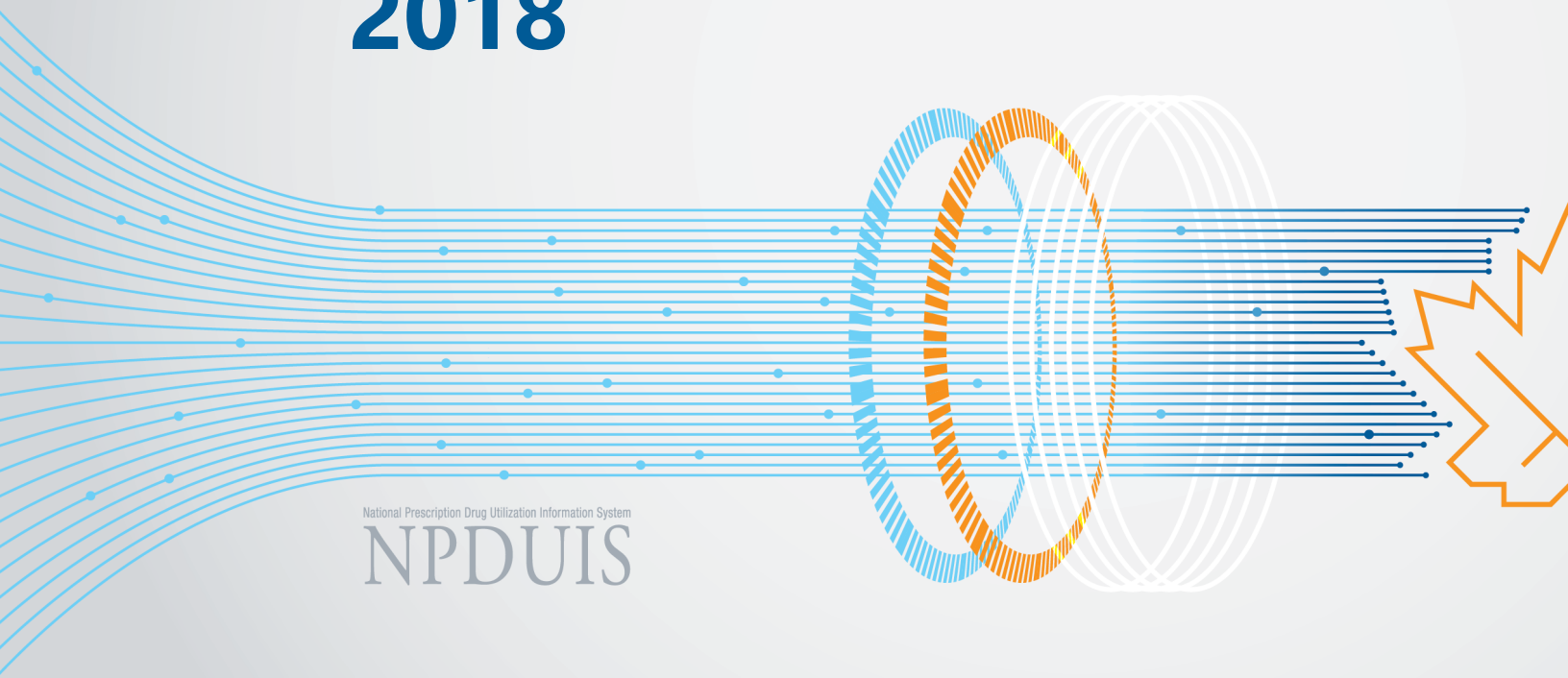
Patented Medicine Prices Review Board

Conseil d'examen du prix des médicaments brevetés

MEDS

PIPELINE MONITOR 2018



National Prescription Drug Utilization Information System

NPDUIS

Canada

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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 generate analysis that provides policy makers and public drug plan managers with critical information and intelligence on price, utilization, and cost trends so that Canada's health care system has comprehensive and accurate information on drug usage and the 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), and the pan-Canadian Pharmaceutical Alliance (pCPA).

Acknowledgements

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We gratefully acknowledge Patricia Carruthers-Czyzewski, BScPhm, MSc, Sintera Inc. for her expert contribution to the development of the methodology, the scientific assessment of the medicines in late stages of development, and the selection of the pipeline candidates featured in this report.

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Disclaimer

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EXECUTIVE SUMMARY

Meds Pipeline Monitor (MPM) is a horizon scanning report that features a selection of new medicines in the late stages of clinical evaluation that may have a significant impact on future clinical practice and drug spending in Canada.

Medicines in Phase III clinical trials or in pre-registration with the US Food and Drug Administration (FDA) are considered as candidates if they have the potential to address an unmet therapeutic need, offer a novel mechanism or therapeutic benefit over existing therapies, or treat a serious condition. The final selection features medicines from a wide range of therapeutic areas and includes a list of gene therapies.

The information in the *Meds Pipeline Monitor* is a continuation of the research formerly published in the *New Drug Pipeline Monitor,* with a renewed approach to the selection of medicines. The new title reflects the link between this series and its companion publication, *Meds Entry Watch*, which explores the post-market dynamics of newly approved medicines. Together these two reports monitor the continuum of new and emerging medicines in Canada and internationally, providing key information to decision makers, researchers, patients, clinicians, and other stakeholders. Future editions of this annual publication will monitor the pipeline list featured in this report.

Highlights of the Meds Pipeline 2018

- In 2018, nearly 6,000 new medicines were undergoing clinical evaluation.
- Cancer treatments dominated the therapeutic mix, accounting for one third of medicines in all phases of clinical evaluation. Other prominent therapeutic areas included treatments for infectious diseases such as HIV and pneumonia (12% of medicines) and medicines for nervous system diseases and disorders such as Alzheimer's disease and depression (11% of medicines).
- Of the 6,000 medicines, 733 (12%) were in Phase III clinical trials or in pre-registration with the FDA, representing a wide range of therapeutic areas.
- 30 of the 733 medicines in the late stages of clinical evaluation were selected for this report based on their potential budgetary impact, including 9 gene therapies. Some of these medicines offer possible breakthroughs in treating previously unmet needs or have the potential to treat large patient populations.
- Of the 30 new medicines selected, 20 were designated as orphan drugs by the FDA or the EMA (including 8 gene therapies); 9 were oncology medicines; and 3 were biologics.[i]

[i] Note that a single medicine may fall into more than one category.

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LIST OF TERMS

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

CLINICAL EFFICACY: The maximum response achievable from a medicine in research settings and the capacity for sufficient therapeutic effect in clinical settings.[ii]

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.[iii]

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*.[iv]

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.[v]

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.

MEDICINE PIPELINE: A set of new medicine candidates under active research and development by a biotechnology or pharmaceutical company.

NEW MEDICINE: A medicinal ingredient that has not previously received market authorization by a regulator.[v]

PHASE III CLINICAL TRIALS: Controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the drug has been demonstrated. These are intended to gather the additional and confirmatory information about the clinical efficacy and safety under the proposed conditions of use for the drug.[iii] 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.[vi]

[ii] 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.

[iii] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/health-canada-clinical-trials-database/glossary.html

[iv] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products.html

[v] http://www.pmprb-cepmb.gc.ca/en/npduis/view.asp?ccid=1310&lang=en

[vi] http://www.appliedclinicaltrialsonline.com/are-phase-labels-still-relevant

INTRODUCTION

Meds Pipeline Monitor (MPM) is a continuation of the horizon scanning research formerly published under the title *New Drug Pipeline Monitor*. It features a selection of medicines in Phase III clinical trials or in pre-registration with the US Food and Drug Administration (FDA) that have the potential to significantly impact clinical practice and drug spending in Canada.

Along with the new series title, this edition of the MPM takes a renewed approach to the selection process, identifying pipeline candidates from a wide range of therapeutic areas. It also features a list of potentially important medicines from the rapidly advancing field of gene therapies. This new methodology, which is detailed in the next section, uses a specific set of criteria to identify the list of pipeline candidates. The medicines featured in this report will be tracked in future editions of the MPM to determine if and when they successfully enter the market.

To provide context for the selection of medicines, the MPM also includes a snapshot of the entire pipeline, with an emphasis on the therapeutic breakdown of each phase of development.

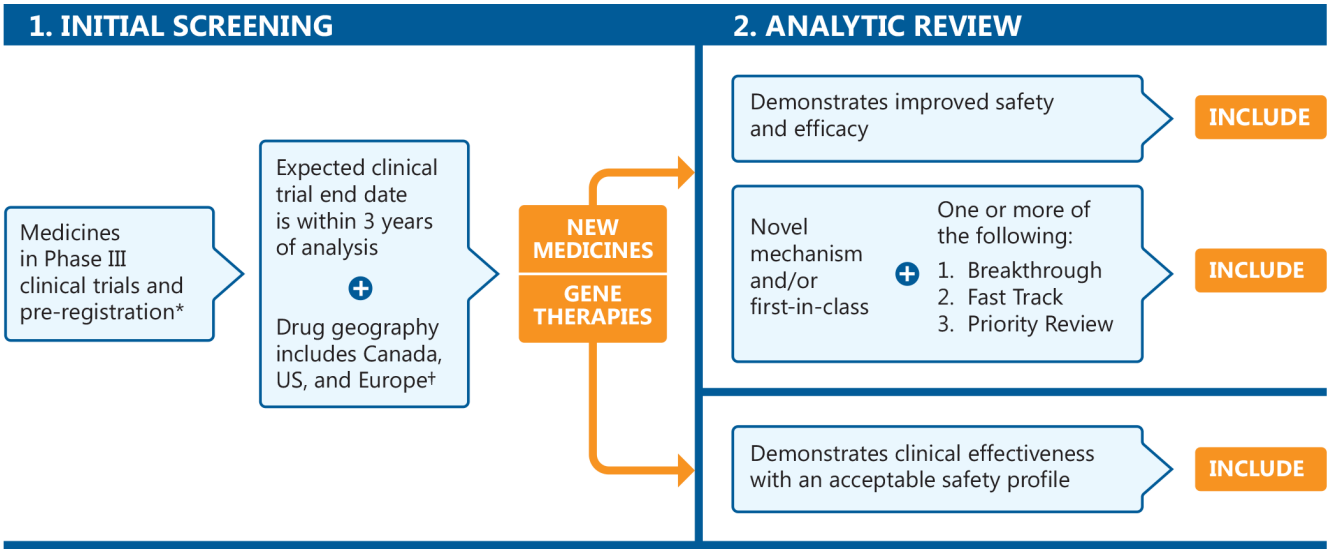
Meds Pipeline Monitor is a companion publication to *Meds Entry Watch*, which analyzes the market dynamics of newly approved medicines in Canada and internationally. Together these two PMPRB reports monitor the market continuum of late-stage pipeline medicines and new launches, providing decision makers,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

METHODOLOGY

The MPM focuses on new medicines in Phase III clinical trials in Canada, the United States, and Europe, or in pre-registration with the FDA. Pipeline medicines are selected for inclusion in this report using a two-stage screening process (Figure 1). The initial screening stage selects medicines in the late phases of clinical evaluation, while the analytic review involves a more rigorous appraisal of each potential candidate to identify medicines that may have a significant clinical and budgetary impact. The second stage considers a specific set of criteria, in addition to the results of a thorough review of clinical evidence and scientific literature.

This methodology is reviewed annually and refined as required.

FIGURE 1. Selection process for medicines featured in the Meds Pipeline Monitor



* In pre-registration with the US Food and Drug Administration (FDA).
† Has Phase III clinical trials in Canada, United States, or geographic Europe (excluding Russia and Turkey).

Stage 1. Initial Screening

The GlobalData Healthcare database is used to identify a list of medicines undergoing Phase III clinical trials or in pre-registration with the FDA. 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 with adequate data on safety and efficacy 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.

The selection process groups pipeline candidates into two categories: (a) new medicines and (b) new gene therapies. As illustrated in Figure 1, the initial screening process for both groups is the same, but the analytic review stage is slightly different, as the available data for gene therapies is more limited.

Stage 2: Analytic Review

Selection criteria: new medicines (excluding gene therapies)

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, alongside their corresponding icons.

TABLE 1. Selection criteria for the Meds Pipeline Monitor: New medicines (excluding gene therapies)

	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

Selection criteria: gene therapies

A broader approach is used for selecting the final list of gene therapies, as the clinical evidence available for this group is relatively limited. Gene therapies are retained on the list if the preliminary (or completed) results from Phase III trials suggest that there is evidence of clinical effectiveness with an acceptable safety profile.

Additional descriptive information

A profile of each successful pipeline candidate is provided, including a brief outline of 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 identified. Table 2 provides a detailed description of key attributes along with their associated icons.

TABLE 2. Key attributes of medicines selected for the Meds Pipeline Monitor

	ATTRIBUTE	RELEVANCE	DATA SOURCES
	Phase III clinical trials in Canada	Medicines tested in Canada are likely to be of interest to Canadians	GlobalData Healthcare Health Canada Clinical Trials Database National Institutes of Health (NIH) Clinical Trial Registry
	Rare or orphan designation	Medicines used to treat rare diseases or conditions 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 treatment 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 greater spending	

The profile also gives details of potential cost implications, if available, including the forecasted global revenues reported by GlobalData and an indication of whether the medicine belongs to a high-cost or top-selling therapeutic area. In this report, therapeutic areas are defined at the ATC4[vii] level. A therapeutic area is considered to be high-cost if it includes at least one medicine with an annual treatment cost exceeding $10,000 or, in the case of oncology, a 28-day course of treatment exceeding $5,000. These costs are based on either assumed dosage regimens or the average treatment cost observed in public and/or private drug plans. Top-selling therapeutic areas include the five classes with the highest annual global revenues in 2018 based on IQVIA MIDAS™ data.

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 have additional indications at various phases of clinical evaluation that are not mentioned in this report. The scientific description provided applies directly to the specified indication(s) for the selected medicines.

Data Sources

The GlobalData Healthcare database is the primary data source for the identification of pipeline medicines and their corresponding clinical information, including the clinical trial end date. 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: phase of clinical development, therapeutic area, molecule type, indication, drug geography, mechanism of action, and FDA designations.

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, European Medicines Agency (EMA), and Health Canada; and information in Health Canada's ClinicalTrials database and ClinicalTrials.org.

[vii] Level four of the Anatomic Therapeutic Chemical (ATC) Classification System maintained by the World Health Organization (WHO).

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.

The cost analysis included in this report flags whether a featured medicine belongs to a high-cost or top-selling therapeutic area based on historical sales information. While this may point to the potential for a featured medicine to become a high-cost or top-selling medicine, it is uncertain at this early stage. Conversely, medicines that are not identified as part of a high-cost or top-selling therapeutic class may still become high-cost or top-selling once they are marketed. High-cost medicines have been introduced in therapeutic areas that have not been historically high-cost, and top-selling medicines are frequently introduced in new therapeutic areas or areas that have not been historically top-selling.

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.

The featured lists are valid as of May 1, 2019. 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, United States, or Europe following this date. Also, pipeline medicines that have not been included in this report because they did not meet the MPM selection criteria at the time of the analysis may presently meet it. These along with the rest of the drug pipeline will be considered for the next edition of the report.

SNAPSHOT OF THE 2018 MEDS PIPELINE

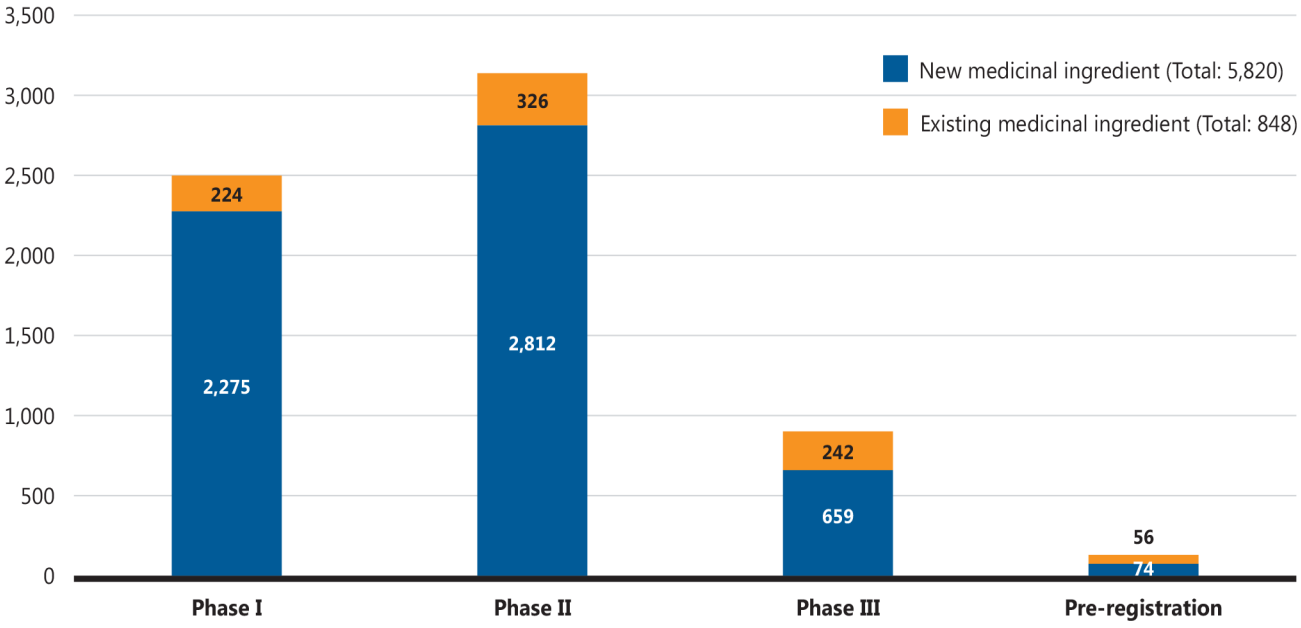
Pharmaceutical innovation is transforming the development and application of medical treatments worldwide. In 2018, nearly 6,000 new medicines were in clinical evaluation or in pre-registration with the FDA, representing 87% of the total pipeline.

Cancer treatments dominated the therapeutic mix, accounting for one third of medicines in all phases of clinical evaluation. Other prominent therapeutic areas included treatments for infectious diseases such as HIV and pneumonia (12% of medicines) and medicines for nervous system diseases and disorders such as Alzheimer's disease and depression (11% of medicines).

Figure 2 provides a snapshot of the pipeline in 2018, including the number of new medicinal ingredients in each phase of clinical evaluation. Of the 5,820 new medicines, 733 (12%) were in Phase III clinical trials or in pre-registration with the FDA.

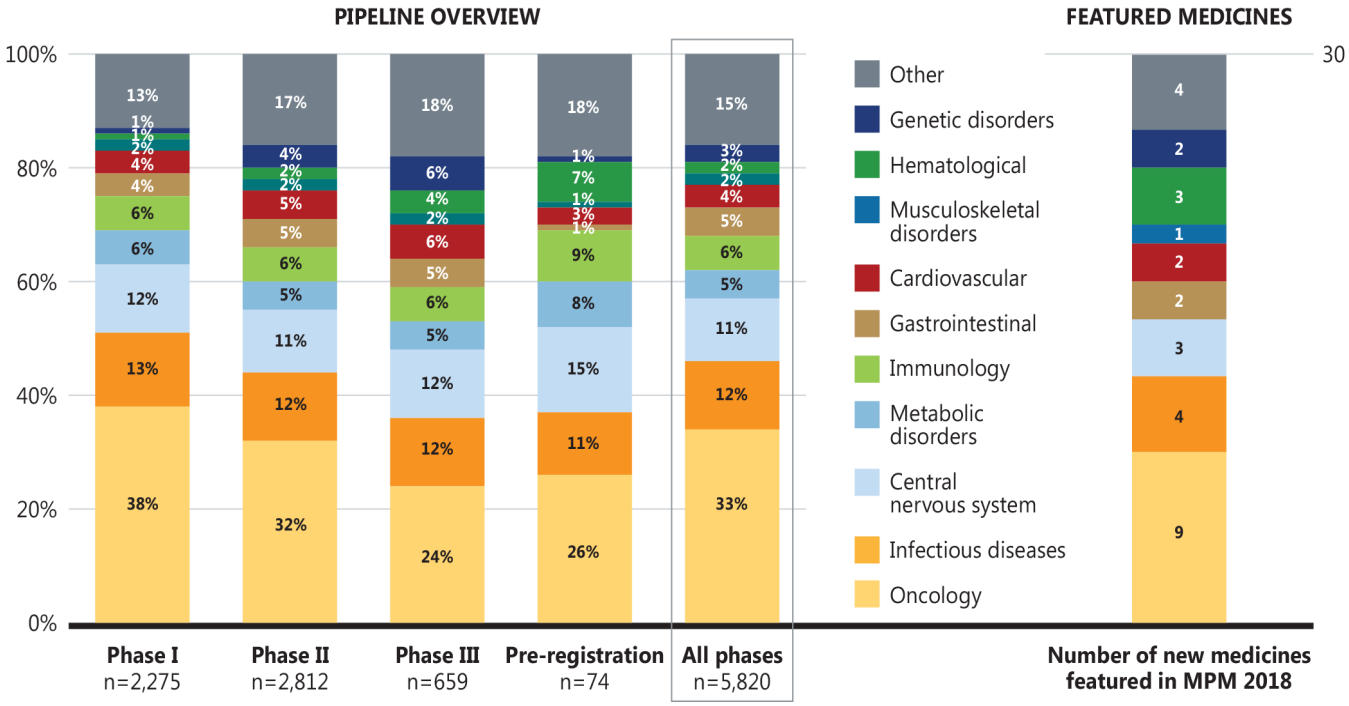
In general, the pipeline medicines represented a wide range of therapeutic areas. Figure 3 illustrates the distribution of new medicines by therapeutic area, including the selection of pipeline candidates in this report.

FIGURE 2. Number of pipeline medicines in each stage of clinical evaluation



Data source: GlobalData Healthcare database (accessed July 2018).

FIGURE 3. Therapeutic class distribution, pipeline overview and MPM selected medicines, 2018



Data source: GlobalData Healthcare database (accessed July 2018).

2018 MEDS PIPELINE MONITOR

Applying the screening criteria described in the Methodology section, 30 of the 733 medicines in late stages of clinical evaluation were selected for this report. Of these 30 new medicines, 20 were designated as orphan drugs by the FDA or the EMA (including 8 gene therapies); 9 are oncology medicines; and 3 are biologics.

Table 3 provides a complete list of the selected pipeline medicines, including the qualifying selection criteria, indications, and attributes organized by broad therapeutic class. Table 4 gives a similar list for gene therapies.

This list is valid as of May 1, 2019. The selected medicines will be monitored in future editions of this report.

TABLE 3. List of selected new medicines for 2018

SELECTION CRITERIA					KEY ATTRIBUTES			
Increased safety and efficacy	Novel mechanism	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
CARDIOVASCULAR		
Elamipretide (Bendavia [US]) Stealth BioTherapeutics Inc	Mitochondrial diseases (myopathy)	• An aromatic-cationic tetrapeptide that increases mitochondrial energy.[1] • Novel therapeutic target in heart failure management.[2] • Increased exercise performance after 5 days of treatment in patients with primary mitochondrial myopathy (PMM) without increased safety concerns.[3]
CENTRAL NERVOUS SYSTEM		
Rapastinel Allergan Plc	Major depressive disorder	• A novel NMDA receptor modulator. • Great unmet need for new medications with novel mechanisms of action that can effectively treat patients who do not benefit from standard antidepressant therapies. • Global revenue forecasted to be $15 million in 2020 and $519 million by 2024.

Ubrogepant Allergan Plc	Migraine	• A next generation oral calcitonin gene-related peptide receptor antagonist. • Safe and effective in the acute treatment of migraine in a wide range of patients, including those who had an insufficient response to a triptan or those in whom triptans were contraindicated, as well as in patients who had moderate to severe cardiovascular risk. • Global revenue forecasted to be $32 million in 2020 and $470 million by 2024.
GASTROINTESTINAL/METABOLIC DISORDERS		
Cenicriviroc Allergan Plc	Liver fibrosis; Non-alcoholic steatohepatitis (NASH)	• A dual chemokine receptor type 2 (CCR2) and type 5 (CCR5) antagonist, in treatment-experienced, HIV-infected individuals.[4] • For oral treatment of non-alcoholic steatohepatitis (NASH) with liver fibrosis.[5] After 1 year of treatment, twice as many patients achieved improvement in fibrosis and no worsening of NASH compared with placebo.[6] • Non-alcoholic fatty liver disease (NAFLD) has an increasing prevalence worldwide. At present, no specific pharmacotherapy is approved for NAFLD.[7] • In studies to date, safety and tolerability were comparable to placebo.[8] • Global revenue forecasted to be $73 million by 2024.
Setmelanotide Rhythm Pharmaceuticals Inc	Obesity	• First-in-class melanocortin-4 receptor (MC4R) agonist to treat rare genetic disorders of obesity. • Leads to weight loss in obese individuals with complete pro-opiomelanocortin (POMC) deficiency. While POMC deficiency is very rare, 1%–5% of severely obese individuals harbour heterozygous mutations in MC4R.[9] • Global revenue forecasted to be $22 million in 2020 and $542 million by 2024.
GENITOURINARY AND SEX HORMONES		
Vilaprisan Bayer AG	Uterine leiomyoma (uterine fibroids)	• A novel powerful selective progesterone receptor modulators (SPRMs). • It has been shown to induce benign changes of endometrium (PR modulator-associated endometrial changes, PAECs). These disappear as treatment is discontinued. Unlike GnRHa treatment, it does not induce hypoestrogenism and associated symptoms.[10] • Global revenue forecasted to be $286 million by 2024.

HEMATOLOGICAL		
Fitusiran Sanofi and Alnylam Pharmaceuticals Inc	Hemophilia A; Hemophilia B	• A small interfering RNA (siRNA) developed to suppress the hepatic synthesis of antithrombin. • Current hemophilia treatment involves frequent intravenous infusions of clotting factors, which is associated with variable hemostatic protection, a high treatment burden, and a risk of the development of inhibitory alloantibodies. • Once-monthly SC administration of fitusiran resulted in dose-dependent lowering of the antithrombin level and increased thrombin generation in participants with hemophilia A or B who did not have inhibitory alloantibodies.[11] • Global revenue forecasted to be $400 million by 2024.
Vadadustat Akebia Therapeutics Inc and Otsuka Holdings Co Ltd	Anemia in chronic kidney disease (CKD; renal anemia)	• A titratable prolyl hydroxylase domain (PHD) enzyme inhibitor that represents a novel pharmacological treatment of anemia. • Has been shown to increase hemoglobin (Hb) levels[12] and to maintain mean Hb concentrations in patients on hemodialysis previously receiving Epoetin.[13] • Global revenue forecasted to be $60 million in 2020 and $1 billion by 2024.
INFECTIOUS DISEASE		
Cabotegravir ViiV Healthcare UK Ltd	HIV infections (AIDS)	• A potent integrase strand transfer inhibitor; formulated as an oral tablet for daily administration and as a long-acting injectable nanosuspension. • Has a long half-life and can be formulated into a long-acting nanosuspension for parenteral administration (IM at 4 weekly and 8 weekly intervals).[14] • Few interactions with commonly used concomitant medications.[15] • May provide an alternative therapeutic option for both the treatment and prevention of HIV-1 infection that does not necessitate adherence to a daily regimen.[16] • In combination with dual NRTI therapy had potent antiviral activity during the induction phase; as a two-drug maintenance therapy, cabotegravir plus rilpivirine provided antiviral activity similar to efavirenz plus dual NRTIs until the end of week 96.[17] • Offers an alternative to daily regimens and may improve preexposure prophylaxis (PrEP) adherence.[18] • Global revenue forecasted to be $81 million in 2019 and $501 million by 2024.

Fostemsavir tromethamine ViiV Healthcare UK Ltd	HIV infections (AIDS)	• A next generation CD4 attachment inhibitor that is active regardless of viral tropism, without cross-resistance to any of the existing antiretroviral compounds.[19] • In one study, 82% of patients treated with fostemsavir and an optimized background ARV regimen achieved virological suppression below 50 copies/mL in HIV-infected treatment-experienced individuals.[20] • Global revenue forecasted to be $19 million in 2020 and $265 million by 2024.
Lefamulin Nabriva Therapeutics Plc	Community-acquired bacterial pneumonia	• Novel pleuromutilin antibiotic; exhibits a unique mechanism of action through inhibition of protein synthesis by binding to the peptidyl transferase center of the 50S bacterial ribosome, thus preventing the binding of transfer RNA for peptide transfer.[21] • Showed potent activity against all gonococcal isolates.[22] • Could be a promising first-line antibiotic for the treatment of sexually transmitted infections (STI), particularly in populations with high rates of resistance to standard-of-care antibiotics.[23] • Global revenue forecasted to be $15 million in 2019 and $311 million by 2024.
Murepavadin Polyphor AG	Ventilator associated pneumonia (VAP); Hospital acquired pneumonia (HAP)	• A pathogen specific antimicrobial peptidomimetic with a novel, non-lytic mechanism of action; first in class of outer membrane protein targeting antibiotics. • Exhibited potent activity against a large collection of clinical XDR *P. aeruginosa* isolates.[24]
MUSCULOSKELETAL SYSTEM		
Palovarotene Clementia Pharmaceuticals Inc	Fibrodysplasia ossificans progressiva (myositis ossificans progressiva)	• A novel highly selective retinoic acid receptor gamma agonist. • Claimed to reverse the structural, functional, and inflammatory features of cigarette smoke-induced emphysema.[25] • Global revenue forecasted to be $15 milllion in 2020 and $261 million by 2024.
ONCOLOGY		
Entinostat Syndax Pharamceuticals Inc	Metastatic breast cancer	• A synthetic benzamide derivative histone deacetylase (HDAC) inhibitor. • Reverses cisplatin resistance.[26] • Global revenue forecasted to be $16 million in 2020 and $423 million by 2024. • High-cost therapeutic area.†

Ipatasertib Array BioPharma Inc and Genentech Inc	Metastatic breast cancer; Metastatic hormone refractory (castration resistant, androgen-independent) prostate cancer	• An oral, v-Akt murine thymoma viral oncogene homolog (Akt) inhibitor. • In metastatic castration-resistant prostate cancer (mCRPC), combined blockade with abiraterone and ipatasertib showed superior antitumour activity to abiraterone alone, especially in patients with phosphatase and tensin homolog (PTEN)-loss tumours.[27] • Improved outcomes in a subset of patients with metastatic triple-negative breast cancer (TNBC) when combined with paclitaxel in the first-line setting.[28,29] Targeted therapies for TNBC, which accounts for ~20% of breast cancers, remain unavailable. • Global revenue forecasted to be $4 million in 2020 and $410 million by 2024. • High-cost therapeutic area†; top-selling therapeutic area.‡
Melphalan flufenamide hydrochloride Oncopeptides AB	Refractory multiple myeloma; Relapsed multiple myeloma	• Peptide-based alkylating agent; a novel dipeptide prodrug of melphalan. • Alone or in combination with cisplatin, gemcitabine, or dasatinib, holds promise as a novel treatment for urothelial carcinoma (UC).[30] • Overcomes drug-resistance, and improves multiple myeloma patient outcomes.[31] • High-cost therapeutic area.†
Quizartinib dihydrochloride Daiichi Sankyo Co Ltd	Refractory acute myeloid leukemia; Relapsed acute myeloid leukemia	• A small molecule receptor tyrosine kinase inhibitor targeting FLT3 that is administered orally once daily. FLT3 is a receptor tyrosine kinase that is commonly expressed in AML and is mutated in approximately 25% of AML patients. • Data from the QuANTUM-R study (NCT02039726) confirmed the efficacy and safety of quizartinib that was observed in previous trials and showed the value of therapy targeting FLT3-ITD. It is the first trial to demonstrate improved overall survival for FLT3-ITD–associated AML patients who are treatment resistant or who relapsed after prior therapy. • Preliminary data from the QuANTUM-R study shows improved overall survival for FLT3-ITD–associated AML patients who are treatment resistant or who relapsed after prior therapy. • Global revenue forecasted to be $20 million in 2019 and $334 million by 2024. • High-cost therapeutic area†; top-selling therapeutic area.‡
Racotumomab (Vaxira) Innogene Kalbiotech Pte Ltd	Non-small cell lung cancer	• An anti-idiotype (anti-Id) monoclonal antibody vaccine directed to NeuGc-containing gangliosides such as NeuGcGM3, a widely reported tumour-specific neoantigen in many human cancers. • Intradermal administration as a cancer vaccine.[32]

		• Demonstrated high immunogenicity and low toxicity.[33] • High-cost therapeutic area†; top-selling therapeutic area.‡
Selinexor Karyopharm Therapeutics Inc	Relapsed or refractory multiple myeloma	• First-in-class, oral selective inhibitor of nuclear export (SINE). It links to and inhibits XPO1 (CRM1), a nuclear export protein. • In a Phase II trial (STORM), it was given in combination with low-dose dexamethasone and shrank tumours in 25.4% of these patients, including two patients whose tumours were completely gone. Responses lasted a median of 4.4 months. • Global revenue forecasted to be $30 million in 2019 and $451 million by 2024. • High-cost therapeutic area.†
Ublituximab TG Therapeutics Inc; LFB SA	Refractory chronic lymphocytic leukemia (CLL); Relapsed chronic lymphocytic leukemia (CLL)	• A next generation glycoengineered anti-CD20 monoclonal antibody. • Next-generation with higher complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity against malignant B-cells.[34] • Demonstrated efficacy in patients with high-risk chronic lymphocytic leukemia (CLL) and B-non-Hodgkin lymphoma in both first line, subsequent lines, and in rituximab refractory patients.[35] • In combination with ibrutinib, resulted in rapid and high response rates.[36] • Global revenue forecasted to be $2 million in 2020 and $297 million by 2024. • High-cost therapeutic area†; top-selling therapeutic area.‡
OPTHAMOLOGICAL		
Zuretinol acetate Novelion Therapeutics Inc	Leber congenital amaurosis (LCA); Retinitis	• Oral retinoid; it is a synthetic retinoid replacement for 11-cis-retinal. • Could "achieve significant improvement in visual function and acuity as an alternative to gene therapy in inherited retinal diseases. Its oral dosing would, if approved, differentiate it as a potential therapy, particularly for patients who may not be amenable to more invasive options, such as younger children, due to intraocular surgical difficulties in underdeveloped eyes."[37] • Global revenue forecasted to be $24 million in 2019 and $91 million by 2024.

* Multiple indications within the same therapeutic area may be assessed in a single clinical trial.
† A therapeutic area is considered to be high-cost if it includes at least one medicine with an annual treatment cost exceeding $10,000 or, in the case of oncology, a 28-day course of treatment exceeding $5,000. Therapeutic areas are defined at the ATC4 level.
‡ Top-selling therapeutic areas include the five classes with the highest annual global revenues in 2018 based on IQVIA MIDAS™ data. Therapeutic areas are defined at the ATC4 level.

Data source: GlobalData Healthcare database (accessed July 2018). High cost analysis data collected from the IQVIA Private Payer database, 2017.

TABLE 4. List of selected gene therapies for 2018

SELECTION CRITERIA			KEY ATTRIBUTES	
 Breakthrough	 Fast Track	 Priority Review	 Clinical trials in Canada	 Rare or orphan designation

MEDICINE (TRADE NAME) COMPANY	INDICATION(S)*	DESCRIPTION AND KEY ATTRIBUTES
CARDIOVASCULAR		
Alferminogene tadenovec (Generx; Ad5FGF-4) Angionetics Inc 	Refractory angina due to myocardial ischemia	 • Angiogenic growth factor gene therapy designed to stimulate the natural growth of microvascular circulation for cardiac microvascular insufficiency for patients with myocardial ischemia and symptomatic angina pectoris due to advanced coronary disease. • A one-time, non-surgical, intracoronary administration from a standard cardiac infusion catheter by a cardiologist in a routine out-patient procedure. • In an ongoing Phase III trial (AFFIRM) in patients 55 to 75 years with refractory angina due to myocardial ischemia.[38]
CENTRAL NERVOUS SYSTEM		
Onasemnogene abeparvovec (ChariSMA; Zolgensma; AVXS-101) AveXis Inc 	Spinal muscular atrophy (SMA)	 • It is a non-replicating recombinant AAV9 containing the complimentary deoxyribonucleic acid (cDNA) of the human survival motor neuron (SMN) gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). • Administered as a one-time infusion. • The START trial (Phase I) demonstrated a dramatic increase in survival and transformative improvement in achievement of developmental milestones compared to the natural history of spinal muscular atrophy (SMA) Type 1.[39] • Phase III trials in infants diagnosed with SMA are ongoing.[40, 41, 42] • In pre-registration in the US and EU. • Global revenue forecasted to be $451 million in 2019 and $2.04 billion by 2024. • High-cost therapeutic area.†
GENETIC DISORDERS		
Elivaldogene tavalentivec (Lenti-D) Bluebird Bio Inc 	Adreno-leukodystrophy (ADL)	 • A Lenti-D gene therapy for X chromosome-linked adrenoleukodystrophy (ADL), a devastating neurologic disorder with an estimated birth

		incidence of 1 in 17,000 newborns. ADL is a metabolic disorder that impairs peroxisomal beta-oxidation of very-long-chain fatty acids. • CD34+ cells are obtained from the patient by means of apheresis and transduced with the Lenti-D lentiviral vector. The patient receives conditioning with busulfan and cyclophosphamide, after which the lenti-D gene product, which is made up of the transduced CD34+ cells, is infused. • Early results of the STARBEAM study (ALD-102; Phase II/III) suggest that Lenti-D gene therapy may be a safe and effective alternative to allogeneic stem-cell transplantation in boys with early-stage cerebral ADL.[43] • Global revenue forecasted to be $11 million in 2019 and $169 million by 2024. • High-cost therapeutic area.†
NSR-REP1 (AAV2-REP1) Nightstar Therapeutics PLC	Choroideremia	 • An adeno-associated viral vector (AAV2) encoding rab escort protein 1. • Administered as a sub-retinal injection after vitrectomy. • Choroideremia is an X-linked inherited chorioretinal dystrophy leading to blindness by late adulthood. It is estimated that the prevalence of CHM is between 1 in 50,000-100,000 people. Currently there is no effective treatment.[44] • Phase I and II studies with NSR-REP-1 in patients with choroideremia have produced encouraging results, suggesting that it is possible not only to slow or stop the decline in vision, but also to improve visual acuity in some patients.[45] • Phase III registrational trial (STAR) in patients with choroideremia has been initiated in many countries, including Canada.[46] • Global revenue forecasted to be $192 million in 2021 and $604 million by 2024.
HEMATOLOGICAL		
BB-305 (LentiGlobin) Bluebird Bio Inc 	Beta-thalassaemia major	 • A gene therapy for the treatment of beta thalassemia major, a rare and potentially debilitating blood disorder. • It is administered as a single dose straight into the blood (IV infusion) following a course of busulfan chemotherapy.[47] • It may improve survival and quality of life by reducing or eliminating the need for blood transfusions and iron-chelation therapy. • In Phase III trials.[48, 49] • In pre-registration in the EU.

OPTHAMOLOGICAL		
Lenadogene nolparvovec GenSight Biologics SA	Leber's hereditary optic neuropathy (LHON)	• A recombinant adeno-associated viral vector serotype 2 (rAAV2/2) containing the wild-type ND4 gene (rAAV2/2-ND4). • It is administered through intravitreal injection containing 9E10 viral genomes in 90 µL balanced salt solution (BSS) plus 0.001% Pluronic F68®. • In Phase III trials for the treatment of optic atrophy or hereditary Leber[50, 51] due to the mutation of the G11778A ND4 gene.
NT-501 (Renexxus) Neurotech Pharmaceuticals Inc	Macular telangiectasia; Retinitis pigmentosa	• A ciliary neurotrophic factor (CNTF) implant that which consists of cells encapsulated within a semi-permeable polymer membrane and supportive matrices. NT-501 contains NTC-201 cells that secrete recombinant human CNTF, which were derived from genetically modified NTC-200 cells. • The encapsulated cell therapy (ECT) platform is inserted during a single outpatient surgical procedure through a small scleral incision, and can also be removed through the same incision, if desired. • Phase II studies in patients with retinitis pigmentosa have been completed with promising results;[52, 53] now starting Phase III trials in patients with macular telangiectasia.[54, 55]
ONCOLOGY		
Tavokinogene telseplasmid (TAVO [US]) OncoSec Medical Inc	Metastatic melanoma	• An immunomodulatory cytokine that delivers the immune-stimulating protein interleukin-12 (IL-12) into the tumour microenvironment. • Administered using ImmunoPulse a device that electroporates into the tumour. • A combination of tavokinogene telseplasmid and pembrolizumab was effective at reducing tumours in advanced melanoma patients who had failed prior anti-programmed cell death protein (PD-1) therapies, according to early results of a Phase IIb trial (includes a Canadian site).[56, 57]
Flucytosine extended release (ER) + vocimagene amiretrorepvec (Toca-511) Tocagen Inc	High-grade glioma; Anaplastic astrocytoma; Recurrent glioblastoma multiforme (GBM)	• Combination is referred to as the Toca regimen: in the first step, patients receive vocimagene amiretrorepvec (Toca 511), a replicating virus that selectively infects cancer cells during surgery; the second step requires patients to receive cycles of extended-release 5-fluorocytosine (Toca FC). • After completion of the successful Phase I study in patients with high-grade glioma, the Toca regimen showed a favourable safety profile, extended patient survival compared with other therapies, and provided complete tumour shrinkage. With the current standard of care treatment, newly diagnosed patients have a median survival of

		approximately 14 to 16 months. After recurrence, this survival time falls to 7 to 9 months, on average. Conversely, Phase I results of the Toca regimen showed a median longevity of 14.4 months for patients with a recurrence.[58] • In Phase III trial in patients with glioblastoma.[59]

* Multiple indications within the same therapeutic area may be assessed in a single clinical trial.
† A therapeutic area is considered to be high-cost if it includes at least one medicine with an annual treatment cost exceeding $10,000 or, in the case of oncology, a 28-day course of treatment exceeding $5,000. Therapeutic areas are defined at the ATC4 level.

Data source: GlobalData Healthcare database (accessed July 2018). High cost analysis data collected from the IQVIA Private Payer database, 2017.

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