist (bms-986207, etigilimab);
		• Transmembrane protein pvrig antagonist (com-701);
		• Tubulin inhibitor (docetaxel);
		• Tumor necrosis factor receptor superfamily member 5 agonist (sotigalimab);
		• Vaccines (maveropepimut-s, modified vaccinia ankara vaccine, ombipepimut-s, uv-1);
		• Wee1 like protein kinase inhibitor (znc-3);
		• Other with an undisclosed MOA (ecubectedin).
		
		There are no other drugs for this indication with the same MOA as relacorilant (a glucocorticoid receptor antagonist) in phase ii development at this time.

Reldesemtiv		Refer to information under "masitinib"

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*
REC-2282	Neurofibromatoses Type II (NF2)	Drugs in Phase II for this indication and their MOA: • 26s proteasome inhibitor (bortezomib). There is no other drug for this indication with the same MOA as REC-2282 (a pan-histone deacetylase inhibitor) in Phase II development at this time.
Resmetirom	Non-alcoholic steatohepatitis (NASH); Non-alcoholic fatty liver disease (NAFLD)	• Acetyl coa carboxylase inhibitor (clesacostat, firsocostat); • Adenosine monophosphate activated protein kinase activator (PXL-770); • Adenosine receptor A3 antagonist (LJ-2698); • Androgen receptor agonist (LPCN-1144); • Arachidonate 5 lipoxygenase inhibitor (tipelukast); • 17-Beta hydroxysteroid dehydrogenase 13 inhibitor (ARO-HSD); • Beta Klotho activator (BOS-580, NN-9499); • Bile acid receptor agonist (EDP-305, EYP-001, HPG-1860, TERN-101, tropifexor); • C-C motif chemokine 24 inhibitor (CM-101); • Cell therapy (hepastem); • Corticosteroid 11 beta dehydrogenase isozyme 1 inhibitor (AZD-4017); • Diacylglycerol O acyltransferase 2 inhibitor (ervogastat, ION-224); • Eotaxin inhibitor (bertilimumab); • Fibroblast growth factor receptor 1 agonist (efruxifermin, MK-3655); • Gastric inhibitory polypeptide receptor agonist (HM-15211); • Glucagon-like peptide 1 activator (BI-456906, efinopegdutide); • Ketohexokinase inhibitor (PF-06835919); • Lipopolysaccharide inhibitor (IMM-124E); • Mineralocorticoid receptor antagonist (apararenone); • Mitochondrial pyruvate carrier inhibitor (PXL-065); • Mitogen activated protein kinase 5 inhibitor (selonsertib); • NADPH oxidase inhibitor (APX-115); • Peptidyl prolyl cis trans isomerase A inhibitor (rencofilstat); • Protein glutamine gamma glutamyltransferase 2 inhibitor (ZED-1227); • Serpin H1 inhibitor (BMS-986263); • Sodium/glucose cotransporter 1 inhibitor (licogliflozin); • T cell surface glycoprotein CD3 Epsilon chain antagonist (foralumab); • Thyroid hormone receptor beta agonist (ASC-41, TERN-501, VK-2809); • Tyrosine protein kinase receptor UFO inhibitor (bemcentinib); • Combinations (cenicriviroc + tropifexor, cilofexor + firsocostat, clesacostat + ervogastat, leucine + metformin + sildenafil); • Other with an undisclosed MOA (ADTP-02, AXA-1125, B-105, epeleuton, gemcabene, HTD-1801, HU-6, icosabutate, INA-010, LM-011, MBK-002, MSDC-0602K, nitazoxanide). There are other drugs (ASC-41, TERN-501, VK-2809) for this indication with a similar MOA to resmetirom (a thyroid hormone receptor beta agonist) in Phase II development at this time.
Rusfertide acetate	Polycythemia vera	There are no other drugs for this indication in Phase II development at this time.

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*
Seladelpar	Primary biliary cholangitis (primary biliary cirrhosis)	○ Bile acid receptor agonist (ASC-42, TQA-3526 , ZG-5266); ○ Catenin Beta 1 inhibitor (PRI-724); ○ Fibroblast growth factor receptor 1 agonist (aldafermin); ○ Gamma-Aminobutyric Acid Type A receptor subunit antagonist (golexanolone); ○ Ileal sodium/bile acid cotransporter (volixibat); ○ T-lymphocyte activation antigen CD80 inhibitor (rhudex). There are no other drugs for this indication with the same MOA as seladelpar (a PPAR-delta agonist) in Phase II development at this time.
Setmelanotide	Obesity	○ Calcitonin receptor agonist (cagrilintide); ○ Enteropeptidase inhibitor (sco-792); ○ Gastric inhibitory polypeptide receptor agonist (ct-868, retatrutide); ○ Glucagon like peptide 1 receptor agonist (bi-456906, danuglipron, ecnoglutide, efinopegdutide, ly-3502970, pegapamodutide, pemvidutide); ○ Glucocorticoid receptor antagonist (miricorilant); ○ Combinations (acarbose + orlistat; leucine + metformin + sildenafil; leucine + sildenafil); ○ Other with an undisclosed MOA (bittera, cbl-514, mbl-949, nn-9775, nov-db2, novob, rzl-12). There are no other drugs for this indication with the same MOA as setmelanotide (a melanocortin-4 receptor agonist) in Phase II development at this time.
Soticlestat	Lennox-Gastaut syndrome; Dravet syndrome (severe myoclonic epilepsy of infancy)	○ 5-hydroxytryptamine receptor 2C agonist (LP-352); ○ Metabotropic glutamate receptor 1 antagonist (JBPOS-0101). There are no other drugs for this indication with the same MOA as soticlestat (a cholesterol 24-hydroxylase inhibitor) in Phase II development at this time.
Sotatercept	Pulmonary arterial hypertension (PAH)	○ ACE 2 replacement (APN-01); ○ Atrial natriuretic peptide receptor 1 agonist (ularitide); ○ Calcineurin inhibitor (tacrolimus); ○ Cgmp specific 3',5' cyclic phosphodiesterase inhibitor (vardenafil inhalation); ○ Dopamine beta hydroxylase inhibitor (zamicastat).histone deacetylase inhibitor (valproic acid); ○ Macrophage colony stimulating factor 1 receptor inhibitor (seralutinib); ○ Prostacyclin receptor agonist (epoprostenol inhalation, treprostinil palmitil inhalation); ○ Tryptophan 5 monooxygenase inhibitor (rodatristat). There are no other drugs for this indication with the same MOA as sotatercept (an activin receptor type IIA-Fc fusion protein) in Phase II development at this time.
Spesolimab*	Generalized pustular psoriasis (GPP)	There are no other drugs for this indication in Phase II development at this time.

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*

Tremelimumab	Hepatocellular carcinoma	• Aldo keto reductase family 1 member C3 inhibitor (TH-3424);
		• Arginine depletor (BCT-100);
		• Aurora kinase A inhibitor (TT-00420);
		• Catenin beta 1 inhibitor (PRI-724);
		• C-C chemokine receptor type 2 antagonist (BMS-813160);
		• CCAAT/enhancer binding protein alpha activator (MTL-CEBPA);
		• Cell therapy (various, activated T lymphocytes; Ilixadencel, NRT-01);
		• Cyclic AMP dependent transcription factor ATF 5 inhibitor (ST-101);
		• Cyclin dependent kinase 1 inhibitor (milciclib);
		• Cyclin dependent kinase 2 inhibitor (fadraciclib);
		• Cytotoxic T lymphocyte protein 4 inhibitor (ADG-126, BMS-986249, ONC-392, PSB-205, zalifrelimab);
		• Cytotoxic to cells expressing:
		  ◦ CD276 Antigen (MGC-018);
		  ◦ Epidermal growth factor receptor (AFM-24I);
		  ◦ Fibronectin (dodekin);
		  ◦ Glypican 3 (codrituzumab);
		  ◦ Intercellular adhesion molecule 1 (gebasaxturev);
		  ◦ Stabilin 1 (bexmarilimab);
		  ◦ Trophoblast glycoprotein (naptumomab estafenatox);
		• Dickkopf related protein 1 inhibitor (DKN-01);
		• DNA polymerase inhibitor (fostroxacitabine bralpamide);
		• DNA synthesis inhibitor (cisplatin + vinblastine; evofosfamide, tirapazamine);
		• Dual specificity protein kinase TTK inhibitor (NMS-153);
		• Epidermal growth factor receptor antagonist (EMB-01, fmab-2);
		• F box like/WD repeat containing protein TBL1X inhibitor (tegavivint);
		• Fibroblast growth factor receptor 4 antagonist (roblitinib);
		• Gene-modified cell therapy (various, BOXR-1030, ET-1402, Fully Human B7H3 CAR-T Cells, IMA-203CD8, JWATM-204, LIOCYXM-004, SCG-101);
		• Growth/differentiation factor 15 inhibitor (visugromab);
		• Hepatocyte growth factor receptor inhibitor (TPX-0022);
		• Histone deacetylase inhibitor (tefinostat);
		• Inducible T cell costimulator agonist (alomfilimab);
		• Interferon beta activator (Voyager-V1);
		• Interleukin 2 receptor agonist (ANV-419, BNT-151, SAR-444245);
		• Interleukin 8 inhibitor (BMS-986253);
		• Interleukin 12 receptor agonist (BMS-986415);
		• Interleukin 15 receptor subunit alpha agonist (SOT-101);
		• Interleukin 18 receptor 1 agonist (ST-067);
		• Interleukin 27 receptor antagonist (SRF-388);
		• Leukocyte immunoglobulin like receptor subfamily B member 1 antagonist (SAR-444881);
		• Lymphocyte activation gene 3 protein inhibitor (INCAGN-2385);
		• MAP kinase interacting serine/threonine protein kinase 1 inhibitor (tomivosertib);
		• Mast/stem cell growth factor receptor Kit inhibitor (MG-010 + sorafenib);

Pipeline candidate	Indication(s)	Drugs in Phase II and mechanism of action (MOA)*
Tremelimumab (continued)	Hepatocellular carcinoma	• Mitogen activated protein kinase kinase kinase kinase 1 inhibitor (CFI-402411, PRJ-13024); • Myc proto oncogene protein inhibitor (OTX-2002); • Na+/K+ exchanging atpase inhibitor (RX-108); • Nuclear factor Kappa B inhibitor (ACT-001); • Opioid receptor antagonist (metenkefalin); • Peroxisome proliferator activated receptor alpha antagonist (TPST-1120); • Phosphatidylinositol 4,5 bisphosphate 3 kinase catalytic subunit delta isoform inhibitor (BGB-10188); • Programmed cell death 1 ligand 1 inhibitor (HB-0036, INCB-86550, spartalizumab); • Protein cereblon activator (avadomide); • Protein tyrosine phosphatase Type IVA 3 inhibitor (PRL3-ZUMAB); • Receptor tyrosine protein kinase ERBB 3 antagonist (HMBD-001); • Serine/threonine protein kinase mtor inhibitor (sapanisertib); • Serine/threonine protein kinase receptor R3 inhibitor (ascrinvacumab); • Serine/threonine protein kinase PLK1 inhibitor (CYC-140); • Sialic acid binding Ig like lectin 15 inhibitor (NC-318); • Stimulator of interferon genes protein activator (CDK-002, IMSA-101, SB-11285); • Telomerase reverse transcriptase inhibitor (KML-001); • TGF beta receptor Type 1 inhibitor (galunisertib); • T lymphocyte activation antigen CD80 inhibitor (BA-3071); • Toll like receptor 9 agonist (SD-101); • Transferrin receptor protein 1 antagonist (CX-2029); • Vaccine (GNOSPV-02, IMA-970A, maveropepimut-s, ombipepimut-s, TAEK-VAC); • Other with an undisclosed MOA (ABX-196, ecubectedin, foslinanib, OC-001, phosphoethanolamine, PM-8003, SAR-444200). There are other drugs (ADG-126, BMS-986249, ONC-392, PSB-205, zalifrelimab) for this indication with a similar MOA to tremelimumab (a cytotoxic T lymphocyte protein 4 inhibitor) in Phase II development at this time.
Ulotaront	Schizophrenia	• Alpha 2 adrenergic receptor antagonist (TR-01); • D amino acid oxidase inhibitor (RSD-7); • Camp and camp inhibited cgmp 3',5' cyclic phosphodiesterase 10A inhibitor (MK-8189); • Cannabinoid receptor 1 agonist (cannabidiol); • D1A dopamine receptor antagonist (tetrahydropalamatine); • 5-hydroxytryptamine receptor 2 antagonist (iloperidone LAI); • Muscarinic acetylcholine receptor M4 agonist (emraclidine); • Potassium voltage gated channel subfamily C member 1 activator (AUT-00206); • Sodium and chloride dependent glycine transporter 1 inhibitor (bitopertin). There is one other drug (ralmitaront) for this indication with a similar MOA to ulotaront (a TAAR1 agonist) in Phase II development at this time.
Zolbetuximab		Refer to information under "bemarituzumab"
Zoliflodacin	Uncomplicated cervical and urethral gonorrhea	There are no other drugs for this indication in Phase II development at this time.

*Under review by Health Canada.

Abbreviations: ACE: angiotensin converting enzyme; ASA: acetylsalicylic acid; BTK: Bruton's tyrosine kinase; CETP: cholesteryl ester transfer protein; CNS: central nervous system; JAK: Janus Kinase; MOA: mechanism of action; PPAR: peroxisomal proliferator-activated receptor; TAAR1: trace amine associated receptor 1.

Data source: GlobalData Healthcare database (accessed September 2022).

REFERENCES

1 Clinical Development Success Rates 2006-2015. https://www.bio.org/sites/default/files/legacy/bioorg/docs/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf (accessed January 13, 2023).

2 Drug and Health Product Submissions Under Review (SUR). https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/submissions-under-review/new-drug-submissions-under-review.html

3 Anthos Therapeutics Announces that Abelacimab Has Received FDA Fast Track Designation for the Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation. September 8, 2022. https://www.globenewswire.com/news-release/2022/09/08/2512472/0/en/Anthos-Therapeutics-Announces-that-Abelacimab-Has-Received-FDA-Fast-Track-Designation-for-the-Prevention-of-Stroke-and-Systemic-Embolism-in-Patients-with-Atrial-Fibrillation.html

4 Verhamme P, Yi BA, Segers A, Salter J, Bloomfield D, et al. *Abelacimab for Prevention of Venous Thromboembolism.* N Engl J Med. 2021 Aug 12;385(7):609-617. doi: 10.1056/NEJMoa2105872. Epub 2021 Jul 19.

5 Li T, Liu J, Wu W. *Factor XI, a potential target for anticoagulation therapy for venous thromboembolism.* Front Cardiovasc Med. 2022 Oct 31;9:975767. doi: 10.3389/fcvm.2022.975767. eCollection 2022.

6 Gómez-Outes A, Suárez-Gea ML, Pérez-Cabeza AI, García-Pinilla JM. *Pharmacotherapy for stroke prevention in nonvalvular atrial fibrillation: current strategies and future directions.* Expert Opin Pharmacother. 2022 Nov 17. doi: 10.1080/14656566.2022.2149323. Online ahead of print.

7 A Multicenter, Randomized, Open-label, Blinded Endpoint Evaluation, Phase 3 Study Comparing the Effect of Abelacimab Relative to Apixaban on Venous Thromboembolism (VTE) Recurrence and Bleeding in Patients With Cancer Associated VTE. NCT05171049 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05171049?term=Abelacimab&draw=2&rank=2

8 A Multicenter, Randomized, Open-label, Blinded Endpoint Evaluation, Phase 3 Study Comparing the Effect of Abelacimab vs. Dalteparin on Venous Thromboembolism (VTE) Recurrence and Bleeding in Patients With GI/GU Associated VTE. NCT05171075 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05171075?term=Abelacimab&draw=2&rank=3

9 GlobalData's Healthcare database (accessed September 2022; Phase II list).

10 McCoy EK, Lisenby KM. *Aprocitentan (a Dual Endothelin-Receptor Antagonist) for Treatment-Resistant Hypertension.* J Cardiovasc Pharmacol. 2021 Jun 1;77(6):699-706. doi: 10.1097/FJC.0000000000001023.

11 Schlaich MP, Bellet M, Weber MA, Danaietash P, Bakris GL, et al; PRECISION investigators. *Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial.* Lancet. 2022 Nov 4:S0140-6736(22)02034-7. doi: 10.1016/S0140-6736(22)02034-7. Online ahead of print.

12 Late-Breaking Data from Pivotal Phase 3 PRECISION Study Demonstrates Significant and Sustained Effect of Aprocitentan on Lowering Blood Pressure for Patients with Difficult-to-Control Hypertension. November 7, 2022. https://www.jnj.com/late-breaking-data-from-pivotal-phase-3-precision-study-demonstrates-significant-and-sustained-effect-of-aprocitentan-on-lowering-blood-pressure-for-patients-with-difficult-to-control-hypertension#:~:text=Specifically%2C%20after%204%20weeks%2C%20aprocitentan,6.8%2C%20%2D0.8%3B%20p%20%3D

13 Höcht C, Allo MA, Polizio AH, Morettón MA, et al. *New and developing pharmacotherapies for hypertension.* Expert Rev Cardiovasc Ther. 2022 Aug;20(8):647-666. doi: 10.1080/14779072.2022.2105204. Epub 2022 Aug 3.

14 Idorsia submits a New Drug Application to the US FDA for aprocitentan for the treatment of patients with difficult-to-control hypertension. December 20, 2022. https://www.biospace.com/article/releases/idorsia-submits-a-new-drug-application-to-the-us-fda-for-aprocitentan-for-the-treatment-of-patients-with-difficult-to-control-hypertension/

15 Multi-center, Blinded, Randomized Study With Aprocitentan in Subjects With Uncontrolled Blood Pressure and Chronic Kidney Disease Stage 3 or 4. NCT04162366 (Withdrawn [A business decision was made to not initiate this study]). https://clinicaltrials.gov/ct2/show/NCT04162366?term=Aprocitentan&phase=2&draw=2&rank=1

16 Multi-center, Blinded, Randomized, Parallel-group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension (RHT). NCT03541174 (completed). https://clinicaltrials.gov/ct2/show/NCT03541174?term=Aprocitentan&phase=2&draw=2&rank=2

17 GlobalData's Healthcare database (accessed September 2022; Phase II list).

18 Weintraub S, Frishman WH. *A Novel Calcium Channel Blocker: Etripamil: What is the Future of Intranasal Drug Delivery in the Treatment of Cardiac Arrhythmias?* Cardiol Rev. 2021 Sep-Oct 01;29(5):253-258. doi: 10.1097/CRD.0000000000000362.

19 An Open Label Extension Study of Etripamil Nasal Spray in Patients With Paroxysmal Supraventricular Tachycardia. NCT04952610 (Enrolling by invitation). https://clinicaltrials.gov/ct2/show/NCT04952610?term=Etripamil&phase=2&draw=2&rank=2

20 RAPID: Positive Top-line Results for Etripamil Nasal Spray in Paroxysmal SVT. October 17, 2022. https://www.tctmd.com/news/rapid-positive-top-line-results-etripamil-nasal-spray-paroxysmal-svt

21 Kashou AH, Noseworthy PA. *Etripamil nasal spray: an investigational agent for the rapid termination of paroxysmal supraventricular tachycardia (SVT).* Expert Opin Investig Drugs. 2020 Jan;29(1):1-4. doi: 10.1080/13543784.2020.1703180. Epub 2019 Dec 12.

22 Multi-Centre, Open-Label, Safety Study of Etripamil Nasal Spray in Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia The NODE-302 Trial (Extension of NODE-301). NCT03635996 (completed). https://clinicaltrials.gov/ct2/show/NCT03635996?term=Etripamil&phase=2&draw=2&rank=4

23 The NODE-303 Study: Multi-Centre, Multi-National,Open Label, Safety Study of Etripamil Nasal Spray for Patients With Paroxysmal Supraventricular Tachycardia. NCT04072835 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04072835?term=Etripamil&phase=2&draw=2&rank=1

24 Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Etripamil Nasal Spray Self-Administration for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia in Chinese Patients. NCT05410860 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05410860?term=Etripamil&phase=2&draw=2&rank=3

25 Multi-Centre, Randomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia. NODE 301 Trial. NCT03464019 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT03464019?term=Etripamil&phase=2&draw=2&rank=5

26 An Open Label Extension Study of Etripamil Nasal Spray in Patients With Paroxysmal Supraventricular Tachycardia. NCT04952610 (Enrolling by invitation). https://clinicaltrials.gov/ct2/show/NCT04952610?term=Etripamil&phase=2&draw=2&rank=2

27 GlobalData's Healthcare database (accessed September 2022; Phase II list).

28 Nurmohamed NS, Ditmarsch M, Kastelein JJP. *Cholesteryl ester transfer protein inhibitors: from high-density lipoprotein cholesterol to low-density lipoprotein cholesterol lowering agents?* Cardiovasc Res. 2022 Nov 10;118(14):2919-2931. doi: 10.1093/cvr/cvab350.

29 Obicetrapib decreases LDL, increases HDL in phase 2 trial. September 2, 2022. https://www.healio.com/news/cardiology/20220909/obicetrapib-decreases-ldl-increases-hdl-in-phase-2-trial

30 Obicetrapib decreases LDL, increases HDL in phase 2 trial. September 2, 2022. https://www.healio.com/news/cardiology/20220909/obicetrapib-decreases-ldl-increases-hdl-in-phase-2-trial

31 A Placebo-Controlled, Double-Blind, Randomized, Phase 3 Study to Evaluate the Effect of 10 mg Obicetrapib in Participants With a History of HeFH Who Are Not Adequately Controlled by Their Lipid Modifying Therapies. NCT05425745 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05425745?term=Obicetrapib&phase=2&draw=2&rank=1

32 A Placebo-Controlled, Double-Blind, Randomized Phase 3 Study to Evaluate the Effect of 10mg Obicetrapib in Participants With HeFH and/or ASCVD Who Are Not Adequately Controlled by Their Lipid Modifying Therapies. NCT05142722 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05142722?term=Obicetrapib&phase=2&draw=2&rank=2

33 Placebo Controlled, Double Blind, Randomized Cardiovascular Outcome Study to Evaluate the Effect of 10 mg Obicetrapib in Participants With ASCVD Not Adequately Controlled Despite Maximally Tolerated Lipid Modifying Therapies. NCT05202509 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05202509?term=Obicetrapib&phase=2&draw=2&rank=3

34 GlobalData's Healthcare database (accessed September 2022; Phase II list).

35 Rayroux C, Lador F, Soccal PM, Plojoux J, Adler D. *[Pulmonology 2021: year in review]* [Article in French; Abstract available in French from the publisher] Rev Med Suisse. 2022 Jan 19;18(764-5):64-68. doi: 10.53738/REVMED.2022.18.764-65.64.

36 Merck Announces Positive Top-line Results from Pivotal Phase 3 STELLAR Trial Evaluating Sotatercept for the Treatment of Adults with Pulmonary Arterial Hypertension (PAH). October 10, 2022. https://www.merck.com/news/merck-announces-positive-top-line-results-from-pivotal-phase-3-stellar-trial-evaluating-sotatercept-for-the-treatment-of-adults-with-pulmonary-arterial-hypertension-pah/

37 Hoeper MM, Badesch DB, Ghofrani HA, Gibbs JSR, Gomberg-Maitland M,et al. Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension. N Engl J Med. 2023 Mar 6. doi: 10.1056/NEJMoa2213558. Online ahead of print.

38 Sotatercept- the breakthrough PAH has been waiting for? November 10, 2022. https://www.clinicaltrialsarena.com/comment/sotatercept-breakthrough-pah/

39 An Open-label Long-term Follow-up Study to Evaluate the Effects of Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH. NCT04796337 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04796337?term=Sotatercept&phase=2&draw=2&rank=1

40 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk Mortality. NCT04896008 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04896008?term=Sotatercept&phase=2&draw=2&rank=2

41 A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy in Newly Diagnosed Intermediate- and High-risk PAH Patients. NCT04811092 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04811092?term=Sotatercept&phase=2&draw=2&rank=3

42 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH. NCT04576988 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04576988?term=Sotatercept&phase=2&draw=2&rank=4

43 GlobalData's Healthcare database (accessed September 2022; Phase II list).

44 von Hundelshausen P, Siess W. *Bleeding by Bruton Tyrosine Kinase-Inhibitors: Dependency on Drug Type and Disease*. Cancers (Basel). 2021 Mar 4;13(5):1103. doi: 10.3390/cancers13051103.

45 Schneider R, Oh J. *Bruton's Tyrosine Kinase Inhibition in Multiple Sclerosis*. Curr Neurol Neurosci Rep. 2022 Nov;22(11):721-734. doi: 10.1007/s11910-022-01229-z. Epub 2022 Oct 27.

46 Merck KGaA, Darmstadt, Germany Highlights New Data for Evobrutinib, First BTKi to Demonstrate Sustained Clinical Benefit for People with RMS through Three and a Half Years of Treatment. October 26, 2022. https://www.emdgroup.com/en/news/evobrutinib-26-10-2022.html

47 A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared With an Interferon Beta 1a (Avonex®), in Participants With RMS to Evaluate Efficacy and Safety. NCT04032171 (terminated early and comparator changed). https://clinicaltrials.gov/ct2/show/NCT04032171?term=Evobrutinib&phase=2&draw=2&rank=1

48 A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared With an Interferon Beta 1a (Avonex®), in Participants With Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety. NCT04032158 (terminated early and comparator changed). https://clinicaltrials.gov/ct2/show/NCT04032158?term=Evobrutinib&phase=2&draw=2&rank=2

49 A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared With Teriflunomide, in Participants With Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety (evolutionRMS 2). NCT04338061 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04338061?term=Evobrutinib&phase=2&draw=2&rank=3

50 A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared With Teriflunomide, in Participants With Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety (evolutionRMS 1). NCT04338022 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04338022?term=Evobrutinib&phase=2&draw=2&rank=4

51 GlobalData's Healthcare database (accessed September 2022; Phase II list).

52 Phase 3 Trial of Reldesemtiv in ALS Announced. August 11, 2021. https://www.neurologylive.com/view/phase-3-trial-reldesemtiv-als-announced

53 Reldesemtiv Earns FDA's Orphan Drug Designation for ALS Treatment. December 19, 2019. https://alsnewstoday.com/news/reldesemtiv-earns-fdas-orphan-drug-designation-for-als-treatment/

54 Cytokinetics Updates Phase 3 COURAGE-ALS Trial of Reldesemtiv. December 14, 2021. https://alsnewstoday.com/news/moderate-to-fast-progressing-als-courage-als-trial-patients-reldesemtiv-cytokinetics/

55 Shefner JM, Andrews JA, Genge A, Jackson C, Lechtzin N, et al. *A Phase 2, Double-Blind, Randomized, Dose-Ranging Trial Of Reldesemtiv In Patients With ALS*. Amyotroph Lateral Scler Frontotemporal Degener. 2021 May;22(3-4):287-299. doi: 10.1080/21678421.2020.1822410. Epub 2020 Sep 24.

56 Cytokinetics Updates Phase 3 COURAGE-ALS Trial of Reldesemtiv. December 14, 2021. https://alsnewstoday.com/news/moderate-to-fast-progressing-als-courage-als-trial-patients-reldesemtiv-cytokinetics/

57 Shefner JM, Andrews JA, Genge A, Jackson C, Lechtzin N, et al. *A Phase 2, Double-Blind, Randomized, Dose-Ranging Trial Of Reldesemtiv In Patients With ALS.* Amyotroph Lateral Scler Frontotemporal Degener. 2021 May;22(3-4):287-299. doi: 10.1080/21678421.2020.1822410. Epub 2020 Sep 24.

58 Rudnicki SA, Andrews JA, Genge A, Jackson C, Lechtzin N, et al; FORTITUDE-ALS STUDY GROUP. *Prescription and acceptance of durable medical equipment in FORTITUDE-ALS, a study of reldesemtiv in ALS: post hoc analyses of a randomized, double-blind, placebo-controlled clinical trial.* Amyotroph Lateral Scler Frontotemporal Degener. 2022 May;23(3-4):263-270. doi: 10.1080/21678421.2021.1946083. Epub 2021 Jul 5.

59 A Phase 3, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Reldesemtiv in Patients With Amyotrophic Lateral Sclerosis (ALS). NCT04944784 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04944784?term=Reldesemtiv&phase=2&draw=2&rank=1

60 A Phase 3, Open-Label Extension of COURAGE-ALS (CY 5031). NCT05442775 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05442775?term=Reldesemtiv&phase=2&draw=2&rank=2

61 GlobalData's Healthcare database (accessed September 2022; Phase II list).

62 Soticlestat, A New Potential Treatment for Epilepsy It Inhibits Cholesterol Catabolism. July 7, 2022. https://journals.lww.com/neurotodayonline/Fulltext/2022/07070/Soticlestat,_A_New_Potential_Treatment_for.9.aspx

63 Nishi T, Metcalf CS, Fujimoto S, Hasegawa S, Miyamoto M, et al. *Anticonvulsive properties of soticlestat, a novel cholesterol 24-hydroxylase inhibitor*. Epilepsia. 2022 Jun;63(6):1580-1590. doi: 10.1111/epi.17232. Epub 2022 Mar 30.

64 Hahn CD, Jiang Y, Villanueva V, Zolnowska M, Arkilo D, et al. *A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox-Gastaut syndrome (ELEKTRA).* Epilepsia. 2022 Oct;63(10):2671-2683. doi: 10.1111/epi.17367. Epub 2022 Aug 4.

65 A Phase 3, Prospective, Open-Label, Multisite, Extension of Phase 3 Studies To Assess the Long-Term Safety and Tolerability of Soticlestat as Adjunctive Therapy in Subjects With Dravet Syndrome or Lennox-Gastaut Syndrome (ENDYMION 2). NCT05163314 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05163314?term=Soticlestat&phase=2&draw=2&rank=1

66 A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Young Adult Subjects With Dravet Syndrome (DS). NCT04940624 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04940624?term=Soticlestat&phase=2&draw=2&rank=2

67 A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Adult Subjects With Lennox-Gastaut Syndrome (LGS). NCT04938427 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04938427?term=Soticlestat&phase=2&draw=2&rank=3

68 GlobalData's Healthcare database (accessed September 2022; Phase II list).

69 Koblan KS, Kent J, Hopkins SC, Krystal JH, Cheng H, et al. *A Non-D2-Receptor-Binding Drug for the Treatment of Schizophrenia.* N Engl J Med. 2020 Apr 16;382(16):1497-1506. doi: 10.1056/NEJMoa1911772.

70 Kane JM. *A New Treatment Paradigm: Targeting Trace Amine-Associated Receptor 1 (TAAR1) in Schizophrenia.* J Clin Psychopharmacol. 2022 Sep-Oct 01;42(5 Suppl 1):S1-S13. doi: 10.1097/JCP.0000000000001596.

71 Synan C, Bowen C, Heal DJ, Froger-Colléaux C, Beardsley PM, et al. *Ulotaront, a novel TAAR1 agonist with 5-HT1A agonist activity, lacks abuse liability and attenuates cocaine cue-induced relapse in rats.* Drug Alcohol Depend. 2022 Feb 1;231:109261. doi: 10.1016/j.drugalcdep.2021.109261. Epub 2021 Dec 31.

72 A 52-week, Open-label Study to Evaluate the Long-term Safety and Tolerability of SEP-363856 in Patients With Schizophrenia in Japan. NCT05359081 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05359081?term=SEP-363856&phase=2&draw=2&rank=1

73 An 8-Week, Open-Label Study Evaluating the Effectiveness, Safety and Tolerability of SEP-363856 in Subjects With Schizophrenia Switched From Typical or Atypical Antipsychotic Agents. NCT05628103 (not yet recruiting). https://clinicaltrials.gov/ct2/show/NCT05628103?term=SEP-363856&phase=2&draw=2&rank=2

74 An Open-label Extension Study to Assess the Safety and Tolerability of SEP-363856 in Subjects With Schizophrenia. NCT04109950 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04109950?term=SEP-363856&phase=2&draw=2&rank=3

75 A Randomized, Double-blind, Parallel-group, Placebo-controlled, Fixed-dose, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Subjects With Schizophrenia. NCT04092686 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04092686?term=SEP-363856&phase=2&draw=2&rank=4

76 A Randomized, Double-blind, Parallel-group, Placebo-controlled, Fixed-dose, Multicenter Study to Evaluate the Efficacy and Safety of SEP-363856 in Acutely Psychotic Subjects With Schizophrenia. NCT04072354 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04072354?term=SEP-363856&phase=2&draw=2&rank=5

77 A Randomized, Double-blind, Active Comparator-Controlled Study to Evaluate the Long-term Safety and Tolerability of SEP-363856 in Subjects With Schizophrenia. NCT04115319 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04115319?term=SEP-363856&phase=2&draw=2&rank=6

78 A Randomized, Double-blind, Parallel-group, Placebo Controlled, Fixed-dose, Multicenter Study to Evaluate the Efficacy and Safety of SEP 363856 in Acutely Psychotic Patients With Schizophrenia, Followed by an Open-label Extension Phase. NCT04825860 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04825860?term=SEP-363856&phase=2&draw=2&rank=8

79 GlobalData's Healthcare database (accessed September 2022; Phase II list).

80 Vyjuvek (Beremagene Geperpavec). Last updated April 1, 2022. https://epidermolysisbullosanews.com/kb103/

81 A Phase III Double Blinded, Placebo-Controlled, Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously "KB103") for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). NCT04491604 (completed). https://clinicaltrials.gov/ct2/show/NCT04491604?term=B-VEC&cond=Dystrophic+Epidermolysis+Bullosa&draw=2&rank=1

82 Guide SV, Gonzalez ME, Bağcı IS, Agostini B, Chen H, et al. Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa. N Engl J Med. 2022 Dec 15;387(24):2211-2219. doi: 10.1056/NEJMoa2206663.

83 Vyjuvek (Beremagene Geperpavec). Last updated April 1, 2022. https://epidermolysisbullosanews.com/kb103/

84 Efficacy of Beremagene Geperpavec in Patients With Dystrophic Epidermolysis Bullosa. December 29, 2022. https://www.practiceupdate.com/content/efficacy-of-beremagene-geperpavec-in-patients-with-dystrophic-epidermolysis-bullosa/146343

85 Open Label Treatment of Beremagene Geperpavec (B-VEC). NCT04917874 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04917874?term=NCT04917874&draw=2&rank=1

86 Fraile JM, Palliyil S, Barelle C, Porter AJ, Kovaleva M. *Non-Alcoholic Steatohepatitis (NASH) – A Review of a Crowded Clinical Landscape, Driven by a Complex Disease*. Drug Des Devel Ther. 2021 Sep 22;15:3997-4009. doi: 10.2147/DDDT.S315724. eCollection 2021.

87 Younossi ZM, Stepanova M, Taub RA, Barbone JM, Harrison SA. *Hepatic Fat Reduction Due to Resmetirom in Patients With Nonalcoholic Steatohepatitis Is Associated With Improvement of Quality of Life*. Clin Gastroenterol Hepatol. 2022 Jun;20(6):1354-1361.e7. doi: 10.1016/j.cgh.2021.07.039. Epub 2021 Jul 27.

88 Positive Topline Phase 3 MAESTRO-NAFLD-1 Data Demonstrate Resmetirom was Safe, Well-Tolerated and Provided Statistically Significant Improvements in Key Measures of Liver and Cardiovascular Health. January 31, 2022. https://ir.madrigalpharma.com/news-releases/news-release-details/positive-topline-phase-3-maestro-nafld-1-data-demonstrate

89 A 52-Week, Phase 3, Open-Label Extension Study, With a Single-blind Lead-in, to Evaluate Safety and Biomarkers of Resmetirom (MGL-3196) in Patients With Non-alcoholic Fatty Liver Disease (NAFLD), MAESTRO-NAFLD-Open-Label-Extension (MAESTRO-NAFLD-OLE). NCT04951219 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04951219?term=Resmetirom&phase=2&draw=2&rank=1

90 A 52-Week, Phase 3 Study to Evaluate Safety and Biomarkers of Resmetirom (MGL-3196) in Patients With Non-alcoholic Fatty Liver Disease (NAFLD) (MAESTRO-NAFLD-1). NCT04197479 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04197479?term=Resmetirom&phase=2&draw=2&rank=2

91 A Randomized Double-blind Placebo-controlled Phase 3 Study to Evaluate the Effect of Resmetirom on Liver-related Outcomes in Patients With Well-compensated (Child-Pugh A) Non-alcoholic Steatohepatitis (NASH) Cirrhosis (MAESTRO-NASH OUTCOMES). NCT05500222 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05500222?term=Resmetirom&phase=2&draw=2&rank=3

92 A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (Resmetirom) in Patients With NASH and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation. NCT03900429 (recruiting). https://clinicaltrials.gov/ct2/show/NCT03900429?term=Resmetirom&phase=2&draw=2&rank=4

93 GlobalData's Healthcare database (accessed September 2022; Phase II list).

94 Kremer AE, Mayo MJ, Hirschfield G, Levy C, Bowlus CL, et al. *Seladelpar improved measures of pruritus, sleep, and fatigue and decreased serum bile acids in patients with primary biliary cholangitis*. Liver Int. 2022 Jan;42(1):112-123. doi: 10.1111/liv.15039. Epub 2021 Aug 26.

95 Kremer AE, Mayo MJ, Hirschfield G, Levy C, Bowlus CL, et al. *Seladelpar improved measures of pruritus, sleep, and fatigue and decreased serum bile acids in patients with primary biliary cholangitis*. Liver Int. 2022 Jan;42(1):112-123. doi: 10.1111/liv.15039. Epub 2021 Aug 26.

96 Bowlus CL, Galambos MR, Aspinall RJ, Hirschfield GM, Jones DEJ, et al. *A phase II, randomized, open-label, 52-week study of seladelpar in patients with primary biliary cholangitis*. J Hepatol. 2022 Aug;77(2):353-364. doi: 10.1016/j.jhep.2022.02.033. Epub 2022 Mar 30.

97 Bowlus CL, Galambos MR, Aspinall RJ, Hirschfield GM, Jones DEJ, et al. *A phase II, randomized, open-label, 52-week study of seladelpar in patients with primary biliary cholangitis*. J Hepatol. 2022 Aug;77(2):353-364. doi: 10.1016/j.jhep.2022.02.033. Epub 2022 Mar 30.

98 A 52-week, Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Safety and Efficacy of Seladelpar in Subjects With Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA). NCT03602560 (completed). https://clinicaltrials.gov/ct2/show/NCT03602560?term=Seladelpar&phase=2&draw=2&rank=2

99 ASSURE: An Open Label Long-Term Study to Evaluate the Safety and Tolerability of Seladelpar in Subjects With Primary Biliary Cholangitis (PBC). NCT03301506 (recruiting). https://clinicaltrials.gov/ct2/show/NCT03301506?term=Seladelpar&phase=2&draw=2&rank=1

100 RESPONSE: A Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA). NCT04620733 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04620733?term=Seladelpar&phase=2&draw=2&rank=3

101 GlobalData's Healthcare database (accessed September 2022; Phase II list).

102 As Delandistrogene moxeparvovec moves closer to clinical approval, what is the likelihood that the drug will be approved? January 3, 2023. https://www.pharmaceutical-technology.com/data-analysis/delandistrogene-moxeparvovec-what-is-the-likelihood-that-drug-will-be-approved/

103 Sarepta Therapeutics Announces That U.S. FDA has Accepted for Filing and Granted Priority Review for the Biologics License Application for SRP-9001, Sarepta's Gene Therapy for the Treatment of Ambulant Individuals with Duchenne Muscular Dystrophy. November 28, 2022. https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-us-fda-has-accepted-filing-and

104 A Phase 3 Multinational, Randomized, Double-Blind, Placebo-Controlled Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9001 in Subjects With Duchenne Muscular Dystrophy (EMBARK). NCT05096221 (active not recruiting). https://clinicaltrials.gov/ct2/show/NCT05096221?term=delandistrogene&draw=2&rank=4

105 Recursion Announces Initiation of Phase 2/3 Trial for the Treatment of NF2-Mutated Meningiomas at Children's Tumor Foundation NF Conference. June 20, 2022. https://www.prnewswire.com/news-releases/recursion-announces-initiation-of-phase-23-trial-for-the-treatment-of-nf2-mutated-meningiomas-at-childrens-tumor-foundation-nf-conference-301570906.html

106 Recursion Announces Initiation of Phase 2/3 Trial for the Treatment of NF2-Mutated Meningiomas at Children's Tumor Foundation NF Conference. June 20, 2022. https://www.prnewswire.com/news-releases/recursion-announces-initiation-of-phase-23-trial-for-the-treatment-of-nf2-mutated-meningiomas-at-childrens-tumor-foundation-nf-conference-301570906.html

107 Recursion Announces Initiation of Phase 2/3 Trial for the Treatment of NF2-Mutated Meningiomas at Children's Tumor Foundation NF Conference. June 20, 2022. https://www.prnewswire.com/news-releases/recursion-announces-initiation-of-phase-23-trial-for-the-treatment-of-nf2-mutated-meningiomas-at-childrens-tumor-foundation-nf-conference-301570906.html

108 A Parallel-group, Two-staged, Phase 2/3, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of REC-2282 in Participants With Progressive NF2 Mutated Meningiomas. NCT05130866 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05130866?term=REC-2282&draw=2&rank=1

109 GlobalData's Healthcare database (accessed September 2022; Phase II list).

110 Craig TJ, Reshef A, Li HH, Jacobs JS, Bernstein JA, et al. Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.Lancet. 2023 Feb 28:S0140-6736(23)00350-1. doi: 10.1016/S0140-6736(23)00350-1. Online ahead of print.

111 CSL Announces Positive Top-Line Phase 3 Results for Garadacimab as Preventive Treatment in Patients with Hereditary Angioedema (HAE). August 17, 2022. https://www.csl.com/news/2022/20220817-csl-announces-positive-results-for-garadacimab#:~:text=About%20HAE%20and%20Garadacimab&text=Garadacimab%20is%20a%20novel%20Factor,form%20of%20bradykinin%2Dmediated%20angioedema.

112 A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-arm Study to Investigate the Efficacy and Safety of Subcutaneous Administration of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema. NCT04656418 (completed). https://clinicaltrials.gov/ct2/show/NCT04656418?term=Garadacimab&phase=2&draw=2&rank=1

113 An Open-label Study to Evaluate the Long-term Safety and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema. NCT04739059 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04739059?term=Garadacimab&phase=2&draw=2&rank=2

114 GlobalData's Healthcare database (accessed September 2022; Phase II list).

115 Horwitz ME, Stiff PJ, Cutler C, Brunstein C, Hanna R, et al. Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study. Blood. 2021 Oct 21;138(16):1429-1440. doi: 10.1182/blood.2021011719.

116 Horwitz ME, Stiff PJ, Cutler C, Brunstein C, Hanna R, et al. Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study. Blood. 2021 Oct 21;138(16):1429-1440. doi: 10.1182/blood.2021011719.

117 Lin C, Sajeev G, Stiff PJ, Brunstein CG, Cutler C, et al. Health-Related Quality of Life Following Allogeneic Hematopoietic Cell Transplantation with Omidubicel versus Umbilical Cord Blood. Transplant Cell Ther. 2023 Jan;29(1):52.e1-52.e9. doi: 10.1016/j.jtct.2022.09.018. Epub 2022 Sep 28.

118 Gamida Cell Provides Regulatory Update on Omidubicel. November 21, 2022. https://www.businesswire.com/news/home/20221121005927/en/Gamida-Cell-Provides-Regulatory-Update-on-Omidubicel#:~:text=Omidubicel%20is%20an%20investigational%20stem,or%20any%20other%20health%20authority

119 Horwitz ME, Stiff PJ, Cutler C, Brunstein C, Hanna R, et al. Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study. Blood. 2021 Oct 21;138(16):1429-1440. doi: 10.1182/blood.2021011719.

120 Posoleucel (Viralym-M, ALVR105): A multi-virus specific T cell therapy (VST) targeting five devastating viral pathogens. https://www.allovir.com/products/alvr105

121 AlloVir Announces Positive Final Results in Phase 2 Posoleucel Multi-Virus Prevention Study In Oral Presentation at the 64th ASH Annual Meeting and Exposition. December 10, 2022. https://www.businesswire.com/news/home/20221210005012/en/AlloVir-Announces-Positive-Final-Results-in-Phase-2-Posoleucel-Multi-Virus-Prevention-Study-In-Oral-Presentation-at-the-64th-ASH-Annual-Meeting-and-Exposition

122 Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial, With Cross-Over, of Posoleucel (ALVR105) for the Treatment of Adenovirus Infection in Pediatric and Adult Participants Receiving Standard of Care Following Allogeneic Hematopoietic Cell Transplantation. NCT05179057 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05179057?term=posoleucel&phase=2&draw=2&rank=1

123 Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of ALVR105 (Viralym-M) Compared to Placebo for the Prevention of AdV, BKV, CMV, EBV, HHV-6, and JCV Infection and/or Disease, in High-Risk Patients After Allogeneic Hematopoietic Cell Transplant. NCT05305040 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05305040?term=posoleucel&phase=2&draw=2&rank=3

124 Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of ALVR105 (Viralym-M) Compared to Placebo for the Prevention of AdV, BKV, CMV, EBV, HHV-6, and JCV Infection and/or Disease, in High-Risk Patients After Allogeneic Hematopoietic Cell Transplant. NCT04693637 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04693637?term=posoleucel&phase=2&draw=2&rank=4

125 Newman LM, Kankam M, Nakamura A, Conrad T, Mueller J, et al. *Thorough QT Study To Evaluate the Effect of Zoliflodacin, a Novel Therapeutic for Gonorrhea, on Cardiac Repolarization in Healthy Adults*. Antimicrob Agents Chemother. 2021 Nov 17;65(12):e0129221. doi: 10.1128/AAC.01292-21. Epub 2021 Oct 4.

126 Bradford PA, Miller AA, O'Donnell J, Mueller JP. *Zoliflodacin: An Oral Spiropyrimidinetrione Antibiotic for the Treatment of Neisseria gonorrheae, Including Multi-Drug-Resistant Isolates*. ACS Infect Dis. 2020 Jun 12;6(6):1332-1345. doi: 10.1021/acsinfecdis.0c00021.Epub 2020 May 12.

127 A Multi-center, Randomized, Open-label, Non Inferiority Trial to Evaluate the Efficacy and Safety of a Single, Oral Dose of Zoliflodacin Compared to a Combination of a Single Intramuscular Dose of Ceftriaxone and a Single Oral Dose of Azithromycin in the Treatment of Patients With Uncomplicated Gonorrhoea. NCT03959527 (recruiting). https://clinicaltrials.gov/ct2/show/NCT03959527?term=Zoliflodacin&phase=2&draw=2&rank=1

128 A Double-Blinded, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of ORMD-0801 in Uncontrolled Type 2 DM Subjects on Diet Control Alone, Metformin Monotherapy, or Two or Three Oral Glucose-lowering Agents. NCT04817215 (not yet recruiting). https://clinicaltrials.gov/ct2/show/NCT04817215?term=ORMD-0801&phase=2&draw=2&rank=1

129 A Double-Blind, Placebo-controlled, Multi-center Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of ORMD-0801 in T2DM Subjects With Inadequate Glycemic Control on Diet Control Only or on Diet Control and Metformin Monotherapy. NCT04754334 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04754334?term=ORMD-0801&phase=2&draw=2&rank=2

130 A Double-Blinded, Placebo-controlled, Double Dummy, Multi-center Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of ORMD-0801 in Subjects With T2DM With Inadequate Glycemic Control on 1, 2 or 3 Oral Glucose-lowering Agents. NCT04606576 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04606576?term=ORMD-0801&phase=2&draw=2&rank=3

131 Kjeldsen TB, Hubálek F, Hjørringgaard CU, Tagmose TM, Nishimura E, et al. *Molecular Engineering of Insulin Icodec, the First Acylated Insulin Analog for Once-Weekly A dministration in Humans*. J Med Chem. 2021 Jul 8;64(13):8942-8950. doi: 10.1021/acs.jmedchem.1c00257. Epub 2021 May 4.

132 Rosenstock J, Bajaj HS, Janež A, Silver R, Begtrup K, et al; NN1436-4383 Investigators. *Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment*. N Engl J Med. 2020 Nov 26;383(22):2107-2116. doi: 10.1056/NEJMoa2022474. Epub 2020 Sep 22.

133 Rosenstock J, Bajaj HS, Janež A, Silver R, Begtrup K, et al; NN1436-4383 Investigators. *Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment*. N Engl J Med. 2020 Nov 26;383(22):2107-2116. doi: 10.1056/NEJMoa2022474. Epub 2020 Sep 22.

134 A 26-week Trial Comparing the Effect and Safety of Once Weekly Insulin Icodec and Once Daily Insulin Degludec, Both With or Without Non-insulin Anti-diabetic Drugs, in Subjects With Type 2 Diabetes Treated With Basal Insulin. NCT04770532 (completed). https://clinicaltrials.gov/ct2/show/NCT04770532?term=Insulin+icodec&phase=2&draw=2&rank=1

135 Effectiveness and Safety of Once Weekly Insulin Icodec Used With DoseGuide Versus Once Daily Basal Insulin Analogues in an Insulin naïve Type 2 Diabetes Population in a Clinical Practice Setting. NCT04760626 (completed). https://clinicaltrials.gov/ct2/show/NCT04760626?term=Insulin+icodec&phase=2&draw=2&rank=5

136 A 26-week Trial Comparing the Effect and Safety of Once Weekly Insulin Icodec and Once Daily Insulin Glargine 100 Units/mL, Both in Combination With Bolus Insulin With or Without Non-insulin Anti-diabetic Drugs, in Subjects With Type 2 Diabetes on a Basal-bolus Regimen. NCT04880850 (completed). https://clinicaltrials.gov/ct2/show/NCT04880850?term=Insulin+icodec&phase=2&draw=2&rank=6

137 A 26-week Double Blinded, Multiregional, Trial Comparing the Effect and Safety of Once Weekly Insulin Icodec and Once Daily Insulin Degludec 100 Units/mL, Both in Combination With Non-insulin Anti-diabetic Drugs, in Insulin naïve Subjects With Type 2 Diabetes. NCT04795531 (completed). https://clinicaltrials.gov/ct2/show/NCT04795531?term=Insulin+icodec&phase=2&draw=2&rank=7

138 A 78-week Trial Comparing the Effect and Safety of Once Weekly Insulin Icodec and Once Daily Insulin Glargine 100 Units/mL, Both in Combination With Non-insulin Anti-diabetic Treatment, in Insulin naïve Subjects With Type 2 Diabetes. NCT04460885 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04460885?term=Insulin+icodec&phase=2&draw=2&rank=2

139 Efficacy and Safety of Once Weekly Insulin Icodec Compared to Once Daily Insulin Degludec 100 Units/mL, Both in Combination With Insulin Aspart, in Adults With Type 1 Diabetes. A 26-week, Randomised, Multicentre, Open-label, Active-controlled, Parallel Group, Two Armed, Treat-to-target Trial Investigating the Effect on Glycaemic Control and Safety of Treatment With Once Weekly Insulin Icodec Compared to Once Daily Insulin Degludec, Both in Combination With Insulin Aspart in Adults With Type 1 Diabetes, With a 26-week Extension Investigating Long Term Safety. NCT04848480 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04848480?term=Insulin+icodec&phase=2&draw=2&rank=3

140 A 52 Week Study Comparing the Efficacy and Safety of Once Weekly IcoSema and Once Weekly Insulin Icodec, Both Treatment Arms With or Without Oral Anti Diabetic Drugs, in Participants With Type 2 Diabetes Inadequately Controlled With Daily Basal Insulin. NCT05352815 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05352815?term=Insulin+icodec&phase=2&draw=2&rank=4

141 A 52 Week Study Comparing the Efficacy and Safety of Once Weekly IcoSema and Daily Insulin Glargine 100 Units/mL Combined With Insulin Aspart, Both Treatment Arms With or Without Oral Anti Diabetic Drugs, in Participants With Type 2 Diabetes Inadequately Controlled With Daily Basal Insulin. COMBINE 3. NCT05013229 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05013229?term=Insulin+icodec&phase=2&draw=2&rank=8

142 A 52 Week Study Comparing the Efficacy and Safety of Once Weekly IcoSema and Once Weekly Semaglutide, Both Treatment Arms With or Without Oral Anti Diabetic Drugs, in Participants With Type 2 Diabetes Inadequately Controlled With a GLP 1 Receptor Agonist. COMBINE 2. NCT05259033 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05259033?term=Insulin+icodec&phase=2&draw=2&rank=9

143 [No authors listed]. *FGFR Inhibitor Stymies Gastric Cancer*. Cancer Discov. 2021 May;11(5):OF3. doi: 10.1158/2159-8290.CD-NB2021-0312. Epub 2021 Feb 11.

144 A Phase 1b/3 Study of Bemarituzumab Plus Chemotherapy and Nivolumab Versus Chemotherapy and Nivolumab Alone in Subjects With Previously Untreated Advanced Gastric and Gastroesophageal Junction Cancer With FGFR2b Overexpression. NCT05111626 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05111626?term=Bemarituzumab&phase=2&draw=2&rank=1

145 A Randomized, Multi-center, Double-blind, Placebo-controlled Phase 3 Study of Bemarituzumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in Subjects With Previously Untreated Advanced Gastric or Gastroesophageal Junction Cancer With FGFR2b Overexpression. NCT05052801 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05052801?term=Bemarituzumab&phase=2&draw=2&rank=2

146 GlobalData's Healthcare database (accessed September 2022; Phase II list).

147 Lonial S, Popat R, Hulin C, Jagannath S, Oriol A, et al. *Iberdomide plus dexamethasone in heavily pretreated late-line relapsed or refractory multiple myeloma (CC-220-MM-001): a multicentre, multicohort, open-label, phase 1/2 trial.* Lancet Haematol. 2022 Nov;9(11):e822-e832. doi: 10.1016/S2352-3026(22)00290-3. Epub 2022 Oct 6.

148 A Phase 3, Two-Stage, Randomized, Multicenter, Open-label Study Comparing Iberdomide, Daratumumab and Dexamethasone (IberDd) Versus Daratumumab, Bortezomib, and Dexamethasone (DVd) in Subjects With Relapsed or Refractory Multiple Myeloma (RRMM). NCT04975997 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04975997?term=Iberdomide&phase=2&draw=2&rank=1

149 GEM21menos65. A Phase III Trial for NDMM Patients Who Are Candidates for ASCT Comparing Extended VRD Plus Early Rescue Intervention vs Isatuximab-VRD vs Isatuximab-V-Iberdomide-D. NCT05558319 (not yet recruiting). https://clinicaltrials.gov/ct2/show/NCT05558319?term=Iberdomide&phase=2&draw=2&rank=2

150 GlobalData's Healthcare database (accessed September 2022; Phase II list).

151 Mascarenhas J, Harrison CN, Kiladjian JJ, Komrokji RS, Koschmieder S, et al. *Imetelstat in intermediate-2 or high-risk myelofibrosis refractory to JAK inhibitor: IMpactMF phase III study design.* Future Oncol. 2022 Jul;18(22):2393-2402. doi: 10.2217/fon-2022-0235. Epub 2022 May 5.

152 Steensma DP, Fenaux P, Van Eygen K, Raza A, Santini V,et al. *Imetelstat Achieves Meaningful and Durable Transfusion Independence in High Transfusion-Burden Patients With Lower-Risk Myelodysplastic Syndromes in a Phase II Study.* J Clin Oncol. 2021 Jan 1;39(1):48-56. doi: 10.1200/JCO.20.01895. Epub 2020 Oct 27.

153 A Randomized Open-Label, Phase 3 Study to Evaluate Imetelstat (GRN163L) Versus Best Available Therapy (BAT) in Patients With Intermediate-2 or High-risk Myelofibrosis (MF) Relapsed / Refractory (R/R) to Janus Kinase (JAK) Inhibitor. NCT04576156 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04576156?term=Imetelstat&phase=2&draw=2&rank=1

154 A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects With IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) That is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment. NCT02598661 (recruiting). https://clinicaltrials.gov/ct2/show/NCT02598661?term=Imetelstat&phase=2&draw=2&rank=4

155 GlobalData's Healthcare database (accessed September 2022; Phase II list).

156 Pandravada S, Sandler S. *The Role of Navitoclax in Myelofibrosis.* Cureus. 2021 Sep 14;13(9):e17976. doi: 10.7759/cureus.17976. eCollection 2021 Sep.

157 Harrison CN, Garcia JS, Somervaille TCP, Foran JM, Verstovsek S, et al. *Addition of Navitoclax to Ongoing Ruxolitinib Therapy for Patients With Myelofibrosis With Progression or Suboptimal Response: Phase II Safety and Efficacy.* J Clin Oncol. 2022 May 20;40(15):1671-1680. doi: 10.1200/JCO.21.02188. Epub 2022 Feb 18.

158 A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Of Navitoclax In Combination With Ruxolitinib Versus Ruxolitinib In Subjects With Myelofibrosis (TRANSFORM-1). NCT04472598 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04472598?term=Navitoclax&phase=2&draw=2&rank=1

159 A Randomized, Open-Label, Phase 3 Study Evaluating Efficacy and Safety of Navitoclax in Combination With Ruxolitinib Versus Best Available Therapy in Subjects With Relapsed/Refractory Myelofibrosis (TRANSFORM-2). NCT04468984 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04468984?term=Navitoclax&phase=2&draw=2&rank=2

160 GlobalData's Healthcare database (accessed September 2022; Phase II list).

161 Corcept Therapeutics to Start Phase 3 Trial of Relacorilant Plus Nab-Paclitaxel in Patients With Platinum-Resistant Ovarian Cancer. June 2, 2022. https://www.globenewswire.com/en/news-release/2022/06/06/2456669/0/en/Corcept-Therapeutics-to-Start-Phase-3-Trial-of-Relacorilant-Plus-Nab-Paclitaxel-in-Patients-With-Platinum-Resistant-Ovarian-Cancer.html

162 Corcept Therapeutics to Start Phase 3 Trial of Relacorilant Plus Nab-Paclitaxel in Patients With Platinum-Resistant Ovarian Cancer. June 2, 2022. https://www.globenewswire.com/en/news-release/2022/06/06/2456669/0/en/Corcept-Therapeutics-to-Start-Phase-3-Trial-of-Relacorilant-Plus-Nab-Paclitaxel-in-Patients-With-Platinum-Resistant-Ovarian-Cancer.html

163 Corcept Therapeutics to Start Phase 3 Trial of Relacorilant Plus Nab-Paclitaxel in Patients With Platinum-Resistant Ovarian Cancer. June 2, 2022. https://www.globenewswire.com/en/news-release/2022/06/06/2456669/0/en/Corcept-Therapeutics-to-Start-Phase-3-Trial-of-Relacorilant-Plus-Nab-Paclitaxel-in-Patients-With-Platinum-Resistant-Ovarian-Cancer.html

164 A Phase 3 Study of Relacorilant in Combination With Nab-Paclitaxel Versus Nab-Paclitaxel Monotherapy in Advanced, Platinum-Resistant, High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian-Tube Cancer (ROSELLA). NCT05257408 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05257408?term=Relacorilant&phase=2&draw=2&rank=4

165 GlobalData's Healthcare database (accessed September 2022; Phase II list).

166 Rusfertide May Eliminate the Need for Phlebotomies in Polycythemia Vera. September 29, 2022. https://www.targetedonc.com/view/rusfertide-may-eliminate-the-need-for-phlebotomies-in-polycythemia-vera

167 Protagonist Therapeutics to Present Updated Phase 2 Rusfertide Clinical Results in Polycythemia Vera (PV) at ASCO 2022. May 26, 2022. https://www.prnewswire.com/news-releases/protagonist-therapeutics-to-present-updated-phase-2-rusfertide-clinical-results-in-polycythemia-vera-pv-at-asco-2022-301556326.html

168 Pemmaraju N, Kuykendall A, Kremyanskaya M, Ginzburg Y, Ritchie E, Gotlib J, et al. *MPN-469 Rusfertide (PTG-300) Treatment Interruption Reverses Hematological Gains and Upon Reinitiation, Restoration of Clinical Benefit Observed in Patients With Polycythemia Vera*. Clin Lymphoma Myeloma Leuk. 2022 Oct;22 Suppl 2:S338-S339. doi: 10.1016/S2152-2650(22)01462-8.

169 Protagonist Therapeutics to Present Updated Phase 2 Rusfertide Clinical Results in Polycythemia Vera (PV) at ASCO 2022. May 26, 2022. https://www.prnewswire.com/news-releases/protagonist-therapeutics-to-present-updated-phase-2-rusfertide-clinical-results-in-polycythemia-vera-pv-at-asco-2022-301556326.html

170 Rusfertide Therapy for Polycythemia Vera Leads to Sustained Hematocrit Control. Mid-July 2022. https://ashpublications.org/ashclinicalnews/news/6294/rusfertide-therapy-for-polycythemia-vera-leads-to

171 A Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients With Polycythemia Vera. NCT05210790 (recruiting). https://clinicaltrials.gov/ct2/show/NCT05210790?term=Rusfertide&draw=2&rank=1

172 GlobalData's Healthcare database (accessed September 2022; Phase II list).

173 Kyuno D, Takasawa A, Takasawa K, Ono Y, Aoyama T, et al. *Claudin-18.2 as a therapeutic target in cancers: cumulative findings from basic research and clinical trials*. Tissue Barriers. 2022 Jan 2;10(1):1967080. doi: 10.1080/21688370.2021.1967080. Epub 2021 Sep 5.

174 Palmieri LJ, Soubeyran I, Pernot S. *[Oesogastric cancer – new therapeutic targets]*. [Article in French] Bull Cancer. 2022 Nov 9:S0007-4551(22)00340-X. doi: 10.1016/j.bulcan.2022.08.005. Online ahead of print.

175 Zolbetuximab With mFOLFOX6 Meets Primary Endpoint in SPOTLIGHT Trial. January 19, 2023. https://dailynews.ascopubs.org/do/zolbetuximab-mfolfox6-meets-primary-endpoint-spotlight-trial

176 A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus CAPOX Compared With Placebo Plus CAPOX as First-line Treatment of Subjects With Claudin (CLDN) 18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma. NCT03653507 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT03653507?term=Zolbetuximab&phase=2&draw=2&rank=1

177 A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared With Placebo Plus mFOLFOX6 as First-line Treatment of Subjects With Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma. NCT03504397 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT03504397?term=Zolbetuximab&phase=2&draw=2&rank=2

178 GlobalData's Healthcare database (accessed September 2022; Phase II list).

179 Vignal-Clermont C(1)(2), Girmens JF(2)(3), Audo I(2)(3)(4), Said SM(2)(3)(4), Errera MH(2)(3)(5), et al. Safety of Intravitreal Gene Therapy for Treatment of Subjects with Leber Hereditary Optic Neuropathy due to Mutations in the Mitochondrial ND4 Gene: The REVEAL Study. BioDrugs. 2021 Mar;35(2):201-214. doi: 10.1007/s40259-021-00468-9. Epub 2021 Feb 10.

180 A Randomized, Double-Masked, Sham-Controlled Clinical Trial to Evaluate the Efficacy of a Single Intravitreal Injection of GS010 in Subjects Affected for 6 Months or Less by LHON Due to the G11778A Mutation in the Mitochondrial ND4 Gene. NCT02652767 (completed). https://clinicaltrials.gov/ct2/show/NCT02652767?cond=NCT02652767&draw=2&rank=1

181 Randomized, Double-Masked, Sham-Controlled Clinical Trial to Evaluate the Efficacy of a Single Intravitreal Injection of GS010 in Subjects Affected for More Than 6 Months and To 12 Months by LHON Due to the G11778A Mutation in the ND4 Gene. NCT02652780 (completed). https://clinicaltrials.gov/ct2/show/NCT02652780

182 Long-term Follow-up of ND4 LHON Subjects Treated With GS010 Ocular Gene Therapy in the RESCUE or REVERSE Phase III Clinical Trials (RESTORE). NCT03406104 completed). https://clinicaltrials.gov/ct2/show/NCT03406104?term=NCT03406104&draw=2&rank=1

183 Carelli V, Newman NJ, Yu-Wai-Man P, Biousse V, Moster ML, et al; the LHON Study Group. Indirect Comparison of Lenadogene Nolparvovec Gene Therapy Versus Natural History in Patients with Leber Hereditary Optic Neuropathy Carrying the m.11778G>A MT-ND4 Mutation. Ophthalmol Ther. 2023 Feb;12(1):401-429. doi: 10.1007/s40123-022-00611-x. Epub 2022 Nov 30.

184 Biousse V, Newman NJ, Yu-Wai-Man P, Carelli V, Moster ML, et al; LHON Study Group. Long-Term Follow-Up After Unilateral Intravitreal Gene Therapy for Leber Hereditary Optic Neuropathy: The RESTORE Study. J Neuroophthalmol. 2021 Sep 1;41(3):309-315. doi: 10.1097/WNO.0000000000001367.

185 Vignal-ClermoH C, Yu-Wai-Man P, Newman NJ, Carelli V, Moster ML, et al; LHON Study Group. Safety of lenadogene nolparvovec gene therapy over 5 years in 189 patients with Leber hereditary optic neuropathy. Am J Ophthalmol. 2022 Dec 7:S0002-9394(22)00464-0. doi: 10.1016/j.ajo.2022.11.026. Online ahead of print.

186 BRIEF—FDA setback for GenSight's Lumevoq. January 19, 2022. https://www.thepharmaletter.com/in-brief/brief-fda-setback-for-gensight-s-lumevoq

187 Toth PP, Schwartz GG, Nicholls SJ, Khan A, Szarek M, et al. Reduction in the risk of major adverse cardiovascular events with the BET protein inhibitor apabetalone in patients with recent acute coronary syndrome, type 2 diabetes, and moderate to high likelihood of non-alcoholic fatty liver disease. Am J Prev Cardiol. 2022 Aug 8;11:100372. doi: 10.1016/j.ajpc.2022.100372. eCollection 2022 Sep.

188 A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Investigate the Efficacy and Safety of CSL112 in Subjects With Acute Coronary Syndrome. NCT03473223 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT03473223?term=NCT03473223&draw=2&rank=1

189 https://www.dicardiology.com/content/memorialcare-heart-and-vascular-institute-participating-global-study-csl112-patients-acute. March 8, 2022.

190 A Phase 3, Multicenter, Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of AL001 in Individuals at Risk for or With Frontotemporal Dementia Due to Heterozygous Mutations in the Progranulin Gene. NCT04374136 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04374136?term=AL001&phase=2&draw=2&rank=1

191 A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Efficacy, Safety and Biomarker Effects of ALZ-801 in Subjects With Early Alzheimer's Disease and APOE4/4 Genotype.NCT04770220 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04770220?term=NCT04770220&draw=2&rank=1

192 Smith KW, Sicignano D), Hernandez AV, White CM. MDMA-Assisted Psychotherapy for Treatment of Posttraumatic Stress Disorder: A Systematic Review With Meta-Analysis. J Clin Pharmacol. 2022 Apr;62(4):463-471. doi: 10.1002/jcph.1995. Epub 2021 Nov 28.

193 A Randomized, Double-Blind, Placebo-Controlled, Multi-Site Phase 3 Study of the Efficacy and Safety of Manualized MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder of Moderate or Greater Severity. NCT04077437 (completed). https://clinicaltrials.gov/ct2/show/NCT04077437?term=NCT04077437&draw=2&rank=1.

194 A Multi-Site Open-Label Safety Extension Study of Manualized MDMA-Assisted Psychotherapy for the Treatment of Participants With Posttraumatic Stress Disorder. NCT04714359 (enrolling by invitation). https://clinicaltrials.gov/ct2/show/NCT04714359?term=NCT04714359&draw=2&rank=1.

195 A Multicenter, Randomized, Active-controlled, Double-blind, Double-dummy, Parallel Group Clinical Trial, Investigating the Efficacy, Safety, and Tolerability of Continuous Subcutaneous ND0612 Infusion in Comparison to Oral IR-LD/CD in Subjects With Parkinson's Disease Experiencing Motor Fluctuations (BouNDless). NCT04006210 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04006210?term=NCT04006210&draw=2&rank=1.

196 An Open-label, Long-term Extension Study of Brazikumab in Participants With Moderately to Severely Active Crohn's Disease (INTREPID OLE). NCT03961815 (enrolling by invitation). https://clinicaltrials.gov/ct2/show/NCT03961815?term=NCT03961815&draw=2&rank=1.

197 A 52-Week, Multicenter, Randomized, Double-blind, Placebo and Active-Controlled, Operationally Seamless Phase 2b/3, Parallel-group Study to Assess the Efficacy and Safety of Brazikumab in Participants With Moderately to Severely Active Crohn's Disease (INTREPID Lead-In). NCT03759288 (recruiting). https://clinicaltrials.gov/ct2/show/NCT03759288?term=NCT03759288&draw=2&rank=1.

198 A Phase 3 Prospective, Randomized, Double-blinded, Placebo-controlled Clinical Study to Evaluate the Efficacy and Safety of RBX2660 (Microbiota Suspension) for the Prevention of Clostridium Difficile InfectionNCT03244644 (completed). https://clinicaltrials.gov/ct2/show/NCT03244644?term=NCT03244644&draw=2&rank=1

199 Khanna S, Assi M, Lee C, Yoho D, Louie T, et al. Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent Clostridioides *difficile* Infection. Drugs. 2022 Oct 26:1-12. doi: 10.1007/s40265-022-01797-x. Online ahead of print.

200 Ferring and Rebiotix Present Landmark Phase 3 Data Demonstrating Superior Efficacy of Investigational RBX2660 Versus Placebo to Reduce Recurrence of *C. difficile* Infection. May 21, 2021. https://www.rebiotix.com/efficacy-rbx2660-vs-placebo-reduce-recurrence-c-difficile-infection/

201 A Phase 3 Open-Label Clinical Study to Evaluate the Safety and Tolerability of Rebiotix RBX2660 (Microbiota Suspension) in Subjects With Recurrent Clostridium Difficile Infection. NCT03931941 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT03931941?term=NCT03931941&draw=2&rank=1.

202 A Phase III, Randomized, Multicenter, Parallel-Group, Double-Blind, Double-Dummy Study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Gepotidacin to Nitrofurantoin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis). NCT04020341 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04020341?term=NCT04020341&draw=2&rank=1.

203 A Phase III, Randomized, Multicenter, Parallel-Group, Double-Blind, Double-Dummy Study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Gepotidacin to Nitrofurantoin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis). NCT04187144 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04187144?term=NCT04187144&draw=2&rank=1.

204 EAGLE-2 and EAGLE-3 phase III trials for gepotidacin stopped early for efficacy following pre-planned interim analysis by Independent Data Monitoring Committee Issued: London UK. November 3, 2022. https://www.gsk.com/en-gb/media/press-releases/gsk-announces-phase-iii-trials-for-gepotidacin/

205 New antibiotic appears to be effective against urinary tract infections, drug company says. November 3, 2022. https://www.cnn.com/2022/11/03/health/new-uti-antibiotic-gepotidacin/index.html

206 GSK to submit drug application for new antibiotic to US FDA. November 4, 2022. https://www.pmlive.com/pharma_news/gsk_to_submit_drug_application_for_new_antibiotic_to_us_fda_1480238

207 Bhatt DL, Pollack, Jr. CV, Mazer D, Angiolillo DJ, Steg G, et al; for the REVERSE-IT Investigators. Bentracimab for Ticagrelor Reversal in Patients Undergoing Urgent Surgery. NEJM Evid 2021; 1 (3) DOI:https://doi.org/10.1056/EVIDoa2100047. https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100047

208 PhaseBio Announces Successful Pre-BLA Meeting with U.S. FDA for Bentracimab. May 16, 2022. https://www.businesswire.com/news/home/20220516005342/en/PhaseBio-Announces-Successful-Pre-BLA-Meeting-with-U.S.-FDA-for-Bentracimab

209 Danicopan (ALXN2040) add-on to Ultomiris or Soliris met primary endpoint in ALPHA Phase III trial for patients with paroxysmal nocturnal haemoglobinuria who experience clinically significant extravascular haemolysis. September 16, 2022. https://www.astrazeneca.com/media-centre/press-releases/2022/danicopan-phase-iii-trial-met-primary-endpoint.html

210 A Phase 3 Study of Danicopan (ALXN2040) as Add-on Therapy to a C5 Inhibitor (Eculizumab or Ravulizumab) in Patients With Paroxysmal Nocturnal Hemoglobinuria Who Have Clinically Evident Extravascular Hemolysis (EVH). NCT04469465 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04469465?term=NCT04469465&draw=2&rank=1.

211 Gene Therapy for Hemophilia Is on the Brink of FDA Approval. November 17, 2022. https://www.managedhealthcareexecutive.com/view/gene-therapy-for-hemophilia-is-on-the-brink-of-fda-approval

212 Press Release: Fitusiran prophylaxis reduced bleeds by 61% in people with hemophilia A or B, with or without inhibitors, compared to prior factor or bypassing agent prophylaxis. July 10, 2022. https://www.sanofi.com/en/media-room/press-releases/2022/2022-07-10-13-45-00-2476896

213 Press Release: Fitusiran prophylaxis reduced bleeds by 61% in people with hemophilia A or B, with or without inhibitors, compared to prior factor or bypassing agent prophylaxis. July 10, 2022. https://www.sanofi.com/en/media-room/press-releases/2022/2022-07-10-13-45-00-2476896

214 An Open-label, Long-term Safety and Efficacy Study of Fitusiran in Patients With Hemophilia A or B, With or Without Inhibitory Antibodies to Factor VIII or IX. NCT03754790 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT03754790?term=Fitusiran&phase=2&draw=2&rank=2

215 Khan AA, Rubin MR, Schwarz P, Vokes T, Shoback DM, et al. Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. J Bone Miner Res. 2022 Oct 21. doi: 10.1002/jbmr.4726. Online ahead of print.

216 TransCon PTH Gets Priority Review for Hypoparathyroidism. November 2, 2022. https://www.empr.com/home/news/drugs-in-the-pipeline/transcon-pth-gets-priority-review-for-hypoparathyroidism/

217 Tuberculosis Pipeline Landscape Analysis of 38+ Companies by DelveInsight. May 4, 2022. https://www.globenewswire.com/en/news-release/2022/05/04/2436001/0/en/Tuberculosis-Pipeline-Landscape-Analysis-of-38-Companies-by-DelveInsight.html

218 Nymox Announces Submission of New Drug Application (NDA) to the FDA for Fexapotide Triflutate. March 03, 2022. https://www.drugs.com/nda/fexapotide_triflutate_220303.html

219 Prothena to Present Data on Survival Benefit Observed in Completed Phase 3 Study of Drug Candidate Birtamimab in Patients with Mayo Stage IV AL Amyloidosis at the ASH 2022 Meeting. November 3, 2022. https://www.businesswire.com/news/home/20221103005351/en/Prothena-to-Present-Data-on-Survival-Benefit-Observed-in-Completed-Phase-3-Study-of-Drug-Candidate-Birtamimab-in-Patients-with-Mayo-Stage-IV-AL-Amyloidosis-at-the-ASH-2022-Meeting

220 A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Birtamimab Plus Standard of Care vs. Placebo Plus Standard of Care in Mayo Stage IV Subjects With Light Chain (AL) Amyloidosis. NCT04973137 (recruiting). https://clinicaltrials.gov/ct2/show/NCT04973137?term=NCT04973137&draw=2&rank=1.

221 CellTrans' Lantidra™ (donislecel) approaches a decision from the FDA. June 15, 2021. https://www.primetherapeutics.com/news/celltrans-lantidra-donislecel-approaches-a-decision-from-the-fda/

222 FDA Meeting Likely to Lead to New Request for PRX-102 Approval. October 22, 2021. https://fabrydiseasenews.com/news/new-fda-approval-request-prx-102-likely-protalix-reports/

223 Protalix Resubmits To FDA The BLA For Pegunigalsidase Alfa For Treatment Of Fabry Disease. November 14, 2022. https://www.nasdaq.com/articles/protalix-resubmits-to-fda-the-bla-for-pegunigalsidase-alfa-for-treatment-of-fabry-disease

224 Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce the Submission of a Marketing Authorization Application to the European Medicines Agency for PRX-102 for the Treatment of Fabry Disease. February 24, 2022. https://www.prnewswire.com/il/news-releases/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-the-submission-of-a-marketing-authorization-application-to-the-european-medicines-agency-for-prx-102-for-the-treatment-of-fabry-disease-301491083.html

225 A Randomized, Multicenter, Parallel-group, Phase III Study to Compare the Efficacy of Arfolitixorin Versus Leucovorin in Combination With 5 Fluorouracil, Oxaliplatin, and Bevacizumab in Patients With Advanced Colorectal Cancer. NCT03750786 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT03750786?term=NCT03750786&draw=2&rank=1.

226 A Phase 3 Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Determine the Efficacy of Topical SGX301 (Synthetic Hypericin) and Fluorescent Bulb-Light Irradiation for the Treatment of Cutaneous T-Cell Lymphoma. NCT02448381 (completed). https://clinicaltrials.gov/ct2/show/NCT02448381?term=NCT02448381&draw=2&rank=1.

227 Kim EJ, Mangold AR, DeSimone JA, Wong HK, Seminario-Vidal L, et al. Efficacy and Safety of Topical Hypericin Photodynamic Therapy for Early-Stage Cutaneous T-Cell Lymphoma (Mycosis Fungoides): The FLASH Phase 3 Randomized Clinical Trial. JAMA Dermatol. 2022 Sep 1;158(9):1031-1039. doi: 10.1001/jamadermatol.2022.2749.

228 FDA Declines to File New Drug Application for SGX301 in T-Cell Lymphoma. February 20, 2023. https://www.cancernetwork.com/view/fda-declines-to-file-new-drug-application-for-sgx301-in-t-cell-lymphoma

229 A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial Testing Ipatasertib Plus Abiraterone Plus Prednisone/Prednisolone, Relative to Placebo Plus Abiraterone Plus Prednisone/Prednisolone in Adult Male Patients With Asymptomatic or Mildly Symptomatic, Previously Untreated, Metastatic Castrate-Resistant Prostate Cancer. NCT03072238 (active, but not recruiting). https://clinicaltrials.gov/ct2/show/NCT03072238?term=NCT03072238&draw=2&rank=1

230 BioLineRx Announces U.S. FDA Acceptance of New Drug Application for Aphexda (motixafortide) in Stem Cell Mobilization. November 2022. https://www.drugs.com/nda/aphexda_221110.html

231 BioLineRx Announces U.S. FDA Acceptance of New Drug Application for Aphexda (motixafortide) in Stem Cell Mobilization. November 2022. https://www.drugs.com/nda/aphexda_221110.html

232 A Phase 3 Multicenter, Randomized, Double Masked, Sham- Controlled Clinical Trial to Assess the Safety and Efficacy of Intravitreal Administration of Zimura (Complement C5 Inhibitor) in Patients With Geographic Atrophy Secondary to Age-Related Macular Degeneration.. NCT04435366 (active, not recruiting). https://clinicaltrials.gov/ct2/show/NCT04435366?term=NCT04435366&draw=2&rank=1.

233 FDA accepts NDA for avacincaptad pegol for the treatment of geographic atrophy. February 17, 2023. https://www.modernretina.com/

view/fda-approves-nda-for-avacincaptad-pegol-for-the-treatment-of-geographic-atrophy

234 U.S. FDA Accepts Astellas' New Drug Application for Fezolinetant. Aug 18, 2022. https://www.prnewswire.com/news-releases/us-fda-accepts-astellas-new-drug-application-for-fezolinetant-301608116.html

235 Astellas Announces Topline 12-week Results from Phase 3 Study of Fezolinetant for the Nonhormonal Treatment of Vasomotor Symptoms in Women in Asia. Mar 15, 2022. https://www.astellas.com/en/news/25421

236 Astellas has menopause accelerated approval ambition thwarted by FDA at last minute. February 20, 2023. https://www.fiercebiotech.com/biotech/astellas-after-using-prv-has-menopause-accelerated-approval-ambition-thwarted-fda-last

237 Leqembi (lecanemab-irmb). FDA Letter or approval: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/761269Orig1s000ltr.pdf

238 Briumvi (ublituximab-xiiy). FDA Letter or approval: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/761238Orig1s000ltr.pdf

239 FDA Approves First Gene Therapy to Treat Adults with Hemophilia B. November 22, 2022. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treat-adults-hemophilia-b

240 Vivjoa *(oteseconazole).* FDA Letter of approval: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/215888Orig1s000ltr.pdf

241 Tzield *(teplizumab-mzwv)* injection. FDA Letter or approval: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761183Orig1s000ltr.pdf

242 Orserdu (elacestrant). FDA Letter or approval: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/217639Orig1s000correctedltr.pdf

243 Mora JS(1), Bradley WG(2), Chaverri D(3), Hernández-Barral M(3), Mascias J(3), et al. Long-term survival analysis of masitinib in amyotrophic lateral sclerosis. Ther Adv Neurol Disord. 2021 Jul 19;14:17562864211030365. doi: 10.1177/17562864211030365. eCollection 2021.

244 AB Science today announced that it has filed an application for conditional Marketing Authorization to the European Medicines Agency (EMA) for Alsitek (masitinib) in the treatment of amyotrophic lateral sclerosis (ALS). August 24, 2022. https://www.ab-science.com/ab-science-announces-that-it-has-filed-an-application-for-conditional-marketing-authorization-to-ema-for-masitinib-in-the-treatment-of-als/

245 Alsitek (*masitinib*). European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/alsitek

246 GlobalData's Healthcare database (accessed September 2022; Phase II list).

247 Pasca S. Concizumab as a Subcutaneous Prophylactic Treatment Option for Patients with Hemophilia A or B: A Review of the Evidence and Patient's Perspectives.J Blood Med. 2022 Apr 16;13:191-199. doi: 10.2147/JBM.S242219. eCollection 2022.

248 Novo Nordisk A/S: Phase 3 data for concizumab show 86% reduction in treated bleeds in haemophilia A or B with inhibitors. July 10, 2022. https://www.globenewswire.com/news-release/2022/07/10/2476898/0/en/Novo-Nordisk-A-S-Phase-3-data-for-concizumab-show-86-reduction-in-treated-bleeds-in-haemophilia-A-or-B-with-inhibitors.html

249 Jiménez-Yuste V, Angchaisuksiri P, Castaman G, et al. Concizumab prophylaxis in patients with haemophilia A or B with inhibitors: Efficacy and safety results from the 32-week primary analysis of the phase 3 explorer7 trial. ISTH 2022 abstracts. Abstract number: LB 01.2. https://abstractsisth?advanced=1&title=Concizumab+prophylaxis+in+patients+with+haemophilia+A+or+B+with+inhibitors&theauthor=&affiliation=&meetingid=&s=

250 Novo Nordisk A/S: Phase 3 data for concizumab show 86% reduction in treated bleeds in haemophilia A or B with inhibitors. July 10, 2022. https://www.globenewswire.com/news-release/2022/07/10/2476898/0/en/Novo-Nordisk-A-S-Phase-3-data-for-concizumab-show-86-reduction-in-treated-bleeds-in-haemophilia-A-or-B-with-inhibitors.html

251 GlobalData's Healthcare database (accessed September 2022; Phase II list).

252 Trial of Spesolimab for Generalized Pustular Psoriasis. December 22, 2021. https://www.mountsinai.org/about/newsroom/2021/trial-of-spesolimab-for-generalized-pustular-psoriasis

253 FDA approves the first treatment option for generalized pustular psoriasis flares in adults. September 1, 2022. https://www.boehringer-ingelheim.us/press-release/fda-approves-first-treatment-option-generalized-pustular-psoriasis-flares-adults

254 Menter A, Van Voorhees AS, Hsu S. Pustular Psoriasis: A Narrative Review of Recent Developments in Pathophysiology and Therapeutic Options. Dermatol Ther (Heidelb). 2021 Dec;11(6):1917-1929. doi: 10.1007/s13555-021-00612-x. Epub 2021 Oct 9.

255 Maçães CO, Lé AM, Torres T. Generalized pustular psoriasis: the new era of treatment with IL-36 receptor inhibitors.J Dermatolog Treat.

2022 Nov;33(7):2911-2918. doi: 10.1080/09546634.2022.2089335. Epub 2022 Jun 21.

256 FDA approves the first treatment option for generalized pustular psoriasis flares in adults. September 1, 2022. https://www.boehringer-ingelheim.us/press-release/fda-approves-first-treatment-option-generalized-pustular-psoriasis-flares-adults

257 Spevigo *(spesolimab-sbzo)* intravenous injection. FDA Letter of approval. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761244Orig1s000ltr.pdf

258 Spevigo *(spesolimab)*. European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/spevigo

259 GlobalData's Healthcare database (accessed September 2022; Phase II list).

260 Chekol Abebe E, Yibeltal Shiferaw M, Tadele Admasu F, Asmamaw Dejenie T. Ciltacabtagene autoleucel: The second anti-BCMA CAR T-cell therapeutic armamentarium of relapsed or refractory multiple myeloma. Front Immunol. 2022 Sep 2;13:991092. doi: 10.3389/fimmu.2022.991092. eCollection 2022.

261 Carvykti. European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti

262 Chekol Abebe E, Yibeltal Shiferaw M, Tadele Admasu F, Asmamaw Dejenie T. Ciltacabtagene autoleucel: The second anti-BCMA CAR T-cell therapeutic armamentarium of relapsed or refractory multiple myeloma. Front Immunol. 2022 Sep 2;13:991092. doi: 10.3389/fimmu.2022.991092. eCollection 2022.

263 Weisel K, Martin T, Krishnan A, Jagannath S, Londhe A, et al. Comparative Efficacy of Ciltacabtagene Autoleucel in CARTITUDE-1 vs Physician's Choice of Therapy in the Long-Term Follow-Up of POLLUX, CASTOR, and EQUULEUS Clinical Trials for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma. Clin Drug Investig. 2022 Jan;42(1):29-41. doi: 10.1007/s40261-021-01100-y. Epub 2021 Nov 25.

264 FDA approves ciltacabtagene autoleucel for relapsed or refractory multiple myeloma. February 28, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ciltacabtagene-autoleucel-relapsed-or-refractory-multiple-myeloma

265 Carvykti. European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti

266 GlobalData's Healthcare database (accessed September 2022; Phase II list).

267 Minson A, Dickinson M. Glofitamab CD20-TCB bispecific antibody. Leuk Lymphoma. 2021 Dec;62(13):3098-3108. doi: 10.1080/10428194.2021.1953016. Epub 2021 Jul 15.

268 Fixed-Duration Glofitamab Elicits Early, Durable Complete Remissions in Relapsed/Refractory LBCL. Sep 2, 2022. https://www.onclive.com/view/fixed-duration-glofitamab-elicits-early-durable-complete-remissions-in-relapsed-refractory-lbcl

269 New Pivotal Data Demonstrate Clinical Benefit of Genentech's Glofitamab, a Potential First-in-Class Bispecific Antibody for People with Aggressive Lymphoma. May 26, 2022. https://www.gene.com/media/press-releases/14954/2022-05-26/new-pivotal-data-demonstrate-clinical-be

270 Minson A, Dickinson M. Glofitamab CD20-TCB bispecific antibody. Leuk Lymphoma. 2021 Dec;62(13):3098-3108. doi: 10.1080/10428194.2021.1953016. Epub 2021 Jul 15.

271 GlobalData's Healthcare database (accessed September 2022; preregistration list)

272 GlobalData's Healthcare database (accessed September 2022; Phase II list).

273 Samaddar A, Grover M, Nag VL. 2020. *Pathophysiology and Potential Therapeutic Candidates for COVID-19: A Poorly Understood Arena*. Front Pharmacol. 11:585888. doi: 10.3389/fphar.2020.585888.