Innomar Strategies Submission to the Patented Medicine Prices Review Board (PMPRB)
***Draft Guidelines* Consultation**

February 14, 2020

Patented Medicine Prices Review Board, Regulatory Affairs and Outreach Branch
Box L40, 333 Laurier Avenue West, Suite 1400
Ottawa ON K1P 1C1

RE: PMPRB *Draft Guidelines*

Thank you for the opportunity to submit written comments in response to the proposed PMPRB *Draft Guidelines* operationalizing the amended *Patented Medicine Regulations* under the *Patent Act.*

ABOUT INNOMAR STRATEGIES

Innomar Strategies Inc. (Innomar), a part of AmerisourceBergen, is Canada's leading specialty medications service provider. Headquartered in Oakville, Ontario, Innomar employs over 2,375 associates across Canada. Innomar owns over 150 infusion clinics employing over 550 nurses; and pharmacies in almost every province.

Through our integrated Patient Support Programs (PSPs), Innomar is a provider to pharmaceutical manufacturers to enable patients to gain access to specialty medicines for chronic and complex diseases. PSPs support patients in many disease areas such as oncology, rare diseases, respirology, immunology, etc. Innomar's infusion clinics and specialty pharmacies closely integrate into over 120 PSPs to allow patients to promptly start their drug treatment, and fill an important need within the Canadian healthcare system.

PSPs and nursing healthcare delivery services provided as part of a PSP are funded by the pharmaceutical manufacturer and not the public or private healthcare system. In some cases, the manufacturer's annual cost to infuse one patient with a typical specialty biologic can be as high as a low double digit percentage of the current drug price[1]. The cost to infuse one patient - incurred outside of the public healthcare system, may include all or some of the following patient support services:

- Patient enrolment, reimbursement navigation
- Education and adherence support
- Specialty nursing and clinic services
- Pharmacovigilance

It is therefore important to take into consideration that public and private payers are currently not covering these services; thus, there is a need for PSPs to fill these gaps.

For new and existing manufacturers launching innovative therapies in Canada, Innomar also provides support to develop and execute commercialization strategies including Health Canada and public/private submissions, as well as Third Party Logistics services, which enables timely drug access.

PSP FILL A GAP IN THE CANADIAN PUBLIC HEALTHCARE SYSTEM

PSPs were created to work in tandem with the healthcare system and to fill the gaps in patients' disease management needs (see appendix A). Patients are not usually aware of how to gain access to their medications, and find it difficult to navigate the healthcare system. In addition, physicians also find it difficult

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[1] **Note**: Nursing cost is based on an infusion 3 hours in length administered every 8 weeks. These costs increase with infusions that are longer and/or more frequent. Furthermore, generally speaking, costs to support a patient in their access to a specialty biologic will vary depending on the type of biologic, i.e. infusible, injectable, and additional patient support services offered by the manufacturer for the specialty medicine.

to keep up with the administration requirements for biologic specialty therapies and coordinate with various stakeholders including pharmacy, hospital, nurses, and payers. PSPs enable manufacturers to execute the following services that benefit patients and physicians: reimbursement navigation; infusion/injection clinic and nursing support; patient education and counseling; diagnostics; risk management and compliance; and specialty pharmacy services. These PSP services go beyond the offerings of the public healthcare system which is not equipped to support patients in gaining timely access to specialty medicines.

PSP VALUE-ADD

In addition to PSPs filling a gap in the Canadian public healthcare system, importantly, PSP service offerings help improve health outcomes for patients with chronic and complex diseases (appendix A; see below). Canadian payers are increasingly looking to manufacturers to present Real-World Evidence (RWE) data to demonstrate health outcomes, including the effectiveness and safety of their products; and to ensure the patient is on the appropriate drug (see appendix B). Innomar's PSPs are a rich data source for RWE. Using PSP data, Innomar has developed numerous real-world case studies to demonstrate the value of PSPs and associated services. Examples include:

- Monitoring and management of patient treatment plans helped to achieve better and more cost-effective patient health outcomes (appendix C).

- Patients who enrolled in an adherence support program benefited from enhanced medication adherence – which in turn led to better health outcomes (appendix D).

- PSP data for rheumatoid arthritis helped to identify reasons for medicine discontinuation and develop a strategy to help patients stay on the medicine that they are responding to (appendix E).

- PSP nursing support for oncology injection treatment at Innomar's clinics and patients' homes, generated savings to the public healthcare system through significantly reduced clinic visits. Economic benefits to patient and health system included reduced time off work to receive injections, reduced travel expenses.

- Private infusion clinics may have a shorter patient time-to-treatment initiation (TTI). This shorter TTI could ease wait time burden for oncology infusion patients currently waiting to receive therapies in public hospitals and cancer centers in Canada.

- Assessing health and quality of life outcomes for patients on a respirology medication was used to increase healthcare payer certainty that the medicine was effective for patients.

- PSP data can help manage required negotiated product listing agreement (PLA) reporting - insurer pays only for patients that meet agreed-upon health outcomes while on a specialty medicine.

OVERVIEW STATEMENT: IMPACT OF DRUG PRICE REDUCTIONS IN CANADA

Impact of drug price reductions in Canada on:
- PSP services: Manufacturers will be unable to finance the full breadth of PSP services to support patients - Canadian patients with chronic and complex diseases will not receive services that aid with access to specialty medicines.[2]

- Innovative medicines: Manufacturers will delay or stop the launch of innovative drugs to Canada - Canadian patients with chronic and complex diseases will not have access to life-saving new specialty medicines as manufacturers will be unable to afford the investment to launch.[2]

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[2] Reference: Life Sciences Ontario. *New federal drug pricing rules are already delaying medicine launches and costing jobs in Canada, survey reveals*. February 3, 2020

Outcome: Canadian patients may suffer in their therapy as without the appropriate support mechanisms of a PSP, they may drop off their medications, miss doses, and/or misuse their medications which can lead to increased burden on the public healthcare system and payers, e.g. increased medical costs, hospitalizations – leads to hallway medicine, and medicine cost wastage.

REQUEST #1: CALCULATION OF MRP

Consequences	Impact on the patient	Recommendation
• Manufacturers' costs invested towards PSP services and clinic services will fluctuate - financial unpredictability and instability for PSPs and associated patient services	• Reduction in services that offer much needed support that Canadian patients cannot access within the public system – delays and significant reductions in patient access to specialty medicines	• Deduct the following "free services" from ATP, to ensure the MRP accounts for the costs incurred by the manufacturers for PSP services: reimbursement navigation services; nursing clinical services (home and in-clinic); pharmacovigilance

REQUEST #2: TRANSITIONAL / GRANDFATHERING PROVISIONS

Consequences	Impact on the patient	Recommendation
• Unilateral drug price reductions for drugs that have been compliant for years and where patients have been supported for years on drug therapy • Existing manufacturers financially penalized for offering PSP benefits • Existing manufacturers may need to reduce the PSP service offerings they provide for patients • Reduced funding for existing and new PSPs, financial assistance programs, clinics	• Viability of existing PSPs, clinics, assistance programs, and specialty pharmacy services affected • Financial burden shifted to patients and clinicians, e.g. infusion clinic and nursing services - inconsistent with PMPRB's Consumer Protection mandate • Manufacturers may delay seeking access/ approval for new indications and/or line extensions • Manufacturers may decrease and change the offerings for patients which will lead to sub-optimal outcomes for patients	• Do not make any changes to Grandfathered drugs, even if the patentee introduces a new DIN • Grandfathered drugs will be subject to the PMPRB11, which would usually translate into a decrease in the MLP - any price decrease should be phased in over time

REQUEST #3: FREQUENT PRICE REASSESSMENTS & ADJUSTMENTS

Consequences	Impact on the patient	Recommendation
• Unstable and unpredictable drug pricing over time • Lack of clarity leading to an environment of instability for patients enrolled in PSPs	• Canadian patients could experience fluctuating patient support services – leads to unpredictable and inconsistent healthcare delivery for the patient in the long-term, making complex diseases less manageable • Inconsistent support provided to patients may lead to misuse of the product, non-adherence and decline in patient outcomes resulting in more costs to the healthcare system as described above	• Create greater clarity and transparency for specific instances in which drug prices will be reassessed. This includes providing price reassessment clarity for medicines with new indications

CONCLUSION

In summary, Innomar has provided key recommendations on the proposed Guidelines in order to ensure that Canadian patients have access to specialty, rare disease and ultra-rare drugs. We believe that the proposed Guidelines will impact manufacturers' ability to fund PSP and clinic services, services that are not currently provided by the public healthcare system; and create barriers and significant disincentives for manufacturers to bring innovative drugs to Canada.

Innomar understands that the PMPRB will host a stakeholder policy forum with its Board after the February 14, 2020 submission deadline. Innomar asks to be included in the upcoming policy forum, if possible.

We thank the PMPRB for the opportunity to submit our comments in response to the proposed Guidelines.

Sincerely,

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Value of Patient Support Programs for Specialty Medications in Canada

The use of specialty medications for the treatment of complex, chronic diseases has led to new requirements for healthcare delivery beyond the traditional dispensing activities of non-specialty products. Although there is no standard definition of a specialty medication, they are generally defined as high cost, low volume agents requiring special administration and product handling, and usually reside in the therapeutic areas of Immunology, Rare Diseases, and Oncology. Due to the complexity of specialty medications and the diseases they treat, there are needs for enhanced management, including patient education, administration, diagnostics, monitoring, and specialty logistics support services. However, the Canadian healthcare system is not equipped to provide the support that many patients need to gain access to reimbursement and drug delivery of a specialty medication, or the ongoing support and monitoring often required to improve clinical outcomes. Manufacturer-funded Patient Support Programs (PSPs) were created to work in tandem with the healthcare system to fill the gaps in these patients' disease management needs.

Gaps in Canadian Healthcare System for Specialty Medications

Many people assume that the cost of all healthcare services are covered in Canada, but this does not apply to all services for specialty medications. Clinical services are required for many specialty medications, including infusion or injections in clinics or via home care, and these services may not be covered by public or private payers. Further, specialty medications often have unique administration requirements that necessitate additional or customized training, and ongoing support of patients and their caregivers, for example: mothers who have to provide regular injections to their young children may need more frequent advice or even respite support; patients prescribed medications dosed by weight may need support for precise dosing administration; and some patients may need more contact with a healthcare professional (HCP) as their

specialty medication is being titrated. Regular disease management support, including patient and caregiver education and frequent touch points, cannot always be provided readily by HCPs due to the administrative and time constraints of clinical practice, and there is often limited support available outside of physician visits, or limited knowledge of the additional public support available.

The journey to gain access to a specialty medication is daunting for patients, particularly when they are quite ill, and there is little support to navigate this difficult process. Lack of knowledge of public and private reimbursement mechanisms and criteria, and coordination of benefits; and the complexity of paperwork and testing requirements, can cause delays in treatment and much anxiety and fear amongst patients and caregivers. Additionally, Special Authorization for specialty medications is

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generally required for public and private reimbursement decision-making, and the process is complex and time-consuming for HCPs and patients alike.

Medication non-adherence leads to suboptimal health outcomes, increased healthcare resource utilization, and increased direct and total medical costs; however, the healthcare system cannot always provide the support that many patients need to stay on therapy and refill their prescriptions. The WHO reported that adherence among patients with chronic diseases averages only 50% in developed countries[1], and up to 30% of patients fail to fill a new prescription.[2,3] Interventions that can address the possible risk factors for non-adherence and sustain patient medication adherence and persistence are needed to reduce the economic and health burdens of complex chronic diseases, but services to support HCP instructions outside of clinic visits are not provided by public or private payers.

Currently, healthcare-related data necessary to determine how a patient is responding to their specialty medication is fragmented and inconsistent as it comes from many different sources. A consolidated view is not readily available to HCPs, e.g. trends in Health Assessment Questionnaire (HAQ) for rheumatoid arthritis and lab values, and there is no data available to a physician to determine whether a prescription has been filled or refilled. A more robust, formal approach to collecting data is important to help facilitate HCP access to patient data, and to enable the collection of health outcomes data that would benefit payer decision-making.

PSPs Provide Value to Help Fill the Gaps in the Healthcare System

Manufacturer-supported PSPs were created over 15 years ago to support patient access to complex medications. Now PSPs provide a more holistic approach to patient, caregiver, and HCP support when specialty medications are prescribed, including: reimbursement navigation; clinic and nursing support (infusion and injection administration/training); patient education and counseling; risk management and adherence; specialty pharmacy and logistics services; and connection to other social support services. PSPs fill the gaps in services not readily available in the current healthcare system to help optimize health outcomes and value in patient-focused care. As a result, PSPs have demonstrated a positive impact on patient adherence, and clinical and economic outcomes.[4,5]

PSPs support patient disease management by providing rapid access to specialty drug administration and education. PSP clinic and field nurses administer injections and infusions, patient self-injection training, and rigorous safety monitoring, in the convenience of local private clinics or in patients' homes. PSP nurse case managers also provide education, and ongoing lifestyle, health and wellness support to patients via frequent touch points.

Reimbursement specialists have experience with the complexity of drug reimbursement navigation, and support patients through their entire journey to help ensure patients get on drug faster and maximize their coverage. Changes in health care policy pose challenges for reimbursement, as do

PSPs fill the gaps in services not readily available in the current healthcare system to help optimize health outcomes.
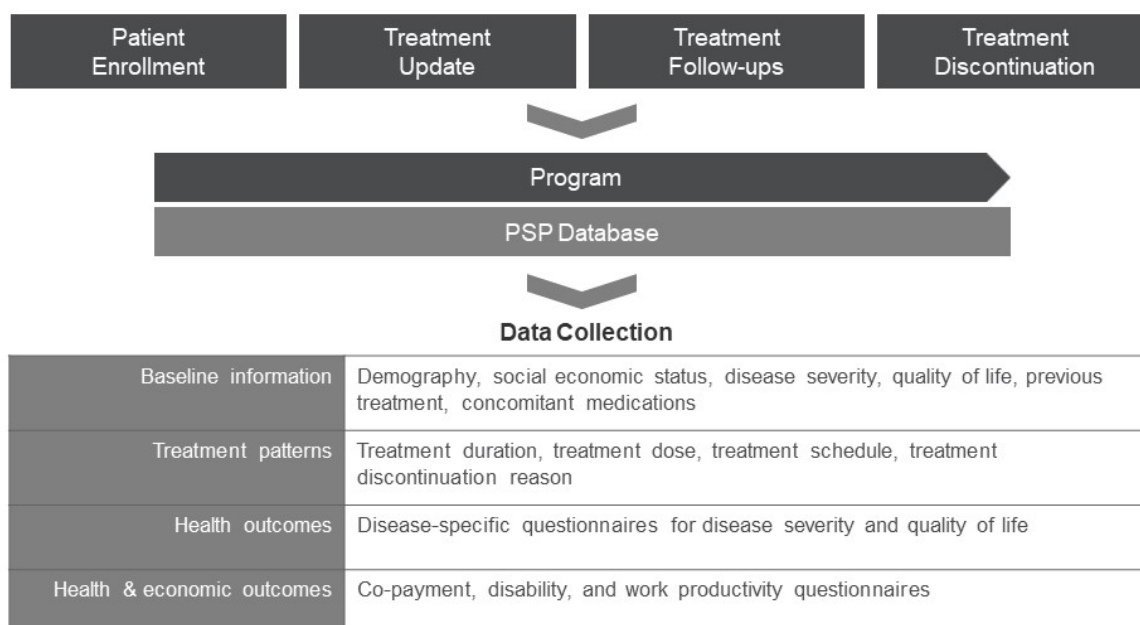
the forms, policies and requirements that can change and vary greatly by provincial and private payers; however, PSP reimbursement specialists are experts in the payer landscape and the technology required to expedite the process. They support patients and HCPs in completing all payer forms, submissions, and escalation of denials. Field case managers also support physicians and nurses in their clinic by helping to coordinate testing and appointments, and to support the administrative burden of the reimbursement process.

PSP nurse case managers are integral in supporting patient adherence to help optimize treatment outcomes. They are a single point of contact for each patient to support patient health literacy; support understanding of the patient's treatment regimen and expected results; coordinate of drug ordering and delivery so there is no gap in their treatment; and to follow up with the patient to ensure they are adhering to their treatment plans. Nurse case managers provide motivation and knowledge to empower patients, assess patients for non-adherence risk factors, and customize patient touch points based on patient need. Touch points can include a variety of mediums, including regular phone calls, and technology-based adherence interventions. Additionally, nurse case managers can connect patients and families to

support services that they may not be aware of, such as, patient advocacy groups, government-funded programs, social workers, etc. If a fully integrated model is used, the access to pharmacy data can also help to quantify patient non-adherence, and nurse case managers can provide this information via a regular feedback loop to the prescribing physician.

Healthcare-generated data obtained by PSPs can provide important insights for HCPs, payers, and manufacturers. Through on-line PSP portals, HCPs can readily access consolidated patient-specific data, such as disease scores, and medication adherence and persistence. As payers look to manufacturers to present real world evidence, patient data from PSPs can be used to assess treatment patterns, and health and economic outcomes (Figure 1). A variety of patient-reported health outcome studies can be performed, including: quality of life, product effectiveness, treatment adherence, safety, health resources utilization, and indirect costs such as productivity loss, out-of-pocket costs and the cost of informal care. From a manufacturer perspective, these health outcomes studies can align to global strategy and be leveraged to support reimbursement and listing.

Figure 1: Data Generated from PSPs

Baseline information	Demography, social economic status, disease severity, quality of life, previous treatment, concomitant medications
Treatment patterns	Treatment duration, treatment dose, treatment schedule, treatment discontinuation reason
Health outcomes	Disease-specific questionnaires for disease severity and quality of life
Health & economic outcomes	Co-payment, disability, and work productivity questionnaires

PSPs provide value by helping patients to better manage chronic diseases and optimize complex treatment by filling the gaps in services that are not provided in the current healthcare system. The future focus of PSPs will be on an evolution in integrating the process and efficiencies for patients, HCPs, payers, and manufacturers that will offer increased value to all stakeholders. By offering a more seamless experience for patients and HCPs, and greater cost effectiveness through investment in digital technology, connectivity to healthcare systems, and the provision of health outcomes data, PSPs will be even more able to maximize patient health outcomes.

References:

1. Sabaté E. Adherence to Long-Term Therapies: Evidence for Action, World Health Organization, Geneva, Switzerland, 2003. Accessed 7 March 2018 http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf
2. Fischer MA et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. *J Gen Intern Med.* 2010;25(4):284-90. Accessed 7 March 2018 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2842539/pdf/11606_2010_Article_1253.pdf
3. Tamblyn R et al. The incidence and determinants of primary nonadherence with prescribed medication in primary care: A cohort study. *Ann Intern Med.* 2014;160(7):441-450. Accessed 9 March 2018 at: http://annals.org/aim/article-abstract/1852865/incidence-determinants-primary-nonadherence-prescribed-medication-primary-care-cohort-study
4. Ganguli A et al. The impact of patient support programs on adherence, clinical, humanistic, and economic patient outcomes: a targeted systematic review. *Patient Pref Adherence.* 2016;10:711-25. Accessed 9 March 2018 at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4854257/pdf/ppa-10-711.pdf
5. Rubin DT et al. Impact of patient support program on patient adherence to adalimumab and direct medical costs in Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis. *J Manag Care Spec Pharm.* 2017;23(8):859-867. Accessed 9 March 2018 at https://www.jmcp.org/doi/full/10.18553/jmcp.2017.16272

This article is one in a series provided by Innomar Strategies to update manufacturers on relevant changes and new information in the specialty pharmaceutical marketplace.

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The Value of Real-World Evidence in Canadian Drug Commercialization – Part 1

The growing need for Canadian biopharmaceutical companies to demonstrate product value to health technology agencies (HTAs) and payers to gain and maintain access is driving changes to commercialization strategies along the product lifecycle. As decision-making amongst these stakeholders is increasingly focused on value and outcome measures, there is a need for additional evidence generation beyond traditional randomized clinical trials (RCTs) during the pre-launch phase. Leveraging real-world evidence (RWE) across the product lifecycle enables manufacturers to fill the evidence gap beyond RCTs to help guide local commercial strategic planning and market access strategy; to provide data-driven insights to proactively inform payer and HTAs decision-making; to maximize payer coverage; and to improve patient outcomes.

This is the first article of a series that will highlight the value of RWE in Canadian drug commercialization.

What is RWE?

Although the definition of real-world evidence may vary amongst experts, it is most simply defined as evidence obtained from analyzing data that is collected outside of a RCT in a real world setting. While data obtained from RCTs provides insights on *drug efficacy* in patients who are recruited based on specific inclusion and exclusion criteria in a specific population with a study drug that is delivered in a controlled environment, RWE is based on data collected in a real-world setting using health system data from a larger, more heterogeneous population. RWE helps to provide insights into *drug effectiveness* in routine clinical practice amongst varying populations, and can help answer important questions in health care, from a regulatory, payer, clinical practice, and product development perspective.

Real-world data can come from a variety of sources, including retrospective or prospective observational studies, observational registries, and the following:

Figure 1: Sources of Real World Data

Industry	Patient support programs, patient or disease registries and surveys, pharmacovigilance, financial assistance information
Logistics	Wholesale and distribution sales information, pharmacy data, product sales information
Institutions	Hospital administrative data, clinical data from electronic health/medical records (EHR/EMR), hospital billing data, molecular and laboratory results data
Public	Payer claims data, public registries, Canadian Institute for Health Information (CIHI), provincial data (e.g. Institute for Clinical Evaluative Sciences (ICES), Alberta Health Services, etc.), population health surveys (e.g. socioeconomic data), hospital data
Private	Pharmacy Benefits Manager and claims data (TELUS Health, ESI Healthcare, etc.), insurance adjudication data, employer benefits plans
Patients	Patient reported outcomes, patient requested data, disease risk assessments, personal digital health applications (includes consumer wearables, sensor data from personal medical devices, and smartphone health apps), social media, patient-powered research networks

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Commercial Application of RWE

There are many opportunities to use RWE to optimize, generate, and discover value along the product lifecycle. To meet post-authorization evidence requirements and derive relevant commercial insights, however, requires development of an evidence generation strategy and proactive plan at the outset, and integration with a cross-functional group of internal stakeholders.

From a commercialization lens, RWE can help manufacturers gain credible insights that can inform commercial decision-making, sales forecasting, resource planning, and reimbursement throughout the lifecycle of the drug (Figure 2).

Leveraging RWE across the product lifecycle enables manufacturers to fill the evidence gap beyond RCTs to help guide local post-authorization evidence requirements, market access, and commercial strategic planning.

Figure 2: Uses of RWE over the Product Lifecycle

Pre-launch	Launch	Growth	Maturity
Commercial Assessment and Planning • Disease epidemiology • Shape target product profile, identify unmet need/ disease burden • Risk planning and label negotiation (describing suitable patients' characteristics, identifying possible criteria) • Forecast potential market and launch uptake • Patient support program design **Market Access** • Cost effectiveness and budget impact data for HTA submissions • Indirect costs (time lost from work, lost earnings)	**Market Access and Payer Trends** • Market access and payer negotiation • Payer trends and time to reimbursement • Tracking post-authorization real-world outcomes • Adherence tracking **Commercial Planning** • Financial assistance planning • Conversion • Drug utilization/ prescribing • Sales operations, targeting, resource allocation • Sales forecasting • Label expansion • Patient data and adherence • Key Performance Indicator (KPI) tracking	**Market Access** • Expansion and reassessment of reimbursement listing criteria, conversion planning • Tracking post-authorization real-world outcomes • Supporting translational research to improve patient outcomes • Informing treatment guidelines • Generation of scientifically relevant publications with steering committee **Commercial Planning** • Drug utilization/ prescribing, persistence and adherence monitoring • Sales operations, targeting, resource allocation • Sales forecasting • Patient data and adherence • KPI tracking	**Commercial Planning** • Sales operations, targeting, resource allocation • Loss of exclusivity (LOE) planning • Benchmarking performance for new entrants (defense of market position) • Sales forecasting • Patient data • KPI tracking

Innomar Value of RWE Series

When launching a specialty drug there are many considerations in the development of an evidence generation strategy that will help guide post-authorization evidence requirements, market access, and commercial strategic planning. In this every-changing, challenging market access environment, leveraging RWE is critical to ensure payers and HTA decision-makers understand the value of your product in a real world setting.   Over the next several months, Innomar will provide a deeper dive into the use of RWE, including how to design your patient support program to be a credible source of data, and how to use RWE to meet the evidence needs of payers and HTAs. We will also use real-world case studies to illustrate how manufacturers can leverage RWE along all phases of drug commercialization.

This article is one in a series provided by Innomar Strategies to update manufacturers on relevant changes and new information in the specialty pharmaceutical marketplace.

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Improved Health Outcomes in Patients Receiving Health Case Management (HCM)

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Background

- The Great-West Life Assurance Company's (GWL) Health Case Management (HCM) program is designed to assist plan members who have been prescribed certain specialty medications to treat complex or chronic conditions like rheumatoid arthritis or Crohn's disease.
- Plan members who have been prescribed certain specialty medications are connected with a health case manager, who is a qualified health care professional, to provide ongoing support and monitoring.
- As part of the HCM program, GWL has engaged HealthForward Inc., an industry leader with extensive specialty medication experience and a broad specialty pharmacy and treatment clinic network, to provide a high level of expertise in patient-centred specialty drug management and distribution.

Objective

- To demonstrate that health case management (HCM) administered with routine care delivers better health outcomes than routine care alone

Conclusions

- HCM administered with routine care delivers significantly better improvement in RA and PsA patients' functional ability (measured by HAQ-DI) compared to routine care alone.
- HCM also achieves significantly higher rate of low disease activity, remission and zero-swollen joint count in RA patients.
- This analysis demonstrates the benefit of nurse-led HCM in improving health outcomes over routine care alone, and helps inform future HCM prospective studies.

- Retrospective study demonstrate that a nurse-led medication management program designed to monitor and manage patient treatment plans helps to achieve better and more cost-effective health outcomes.

- Four-years of program information (containing patient demographics and multiple health outcomes endpoints) was extracted from database and analyzed.

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Poster presented at the CADTH Symposium, April 23-25, 2017, Ottawa

Poster presented at ISPOR Europe, November 10-14, 2018, Barcelona

Summary
- Retrospective analysis conducted using program claims data to demonstrate that patients who enrolled in an adherence support program benefit from enhanced medication adherence.

ENHANCING MEDICATION ADHERENCE THROUGH AN ADHERENCE SUPPORT PROGRAM

Hanna M[1], **Yap B**[2], Crooks M[1], Pojskic N[3], Mandlsohn L[3], Jung M[3], MacDonnell A[4], Hink D[4], Drinkwater A[1], Anderson S[1], Peters P[4], West K[4]

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OBJECTIVES: To evaluate whether patients who receive systematic adherence phone calls from an Adherence Support (AS) program achieve better medication adherence than a matched control group of patients. This AS program is a HealthForward service provided on behalf of Green Shield Canada (GSC) and implemented as an enhanced service which focuses on adherence support for GSC plan members.

METHODS: During the identification period (October 2015 through September 2016), GSC pharmacy claims data from the following two cohorts were compared - A) Patients who received adherence support through the AS program (intervention group); B) Patients who did not participate in the AS program (control group). Medication adherence was measured by modified medication possession ratio (mMPR).

RESULTS: The final claims data for analysis consisted of 79 AS program patients who were able to be matched with 331 control patients. The top 3 (out of 11) disease conditions amongst these patients were rheumatoid arthritis, Crohns/ulcerative colitis, and psoriasis.

AS program patients demonstrated higher medication adherence than control patients after matching the cohorts on 4 variables - drug, disease condition, gender, and age group (mMPR: 95.2% vs. 93.8%; $p=0.002$). The percentage of patients who met the mMPR threshold of 90% was also higher in the AS program patients compared to control patients (73.8% vs. 49.2%; $p=0.004$).

CONCLUSIONS: The analysis demonstrates that AS program patients' benefit from enhanced medication adherence. Further research is needed to understand whether this difference in adherence is clinically meaningful.

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Enhancing Medication Adherence through an Adherence Support Program

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* These authors contributed equally to this work

BACKGROUND

- Green Shield Canada (GSC) is one of Canada's premier group and individual benefits specialists, and is one of Canada's not-for-profit health insurance carriers.
- GSC has partnered with HealthForward (HF), an industry leader with extensive specialty medication experience and a broad specialty pharmacy network, to provide GSC claimants with patient-centric, value-added services.
- The **Adherence Support (AS) Program** is a HF service provided on behalf of GSC and implemented as an enhanced service which focuses on adherence support for GSC plan members.
- A Program Coordinator (PC) from HF periodically contacts the plan member to determine if they are still on medication and how treatment is going. The PC will also identify if there are any barriers to adherence; if so, the AS Program offers support to the plan member in overcoming the barrier.

OBJECTIVE

To evaluate whether patients who receive systematic adherence phone calls from the AS Program achieve better medication adherence than a matched control group of patients.

METHODOLOGY

STUDY DESIGN
- Data source: GSC pharmacy claims data between Oct 2015 through Sept 2016
- Comparison of two cohorts
  - AS Program (Intervention): Patients who received adherence support through the AS Program
  - Control: Patients who did not participate in the AS Program

ELIGIBILITY
Inclusion
- All ages
- All drug treatment and known disease conditions
- At least 2 consecutive non-excluded claims

Exclusion
- Claims with:
  - 'Drug holiday': 90 days gap between consecutive claims
  - Consecutive claims less than 2 days

ADHERENCE MEASUREMENT
- Modified Medication Possession Ratio (mMPR) to determine level of patient adherence

$$\frac{\Sigma \ Claim \ Days \ Supply}{(Last \ Claim \ Date - First \ Claim \ Date) + Last \ Claim \ Day \ Supply} * 100\%$$

STATISTICAL METHODS
- Propensity score matching of cohorts on 4 variables – drug, disease condition, gender and age group
- Regression/ANOVA tests to determine statistically significant difference between cohorts

RESULTS

Table 1. Patient demographics

	AS Program (n=79)	Control (n=331)
Age (years)	49.5 (12.6)	48.7 (12.7)
Age group (years)		
0 to <20	2 (2.5%)	10 (3.0%)
≥20 to <40	16 (20.3%)	80 (24.2%)
≥40 to <70	61 (77.2%)	238 (71.9%)
≥70 to <90	0 (0.0%)	3 (0.9%)
Gender		
Male	35 (44.3%)	142 (42.9%)
Female	44 (55.7%)	175 (52.9%)
Unknown	0 (0.0%)	14 (4.2%)

- 79 AS Program patients who were able to be matched with 331 control patients
- The top 3 (out of 11) disease conditions amongst these patients were Rheumatoid Arthritis, Crohns/ Ulcerative Colitis, and Psoriasis
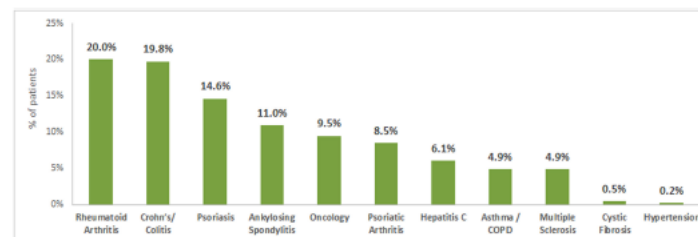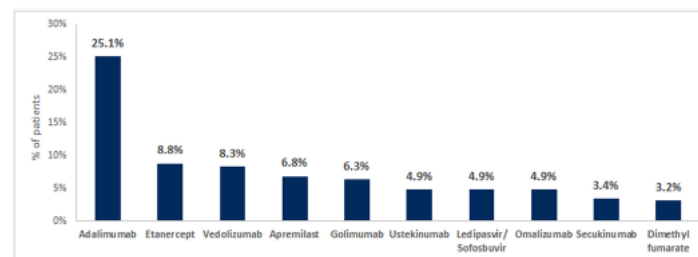
Figure 1. Disease conditions

Rheumatoid Arthritis 20.0%, Crohn's/ Colitis 19.8%, Psoriasis 14.6%, Ankylosing Spondylitis 11.0%, Oncology 9.5%, Psoriatic Arthritis 8.5%, Hepatitis C 6.1%, Asthma / COPD 4.9%, Multiple Sclerosis 4.9%, Cystic Fibrosis 0.5%, Hypertension 0.2%

Figure 2. Drugs taken

Adalimumab 25.1%, Etanercept 8.8%, Vedolizumab 8.3%, Apremilast 6.8%, Golimumab 6.3%, Ustekinumab 4.9%, Ledipasvir / Sofosbuvir 4.9%, Omalizumab 4.9%, Secukinumab 3.4%, Dimethyl fumarate 3.2%

- The top 3 drugs amongst patients were Adalimumab, Etanercept and Vedolizumab

Table 2. mMPR

mMPR		AS Program	Control
	Mean	95.2%	93.8%
	SD	18.8%	15.3%
	P-value	0.002	

- AS Program patients demonstrated **higher medication adherence** than control patients after matching the cohorts on 4 variables - drug, disease condition, gender, and age group (mMPR: 95.2% vs. 93.8%; p=0.002)

Figure 3. Percentage of patients with mMPR ≥ 90%
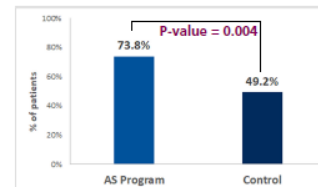
AS Program 73.8%, Control 49.2%; P-value = 0.004

- The **percentage of patients** who met the mMPR threshold of **90%** was also higher in the AS Program patients compared to control patients (73.8% vs. 49.2%; p=0.004)

** Statistically significant higher medication adherence in AS Program patients compared to control patients was similarly demonstrated in analysis using cohort matching on 2 or 3 variables

CONCLUSION

- Adherence Support (AS) Program patients benefit from enhanced medication adherence.
- Enhanced medication adherence has the potential to increase the ROI on healthcare dollars spent on benefit plans.
- Further research is needed to understand whether the difference in adherence (Intervention vs. Control group) is clinically meaningful.

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RHEUMATOLOGY

Concise report

Experience with tofacitinib in Canada: patient characteristics and treatment patterns in rheumatoid arthritis over 3 years

Janet Pope [1], Louis Bessette[2], Niall Jones[3], Lara Fallon[4], John Woolcott[5], David Gruben[6], Michael Crooks[7], David Gold[8] and Boulos Haraoui[9]

Abstract

Objectives. To describe characteristics, treatment patterns and persistence in patients with RA treated with tofacitinib, an oral Janus kinase inhibitor, in Canadian clinical practice between 1 June 2014 and 31 May 2017.

Methods. Data were obtained from the tofacitinib eXel support programme. Baseline demographics and medication history were collected via patient report/special authorization forms; reasons for discontinuation were captured by patient report. Treatment persistence was estimated using Kaplan–Meier methods, with data censored at last follow-up. Cox regression was applied to analyse baseline characteristics associated with treatment discontinuation.

Results. The number of patients with RA enrolled from 2014 to 2017 was 4276; tofacitinib utilization increased during that period, as did the proportion of biologic (b) DMARD-naïve patients prescribed tofacitinib. Of patients who initiated tofacitinib, 1226/3678 (33.3%) discontinued, mostly from lack of efficacy (35.7%) and adverse events (26.9%). Persistence was 62.7% and 49.6% after 1 and 2 years of treatment, respectively. Prior bDMARD experience predicted increased tofacitinib discontinuation (vs bDMARD-naïve, $P < 0.001$). Increased retention was associated with older age (56–65 years and >65 years vs ⩽45 years; $P < 0.05$), and time since diagnosis of 15 to <20 years (vs <5 years; $P < 0.01$). In bDMARD-naïve, post-1 bDMARD, post-2 bDMARD and post-⩾3 bDMARD patients, median survival was >730, 613, 667 and 592 days, respectively.

Conclusion. Since 2014, tofacitinib use in Canadian patients with RA increased, especially among bDMARD-naïve/post-1 bDMARD patients. Median drug survival was ∼2 years. Likelihood of persistence increased for bDMARD-naïve (vs bDMARD-experienced) patients and those aged ⩾56 (vs ⩽45) years.

Key words: drug persistence, patient-support programme, real-world data, rheumatoid arthritis, tofacitinib, utilization

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Rheumatology key messages

- Utilization of tofacitinib for RA treatment increased in Canada from 2014 to 2017.
- Tofacitinib persistence in Canadian patients with RA was ∼1/2 over 2 years.
- Tofacitinib persistence for RA in Canada was higher in bDMARD-naïve (vs bDMARD-experienced) and older patients.

Introduction

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. Tofacitinib clinical studies have shown comparable efficacy [1, 2] and safety with biologic (b) DMARDs, except for higher herpes zoster rates in tofacitinib-treated patients [3–6]. Additionally, emerging real-world safety data align with data from the tofacitinib clinical development programme [7].

Tofacitinib 5 mg twice daily (BID), in combination with methotrexate, was the first JAK inhibitor approved in Canada for the treatment of adult patients with moderately to severely active RA and an inadequate response to methotrexate. In June 2014, tofacitinib became available

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CLINICAL SCIENCE

in Canada and the ongoing Pfizer-sponsored eXel patient support programme was initiated; this programme supports patients and care teams by coordinating tofacitinib access (e.g. making tofacitinib available before public/private coverage) and providing treatment/disease education and adherence support. Patient support programmes can improve cost savings, disease management, persistence, adherence and health-related quality of life, and several exist in Canada for rheumatic diseases [8, 9].

This analysis aimed to characterize tofacitinib use in patients with RA in Canada using data captured by the eXel support programme between June 2014 and May 2017. Patient demographics, disease characteristics and medication history were used to determine factors associated with drug persistence, the likelihood of treatment discontinuation and reasons for discontinuation.

Methods

Study setting and patient population

This analysis included patients with RA who were prescribed tofacitinib 5 mg BID or once daily (QD; e.g. due to hepatic impairment) and enrolled in the eXel support programme from 1 June 2014 to 31 May 2017. All patients provided written consent to participate in the eXel programme. This post hoc observational aggregated report was deemed exempt from Institutional Review Board oversight.

Following enrolment via a faxed form, a 'care coach' conducted a telephone interview, capturing much of the data for this analysis. For a sub-group of patients, data on medication history and disease characteristics were supplemented by information from Special Authorization (SA) insurance forms.

Upon enrolment, tofacitinib initiation may have been postponed for various reasons (including pending reimbursement or tests) and patients may also have dropped out of the programme before initiating treatment.

Assessments, outcomes and statistical analyses

Patient-reported demographics, treatment history and disease characteristics (SA form-collected) are reported descriptively. Most patients were regularly contacted for up to 2 years, and thus discontinuations could be identified reliably. Reasons for discontinuation were requested by programme staff from direct contact with the patient, their physician or pharmacist, and aggregated in structured categories for this analysis. However, provision of reasons for discontinuation was not mandatory. After 2 years, remaining patients were not proactively contacted.

Persistence was measured as the percentage of patients remaining on tofacitinib after receiving $\geqslant 1$ dose. Statistical hypothesis testing was conducted using a Kaplan–Meier estimate and modelled using a Cox proportional hazard regression to determine whether covariates were associated with treatment discontinuation. Patients with unknown current treatment status were excluded from the analysis.

Cox modelling covariates included line of therapy [i.e. bDMARD-naïve (post-methotrexate-inadequate response); then following previous experience with 1, 2 or $\geqslant 3$ bDMARDs], age, gender and time since diagnosis. Different models were fit for 'line of therapy'; otherwise, the models used the same covariates. Analyses were performed using Real Statistics Resource Pack software (Release 4.3) © (2013–2015) Charles Zaiontz (www.real-statistics.com).

Results

Patients

Between 1 June 2014 and 31 May 2017, 4276 patients prescribed tofacitinib were enrolled in the eXel programme [5 mg BID: 4092 (95.7%); and 5 mg QD: 184 (4.3%)]; 3678/4276 (86.0%) patients initiated therapy (Supplementary Table S1, available at *Rheumatology* online), whereas 598 (14.0%) did not [273/4276 (6.4%) patients withdrew from the programme before tofacitinib initiation and 325/4276 (7.6%) were on hold/pending; Supplementary Table S2, available at *Rheumatology* online]. Demographics and disease characteristics were similar for all enrolled patients compared with those who initiated tofacitinib (Supplementary Table S1, available at *Rheumatology* online).

In June 2014, 25 patients with RA enrolled and 13 initiated tofacitinib. Enrolments and initiations generally increased each month, with an average of 167 enrolments (144 initiations) per month over the final 12 months of this analysis (Fig. 1A).

Of the 3540 patients with a complete drug history, 2372 (67.0%) had previously received $\geqslant 1$ bDMARD [mean (S.D.) number of bDMARDs: 2.6 (1.6)] (Fig. 1B). The percentage of bDMARD-naïve patients remained relatively stable from the last 7 months of 2014 (31.7%; 121/382) to 2016 (33.4%; 531/1591) and increased to 39.7% (199/501) in the first 5 months of 2017. Similarly, the percentage of patients who had previously received one bDMARD increased, whereas the percentage of patients who had previously received $\geqslant 3$ bDMARDs decreased over the same period (Fig. 1B).

Information on the last treatment received before initiating tofacitinib was available for 3608 patients (including bDMARD-experienced and bDMARD-naïve patients). The proportion of patients who received TNF inhibitors immediately before initiating tofacitinib increased from 30.5% (115/377) in the last 7 months of 2014 to 38.0% (202/531) in the first 5 months of 2017, whereas the proportion of patients who received non-TNFi bDMARDs immediately before initiating tofacitinib decreased from 37.4% (141/377) to 24.5% (130/531) during the same period (Supplementary Fig. S1, available at *Rheumatology* online). Most patients (63.0%; 704/1118) who reported a non-TNFi bDMARD as their latest treatment had previous experience with $\geqslant 3$ bDMARDs. The most commonly received most-recent bDMARDs were abatacept (13.1%; 473/3608), etanercept (12.8%; 461/3608) and tocilizumab (12.4%; 446/3608).

Fɪɢ. 1 Patterns of tofacitinib utilizaton across the eXel programme
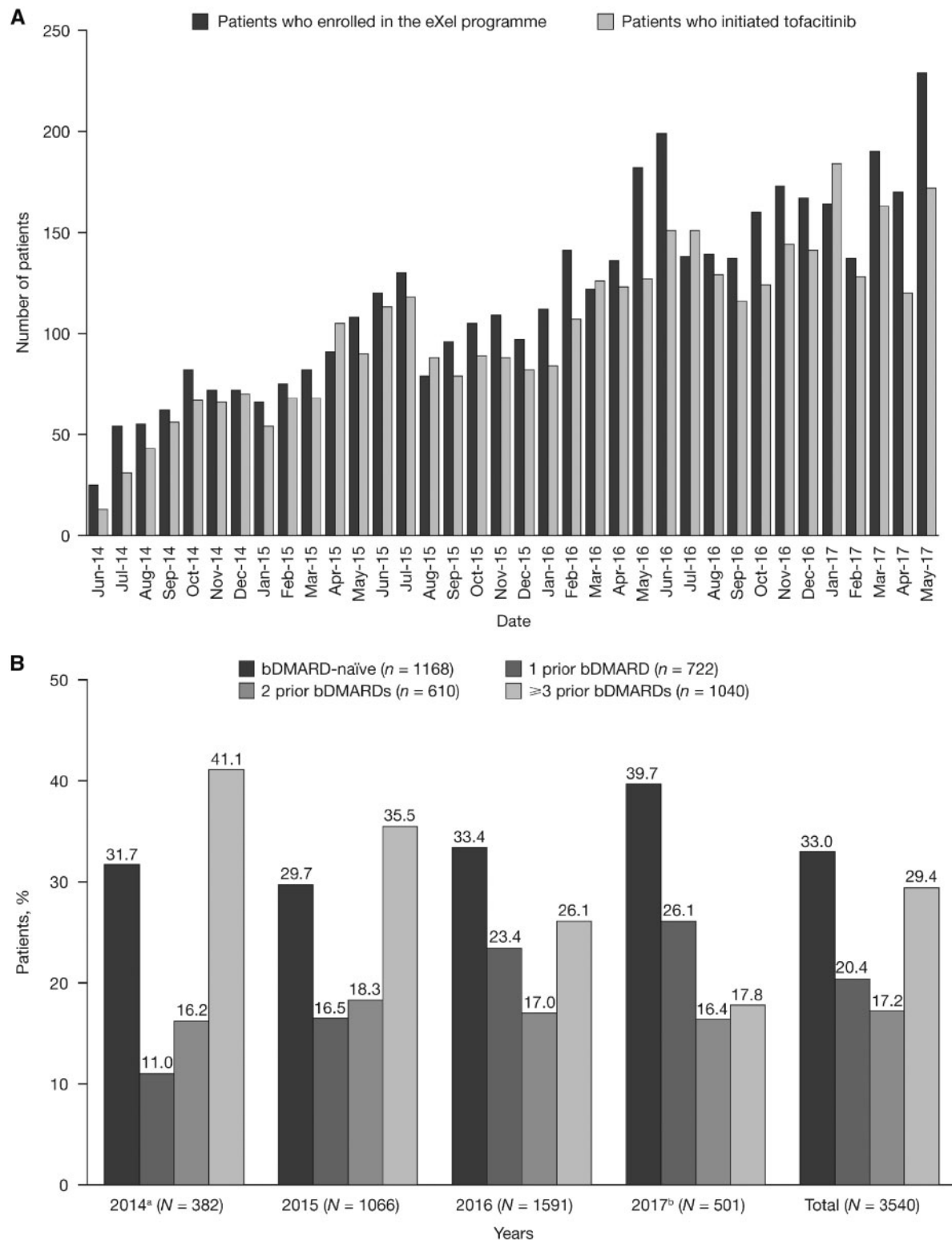
(**A**) Monthly enrolment (non-cumulative) in the eXel programme and initiation of tofacitinib from June 2014 to May 2017. (**B**) Stratification of patients who initiated tofacitinib per year by bDMARD history. [a]Data from June to December 2014. [b]Data from January to May 2017. *N* is the total number of patients each year with a complete drug history; *n* is the total number of patients by bDMARD history. bDMARD: biologic DMARD.

Outcomes

Persistence of tofacitinib was estimated as 62.7% after 1 year (365 days) and 49.6% after 2 years (730 days), and was generally highest in bDMARD-naïve patients (55.8% after 2 years) and lowest in post-⩾3 bDMARD patients (45.4% after 2 years; Fig. 2A). Median drug survival overall, and in bDMARD-naïve, post-1 bDMARD, post-2 bDMARD and post-⩾3 bDMARD patients, was 722, >730, 613, 667 and 592 days, respectively.

The likelihood of tofacitinib discontinuation was significantly greater in bDMARD-experienced *vs* bDMARD-naïve patients, and significantly lower in patients aged ⩾56 *vs* ⩽45 years and patients diagnosed 15 to <20 *vs* <5 years before starting tofacitinib (Fig. 2B).

As of 31 May 2017, 1226/3678 patients (33.3%) had discontinued tofacitinib treatment. The most common reasons for discontinuation included patient-reported lack of efficacy (LOE; 35.7%; 438/1226), patient-reported adverse events (AEs; 26.9%; 330/1226), and patient decision/try another therapy (12.0%; 147/1226); others are listed in Supplementary Table S3, available at *Rheumatology* online. AEs and LOE were the most common reasons for discontinuation within the first 90 days and after >90 days of treatment, respectively. Across all lines of therapy, LOE was the most common reason for discontinuation; however, the proportion of bDMARD-naïve patients who discontinued from LOE (29.1%; 93/320) was lower *vs* post-⩾2 bDMARD patients (38.3%; 334/872) and comparable to that of bDMARD-naïve patients who discontinued from AEs (28.4%; 91/320).

Discussion

This study demonstrates the utilization and persistence of tofacitinib 5 mg BID and QD over 3 years within a patient support programme. The use of tofacitinib for RA in Canada increased from 2014 to 2017, similar to the trend observed in the USA [10]. This increase could be due to a number of factors, including physician experience with tofacitinib, the publication of data on tofacitinib in RA showing consistent safety and efficacy, patient preference for oral over injectable medication and improved access to tofacitinib [11]. Additionally, during the analysis period, a greater proportion of patients began receiving tofacitinib earlier in the course of treatment (before receiving bDMARDs or post-1 bDMARD). The increased utilization of tofacitinib and earlier placement in the treatment algorithm may have been influenced by the reimbursement recommendation and subsequent formulary additions of tofacitinib comparable to bDMARDs by the Canadian health technology assessment bodies and provincial formularies, respectively.
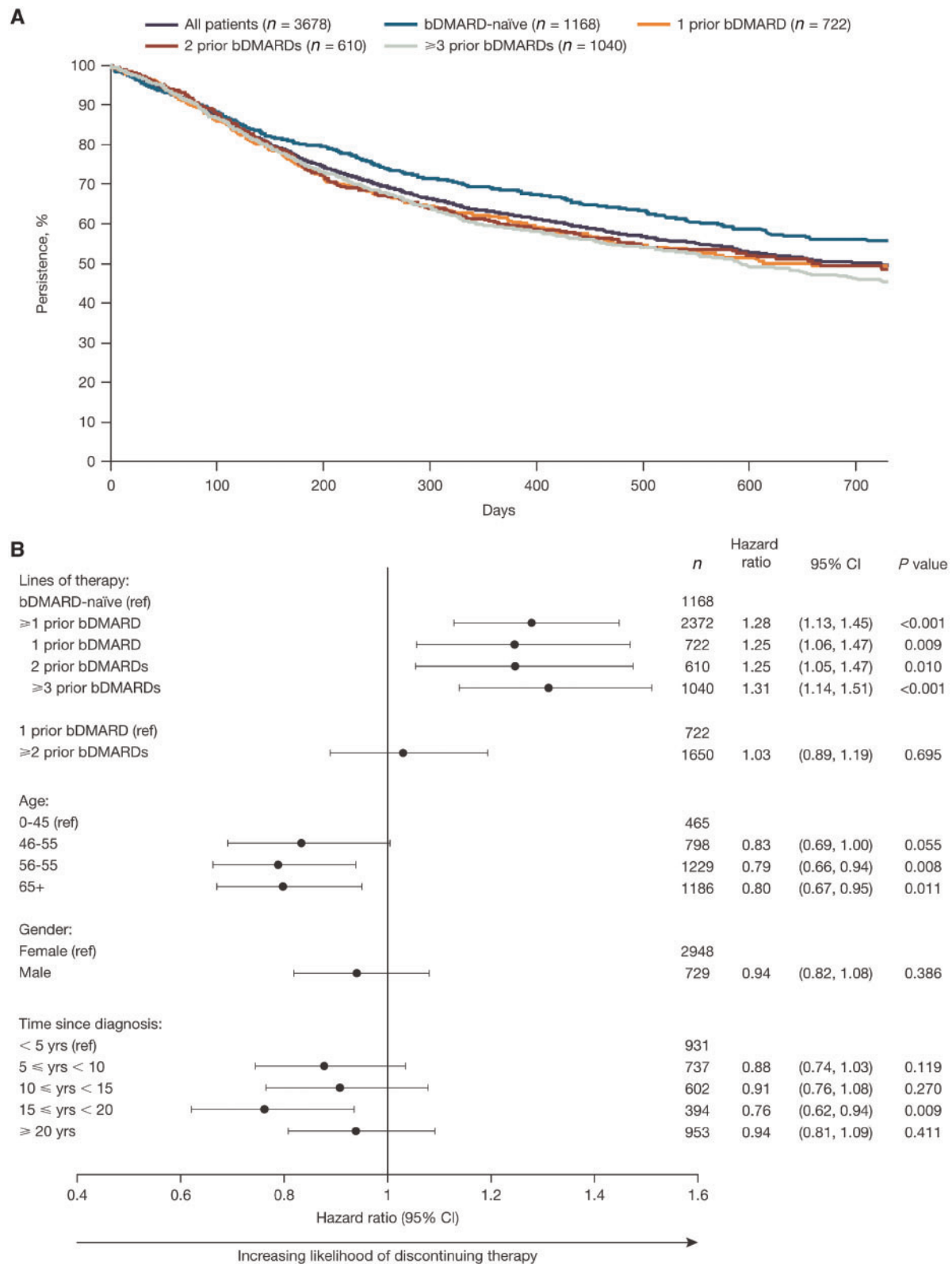
Patients in the eXel support programme who initiated tofacitinib had long-standing disease and most had received prior bDMARD treatment. This is similar to the available data from the US Corrona registry, where patients who initiated tofacitinib had a mean (s.d.) disease duration of 13.4 (10.0) years and a median (interquartile range) of 3 (1–4) previous bDMARDs [12].

In the Canadian eXel programme, tofacitinib persistence was 62.7% and 49.6% at 1 and 2 years, respectively, which was higher than that in the Truven and MarketScan/Medicare databases where retention was reported to be 46.2% over 12 months in bDMARD-naïve patients who previously received methotrexate [13], and 42.6% over 12 months in patients who received one prior bDMARD [14]. In this analysis, patients with more bDMARD experience (⩾1 prior bDMARD) were more likely to discontinue treatment, whereas older patients (⩾56 years) with a history of diagnosis between 15 and <20 years were less likely to discontinue treatment, although a disease duration ⩾20 years was not a significant factor for persistence. This may be partially due to the sample sizes in each age group: 394 patients in the 15 to <20 years group *vs* >600 patients in each of the other groups. Information on concomitant medications was not captured; however, an analysis of data from a Canadian clinical database and registry reported similar persistence of patients receiving tofacitinib with or without methotrexate [15].

In this analysis, more patients were bDMARD-naïve (33.0% *vs* 22.4%), the average age of enrolled patients was higher (59 *vs* 55 years), and patients had longer time since diagnosis (mean disease duration: 14.9 *vs* 2.6 years) *vs* US data from the MarketScan/Medicare database, which may account for the differences in persistence observed in the Canadian and US populations [14]; this may also be due to other practice and reimbursement differences between the countries.

In the current report, one-third of patients discontinued tofacitinib (with variable follow-up length up to 2 years), which was a lower rate than in the US: in a retrospective cohort analysis, 44% and 57% of 862 US patients with RA discontinued after 12 and 24 months, respectively [10]. Patients in the eXel programme most commonly discontinued tofacitinib due to LOE. Similarly, in a meta-analysis of European and non-European bDMARD registry studies, LOE was the most common reason for discontinuation of bDMARDs (∼2 in 3 patients), with a 1-year discontinuation rate for bDMARDs of 22% [16].

This study is limited by constraints on baseline demographic and disease characteristics due to the data collection method. Demographics and medication history were primarily obtained from patients by telephone interview, whereas disease characteristics were collected using SA forms in a minority of patients although the exact proportion of data obtained through SA forms is unable to be determined. Data were not reliably collected on the continuation or discontinuation of conventional synthetic DMARDs, including methotrexate, after enrolment. The effect of background DMARDs and serostatus on retention could not be determined due to lack of collection of these data. Data were limited to those collected as part of usual care and enrolment in the eXel programme. Within the programme, data are not collected on tofacitinib efficacy over time, so the response to treatment is unknown; however, persistence in the programme can be used as a surrogate for effectiveness, tolerability,

Fɪɢ. 2 Persistence and analysis of variables associated with the likelihood of tofacitinib discontinuation

(**A**) Persistence of patients initiating tofacitinib within the eXel support programme using Kaplan–Meier estimates, stratified by line of therapy. Only patients who initiated tofacitinib treatment were included, and patients were excluded if their treatment status was unknown. (**B**) Cox regression analysis of variables associated with the likelihood of treatment discontinuation with tofacitinib. bDMARD: biologic DMARD; CI: confidence interval.

safety and access [17]. Missing data were not imputed. Additionally, the frequency of follow-up decreased after 2 years, becoming annual follow-ups that focused on re-imbursement assistance only; the frequency of contact may have impacted persistence. In our analysis, patients who could not be contacted were assumed to be receiving tofacitinib until the programme received confirmation that they were no longer on the drug. Data were also not collected on the number of patients who restarted treatment after a 90-day cessation. Additionally, data for 2017 were only up to mid-year, with only 531 patients, so comparisons with this time point should be made with caution. Furthermore, the eXel programme was not mandatory and both physicians and patients could choose to access the drug without using the programme. Finally, there was no comparator group, and therefore the results cannot be compared with those of other RA treatments in patients recruited in the same way.

Despite limitations, the data collected from the eXel programme provide insight into the utilization and retention of tofacitinib from a large cross-country platform, and show changes in prescribing patterns over time.

The use of tofacitinib for the treatment of patients with RA in Canada increased from 2014 to 2017, with treatment patterns showing a shift towards an earlier line of therapy. Persistence of treatment was 62.7% and 49.6% at 1 and 2 years, respectively, and decreased with bDMARD experience and increased with age.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Singh JA, Hossain A, Tanjong Ghogomu E *et al.* Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA). Cochrane Database Syst Rev 2016;11:CD012437.

2 Fleischmann R, Mysler E, Hall S *et al.* Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017;390:457–68.

3 Cohen SB, Tanaka Y, Mariette X *et al.* Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis 2017;76:1253–62.

4 Maneiro JR, Souto A, Gomez-Reino JJ. Risks of malignancies related to tofacitinib and biological drugs in rheumatoid arthritis: systematic review, meta-analysis, and network meta-analysis. Semin Arthritis Rheum 2017;47:149–56.

5 Tarp S, Furst DE, Boers M *et al.* Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis. Rheumatology (Oxford) 2017;56:417–25.

6 Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol 2017;13:234–43.

7 Cohen S, Curtis JR, DeMasi R *et al.* Worldwide, 3-year, post-marketing surveillance experience with tofacitinib in rheumatoid arthritis. Rheumatol Ther 2018;5:283–91.

8 Dall TM, Askarinam Wagner RC, Zhang Y *et al.* Outcomes and lessons learned from evaluating TRICARE's disease management programs. Am J Manag Care 2010;16:438–46.

9 Marshall JK, Bessette L, Thorne C *et al.* Impact of the adalimumab patient support program's care coach calls on persistence and adherence in Canada: an observational retrospective cohort study. Clin Ther 2018;40:415–29.e6.

10 Marshall AC, Bowen K, Starner CI, Gleason PP. Tofacitinib (Xeljanz) utilization patterns and persistency among 4.4 million continuously enrolled commercially insured members over 4 years. AMCP Nexus 2016; Poster 18349.

11 Louder AM, Singh A, Saverno K *et al*. Patient preferences regarding rheumatoid arthritis therapies: a conjoint analysis. Am Health Drug Benefits 2016;9:84–93.

12 Kavanaugh A, Reed GW, Saunders KC *et al*. Clinical characteristics of RA patients newly prescribed tofacitinib citrate (tofacitinib) in the United States after food and drug administration approval: results from the CORRONA US rheumatoid arthritis registry. Ann Rheum Dis 2015;74:1041.2.

13 Smith T, Harnett J, Gruben D *et al*. Real-world experience with tofacitinib versus adalimumab and etanercept in biologic-naive patients with RA previously treated with methotrexate: data from a US administrative healthcare insurance claims database. Arthritis Rheumatol 2017;69:4040–1. Abstract 2831.

14 Harnett J, Gerber R, Gruben D, Koenig AS, Chen C. Evaluation of real-world experience with tofacitinib compared with adalimumab, etanercept, and abatacept in RA patients with 1 previous biologic DMARD: data from a U.S. administrative claims database. J Manag Care Spec Pharm 2016;22:1457–71.

15 Choquette D, Bessette L, Brown J *et al*. Tofacitinib show similar retention when used with and without methotrexate. Analysis from Rhumadata® Clinical Database and Registry. Arthritis Rheumatol 2018;70(suppl 10). Abstract 1531.

16 Souto A, Maneiro JR, Gómez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford) 2016;55:523–34.

17 Neovius M, Arkema EV, Olsson H *et al*. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 2015;74:354–60.