CPASS and Clinical Science Projects Overview

Marketed Products Development Internship

Amy Nguyen
Summer Intern
Marketed Products Development – CPASS Team
6-Aug-2024

Agenda

- About me
- Internship Overview
- CPASS Projects
- Clinical Science Projects
- Other Involvements
- Important Takeaways
- Future Plans and Goals
- Conclusion

About me ☺

Amy Nguyen

- 3rd year PharmD student at the University of Connecticut - School of Pharmacy
- Expected graduation year: 2026
- Current hobbies:
  - Trying new foods/restaurants
  - Playing billiards
  - E-biking
  - Listening to podcasts
  - Making flower bouquets

Internship Overview

Internship Overview

Internship Duration

- 28 May to 16 Aug 2024 (12 weeks)

CPASS Mentors (Tomodachi)

- Vivek, Sara and CPASS Leads

Clinical Science Mentor (Tomodachi)

- Alissa Dangel

Learning Objectives:

- Gain understanding of the Regulatory context and framework for Post Marketing Safety Studies
- Gain real-world, hands-on work experience in Post Marketing Safety Studies and learn how to apply these new skills to a potential future career at Takeda

CPASS Contributions

Comparative Analysis of CPASS Study Templates

Comparative Analysis of CPASS Study Templates

Background:

- **MEDIVA**
  - Regulatory Information Management (RIM) system for regulatory tracking
  - Electronic document management system (EDMS)
- **Veeva QMS (Quality Management Systems)**
  - House controlled documents that support process and procedures
    - SOPs/FORMs/TOOLs/TRMTs
- CPASS Veeva QMS templates reformatted for MEDIVA
  - ***FORM-269798 Takeda Non-interventional Safety Study Report Template***
  - ***FORM-269950 Takeda Non-Interventional Safety Study Protocol Template***
  - ***FORM-269721 Takeda Non-Interventional Safety Study Protocol Synopsis Template***

Project Objectives:

- Review reformatted CPASS NI Safety Study templates for inclusion into MEDIVA
- Ensure consistency and compliance across study templates and regulatory requirements

Comparative Analysis of CPASS Study Templates

Responsibilities:

- Conduct two thorough rounds of review for MEDIVA templates
- Identify and address discrepancies between **MEDIVA** draft templates and **Veeva QMS** templates
- Compare **MEDIVA** templates against **EMA Guidance documents** to ensure compliance with format and content standards
- Develop a method to effectively present findings

Impact:

- Make CPASS templates user-friendly for Medical Writing teams using MEDIVA
- Ensure study templates meet Takeda regulatory requirements
- Ensure compliance with EMA guidance to prevent audit/inspection findings

	B	C	D	E
2	Type of Discrepancy	Page #	Original Content in **Veeva QMS**	Updated Content in **Mediva** Attachment
3	Change	Header	**Takeda** Study number_protocol/protocol amendment # Version Date: MMDDDYYYY **Product name**	**<Compound>** **Study No. <#>** **Non-interventional Safety Study Protocol {Incorporating Amendment No. <#>}** **<Date> [dd Month yyyy]**
4	Addition	5	None	"Signature Page" section added to the Table of Contents
5	Addition	5	None	"List of In-Text Tables" section added to the Table of Contents
6	Addition	5	None	"List of In-Text Figures" section added to the Table of Contents
7	Addition	5	None	"List of Annexes" section added to the Table of Contents
8	Addition	5	None	"10.6 Adverse Events/Adverse Reactions" section added to the Table of Contents
9	Addition	6	None	"LIST OF IN-TEXT TABLES" section added to the Table of Contents
10	Addition	6	None	"LIST OF IN-TEXT FIGURES" section added to the Table of Contents
11	Change	14	"[List of references using the *Vancouver* style.]"	"[List of references using *EndNote and the Harvard Copy* style.]"

Comparative Analysis of CPASS Study Templates

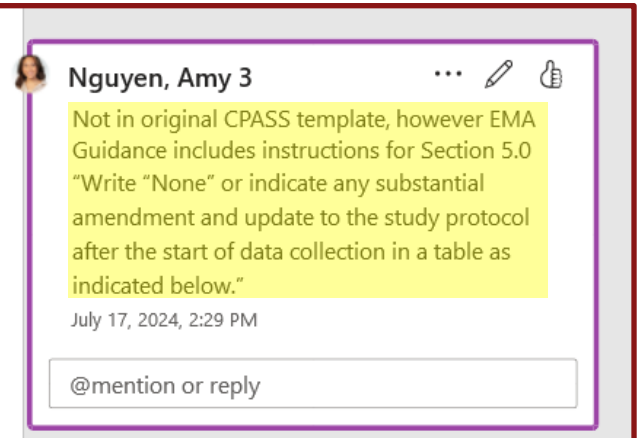
MEDIVA Draft Template

5.0 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	<date>	<text>	<text>	<text>
2	<date>	<text>	<text>	<text>
…	<date>	<text>	<text>	<text>

6.0 MILESTONES

[Planned dates for study milestones should be indicated in a table as indicated below. Milestones between <> are optional and should be included only if applicable. Start of data collection and End of data collection are defined in



EMA Guidance Document

5. Amendments and updates

Write "None" or indicate any substantial amendment and update to the study protocol after the start of data collection in a table as indicated below.

Number	Date	Section of study protocol	Amendment or update	Reason
1	*Date*	*Text*	*Text*	*Text*
2	*Date*	*Text*	*Text*	*Text*
…	*Date*	*Text*	*Text*	*Text*

ADYNOVATE® Japan PMS Study Report

ADYNOVATE® Japan PMS Study Report Review

STUDY: TAK-660-5002 ADYNOVATE Special Drug Use Result Survey (Perioperative administration)

ADYNOVATE is a human antihemophilic factor indicated in children and adults with hemophilia A (congenital factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes
- Perioperative management
- Routine prophylaxis to reduce the frequency of bleeding episodes

Study Background:

- Imposed by Japan health authorities to allow marketing of ADYNOVATE for perioperative administration in Japan
  - Post Marketing Surveillance (PMS) involves systematic monitoring of medications while they are used in real-life scenarios collect real-world safety data
  - Perioperative – period surrounding a surgical procedure, encompassing three main phases: preoperative, intraoperative, postoperative

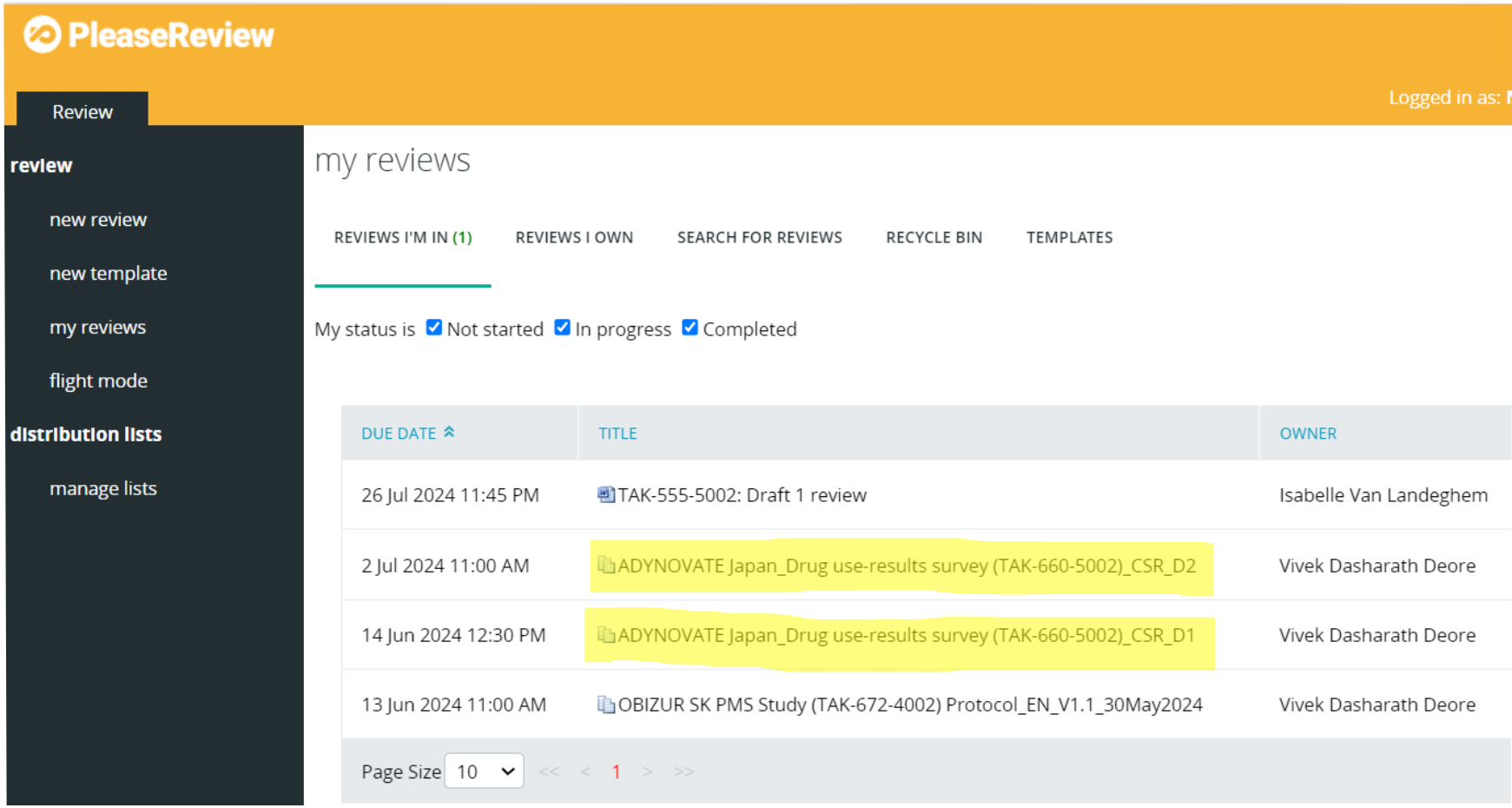
Learning Goals:

- Acquire familiarity with ADYNOVATE'S drug profile
- Understand ADYNOVATE'S associated safety concerns
- Gain a comprehensive understanding of the report review process
- Develop robust understanding of rationale behind conducting PMS studies
- Facilitate global review for final study reports
- Gain understanding of the approval processes required for finalizing and validating study reports

ADYNOVATE® Japan PMS Study Report Review

General Responsibilities:

- Develop proficiency in navigating PleaseReview
- Learn how to create new reviews, add essential reviewers, and close out reviews effectively



ADYNOVATE® Japan PMS Study Report Review

Review Execution:

- Conduct two comprehensive rounds of review
- Provide comments/suggestions

Impact:

- Identified the absence of the patient disposition figure in the CSR appendix and took necessary steps to address the issue
- Correcting errors fosters trust within the team, demonstrating a collective commitment to maintaining high standards

Example:

3.2 Patient Disposition

The disposition of patients is shown in Figure 1.1 in Appendix Tables and Figures.
Of the 16 registered patients, survey forms were collected from 15 patients and not collected from 1 patient (physician's busy schedule).
All the patients whose survey forms were collected were evaluated for safety and efficacy.

ADYNOVATE® Japan PMS Study Report Review

Professionalism and Review Etiquette

- Acquire skills to organize email chains
- Maintain professional email etiquette in all communications
- Learn how to automate reminders in PleaseReview
- Strictly adhere to set project timelines

Impact:

- Adherence to timelines ensures projects progress forward and deadlines are met
- Importance of professional communication strategies
    - Foster a collaborative environment
    - Minimize misunderstandings

ADYNOVATE Japan PMS study (TAK-660-5002): Final Study Report

Task Name	Duration	Start	Finish	Comments
"Survey Completion date (Estimated completion date of Statistical Analysis)"			15 Mar 2024	• PMS Survey Period: June 2021 to 31 December 2023 • Survey completion date (final analysis completion date): 15 May 2024
First draft of CSR in English				
Please Review 1				• Takeda MW: COA will be prepared in parallel with final report • COA timelines will be prepared by Takeda Medical Writing based on CS review timelines. • CSR references, if applicable should be archived in ~~SHEDS~~ MEDIVA.
First CSR draft in English for team for review in Please Review	5 days	07 Jun 2024	14 Jun 2024	CPASS Lead to provide TAK-660-5002 CSR D1 with Comments to Japan team by 14Jun2024
Japan /CRO MW consolidate comments	1 day	17Jun2024	18Jun2024	
Japan /CRO conducts 1st Roundtable Review Meeting, if require	1 day	19Jun2024	19Jun2024	
Japan /CRO MW to update CSR Document following RTR discussion	4 days	20Jun2024	25Jun2024	
Please Review 2				
Second CSR draft in English for team for review in Please Review	**5 days**	26Jun2024	02July2024	• Japan-CRO will ensure internal linking, bookmarks, and table of content is available for the CSR • Japan CRO will provide CSR and any appendices, references to the study report (such as TLFs, protocol amendments, literature references etc.) to Japan study team • Japan -CRO will pre-publish CSR appendices with bookmarks by 02July2024 • CPASS Lead to provide TAK-660-5002 CSR D1 with Comments to Japa team by 02July2024
Japan /CRO MW consolidates comment	1 day	03July2024	05July2024	04July and 05July Takeda/Public Holiday
Japan /CRO conducts 2nd Roundtable Review Meeting, if require	1 day	08July2024	08July2024	
Japan /CRO MW to update CSR Document following RTR discussion	4 days	03July2024	11July2024	
Japan /CRO QC, Teach edits, internal linking of CSR and finalize CSR Document	4 days	12July2024	17July2024	• Japan -CRO will provide publication ready CSR to Takeda EU Regulator which means the internal linking, bookmarks, and table of content should also be available in the CSR and all applicable appendices. • CSR external links if any will be shown by using blue font. • Japan study manager will provide all applicable appendices (such as TLFs, protocol amendments, literature references etc.) to Takeda EU regulatory within MEDIVA for EMA submission.
Investigator to approve CSR, if applicable	**3 days**	17July2024	19July2024	If not applicable then please utilize these days for uploading documents for EMA submission in MEDIVA by 19July2024
Takeda to approve CSR	**3 days**	19July2024	23July2024	CPASS Lead to obtain approvals by 23July2024
Takeda CSR submission preparation, regulatory publishing and submission	**7 days**	24July2024	01Aug2024	Timelines are reduced to 5 days as • CRO will ensure internal linking of the CSR • CRO will provide publication ready CSR to Takeda which means the bookmarks should also be available in the CSR and all appendices.

ADYNOVATE® Japan PMS Study Report Review

Global Impact:

- **Fulfill Post Marketing Commitment for PMDA in Japan**
  - This PMS study aimed to provide robust **real-world data** to prove the **safety and efficacy** of Adynovate in the **Japanese population**
    - Data can be used to support marketing applications in other countries, demonstrating the Adynovate's reliability and performance
- **Enhanced Brand Reputation**
  - Conducting thorough PMS studies showcase Takeda's commitment to patient safety and regulatory compliance

Key Takeaways:

- Meticulousness and precision is crucial in ensuring the accuracy and reliability of study reports
- Repeated reviews can help catch errors and validate findings
- Collaboration within global landscape (e.g. considering time zone differences, respective cultural holidays)

PASS Study List Country and Country Status Inspection

PASS Study List Country and Country Status Inspection

Background:

- *explain what this list is, who uses it*
- PASS Study List is updated and distributed on the 15th of each month
- List contains studies that are planned, ongoing, and closed (within 2 years)
- Nexus – system that pulls data from the various sources through a data hub and into a centralized location to provide accurate trial listing reports

Project Objectives:

- Ensure accurate and up-to-date management of PASS study country and country statuses
- Develop and refine skills in using Nexus for effective study tracking and reporting
- Implement traceable system for updating study country and country statuses

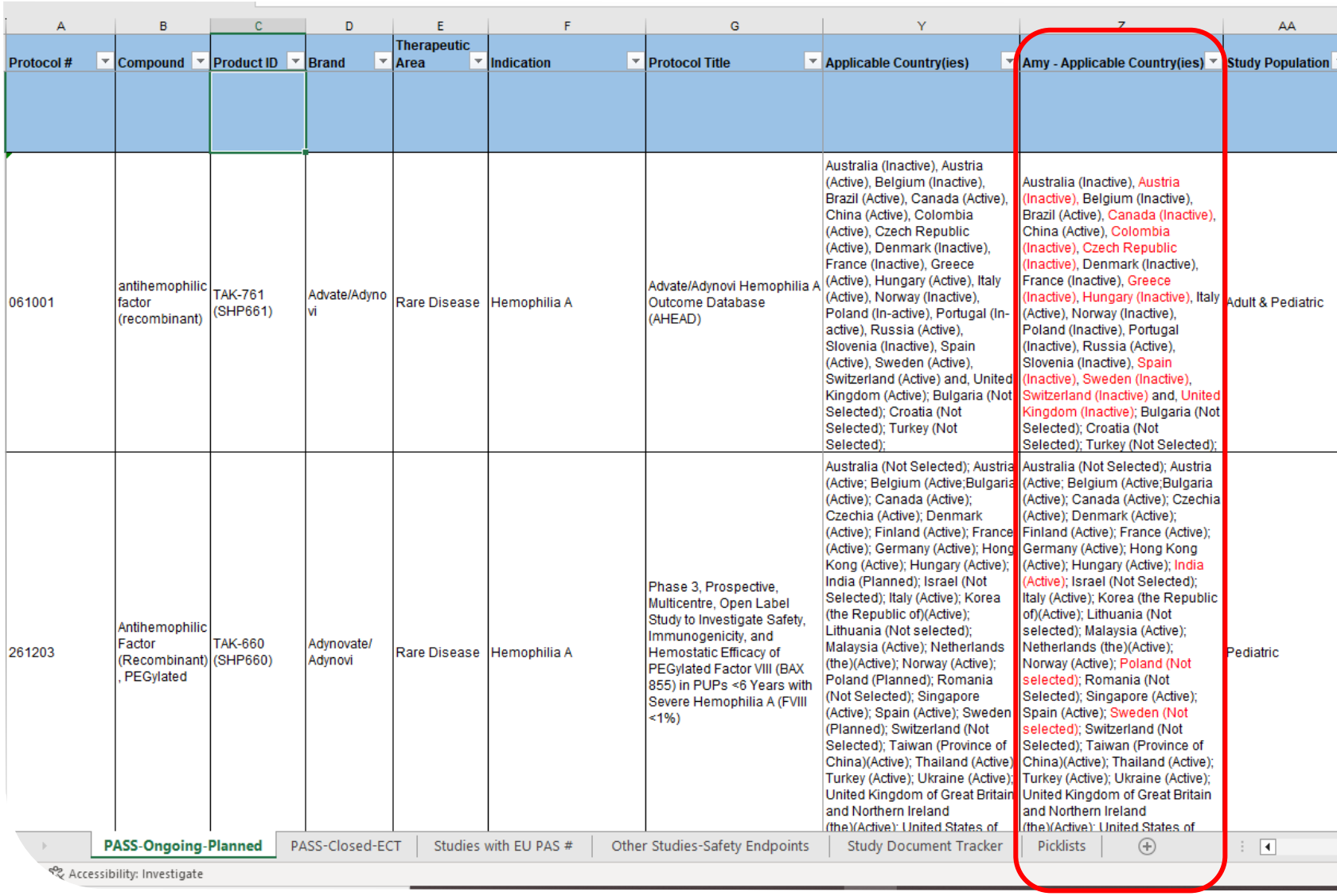
PASS Study List Country and Country Status

Responsibilities:

- Participate in Nexus training sessions
- Utilize Nexus to check for the most recent study country and country status updates
- Manually review country and country statuses for **108 PASS studies**
- Identify discrepancies between PASS List and Nexus data
- Update country statuses in the study list as needed in RED

Impact:

- Ensure the accuracy of the PASS list to provide reliable information for individuals utilizing the list for ____



Protocol #	Compound	Product ID	Brand	Therapeutic Area	Indication	Protocol Title	Applicable Country(ies)	Amy - Applicable Country(ies)	Study Population
061001	antihemophilic factor (recombinant)	TAK-761 (SHP661)	Advate/Adynovi	Rare Disease	Hemophilia A	Advate/Adynovi Hemophilia A Outcome Database (AHEAD)	Australia (Inactive), Austria (Active), Belgium (Inactive), Brazil (Active), Canada (Active), China (Active), Colombia (Active), Czech Republic (Active), Denmark (Inactive), France (Inactive), Greece (Active), Hungary (Active), Italy (Active), Norway (Inactive), Poland (In-active), Portugal (In-active), Russia (Active), Slovenia (Inactive), Spain (Active), Sweden (Active), Switzerland (Active) and, United Kingdom (Active); Bulgaria (Not Selected); Croatia (Not Selected); Turkey (Not Selected);	Australia (Inactive), Austria (Inactive), Belgium (Inactive), Brazil (Active), Canada (Inactive), China (Active), Colombia (Inactive), Czech Republic (Inactive), Denmark (Inactive), France (Inactive), Greece (Inactive), Hungary (Inactive), Italy (Active), Norway (Inactive), Poland (Inactive), Portugal (Inactive), Russia (Active), Slovenia (Inactive), Spain (Inactive), Sweden (Inactive), Switzerland (Inactive) and, United Kingdom (Inactive); Bulgaria (Not Selected); Croatia (Not Selected); Turkey (Not Selected);	Adult & Pediatric
261203	Antihemophilic Factor (Recombinant), PEGylated	TAK-660 (SHP660)	Adynovate/Adynovi	Rare Disease	Hemophilia A	Phase 3, Prospective, Multicentre, Open Label Study to Investigate Safety, Immunogenicity, and Hemostatic Efficacy of PEGylated Factor VIII (BAX 855) in PUPs <6 Years with Severe Hemophilia A (FVIII <1%)	Australia (Not Selected); Austria (Active; Belgium (Active;Bulgaria (Active); Canada (Active); Czechia (Active); Denmark (Active); Finland (Active); France (Active); Germany (Active); Hong Kong (Active); Hungary (Active); India (Planned); Israel (Not Selected); Italy (Active); Korea (the Republic of)(Active); Lithuania (Not selected); Malaysia (Active); Netherlands (the)(Active); Norway (Active); Poland (Planned); Romania (Not Selected); Singapore (Active); Spain (Active); Sweden (Planned); Switzerland (Not Selected); Taiwan (Province of China)(Active); Thailand (Active); Turkey (Active); Ukraine (Active); United Kingdom of Great Britain and Northern Ireland (the)(Active); United States of	Australia (Not Selected); Austria (Active; Belgium (Active;Bulgaria (Active); Canada (Active); Czechia (Active); Denmark (Active); Finland (Active); France (Active); Germany (Active); Hong Kong (Active); Hungary (Active); India (Active); Israel (Not Selected); Italy (Active); Korea (the Republic of)(Active); Lithuania (Not selected); Malaysia (Active); Netherlands (the)(Active); Norway (Active); Poland (Not selected); Romania (Not Selected); Singapore (Active); Spain (Active); Sweden (Not selected); Switzerland (Not Selected); Taiwan (Province of China)(Active); Thailand (Active); Turkey (Active); Ukraine (Active); United Kingdom of Great Britain and Northern Ireland (the)(Active); United States of	Pediatric

Other CPASS Contributions

Other CPASS Contributions

Review and understand the regulatory guidelines for Post Marketing Safety Studies

Understand and define PASS and PMS

Read and understand CPASS SOPs

- SOP-218455 Global SOP, Post Authorization Safety Studies
- SOP-218456 Non-interventional Post Authorization Safety Studies
- SOP-218765 Operational Aspects of Non-interventional Post-Authorization Safety Studies
- SOP-217613 Development of Protocols and Study Reports for Non-interventional Post Authorization Safety Studies
- TRMT-223577 Post Authorization Safety Studies Training
- FORM-266094 Checklist for Non-interventional Post Authorization Safety

Review Obizur PMS South Korea report

Attend PASS Bi-Monthly Review Meeting and record supplementary meeting minutes

Attend CPASS and ChatCPASS meetings

TRAINING: Paediatric study results submission in EU & UK (SOP-248839)

Participate in MHRA inspection close out meeting

Participate in Adynovate EU PASS study meetings

Attend PBRER meeting for Adynovate

Attend Adynovate quarterly Safety Management Team meeting

Attend IOS potential scientific misconduct meeting with PASS Compliance Lead

Clinical Science Contributions

MOTEGRITY® Post Marketing Requirement (PMR) Pregnancy Safety Studies

add project titles in unbolded font and small

motegrity®
(prucalopride) tablets 1mg, 2mg

MOTEGRITY® PMR Pregnancy Safety Studies

Background:

- MOTEGRITY® is a serotonin-4 (5-HT4) receptor agonist indicated for the treatment of **chronic idiopathic constipation** (CIC) in adults
- Patients and prescribers lack important safety information to evaluate the risk-benefit profile of MOTEGRITY use during pregnancy

- FDA imposed **3 Post Marketing Requirements (PMRs)** under FDAAA Section 505(o)(3) **to assess MOTEGRITY's safety in pregnancy**
  - 1) PMR 3529-3: A prospective, registry based observational exposure cohort study → TAK-555-5001
  - 2) PMR 3529-4: An additional pregnancy study that uses a different design from the Pregnancy Registry → TAK-555-5002
    - A pregnancy registry actively collects information on drug or biological product exposure during pregnancy and associated pregnancy outcomes, which can be used to conduct a prospective observational study
  - 3) PMR 3529-5: Perform a milk only lactation trial → TAK-555-4006

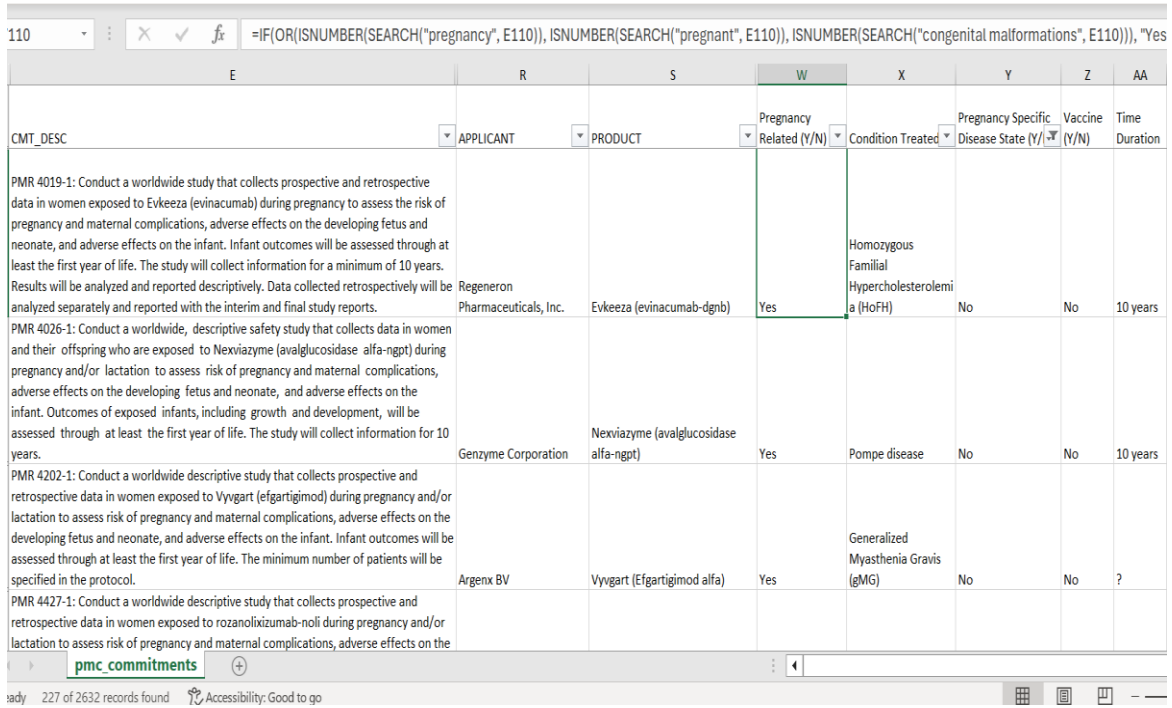
- **Current Situation: Insufficient patient enrollment**
  - Possibly reasonings:
    - Label recommendation for concurrent contraception use
    - Many other forms of constipation treatment available, especially OTC
    - Patient concern about unknown safety profile

MOTEGRITY® PMR Pregnancy Safety Studies Projects

Project 1: List of Prescription and OTC IBS-C/CIC Drugs

Drug Name	Manufacturer(s)	Class	Indication	Initial Approval	Systemic Absorption?	Was a Pregnancy Study Requested?	Type o Requ
Linaclotide (Linzess)	AbbVie and Ironwood	guanylate cyclase-C agonist	IBS-C and CIC	8/30/2012	no - "negligibly absorbed systemically"	No	N
Lubiprostone (Amitiza)	Sucampo	chloride channel activator	IBS-C and CIC	1/31/2006	no - "low systemic availability"	No	N
Plecanatide (Trulance)	Salix	guanylate cyclase-C agonist	IBS-C and CIC	1/19/2017	no - "negligibly absorbed systemically"	No	N
Tegaserod (Zelnorm) DISCONTINUED	Alfasigma	serotonin-4 (5-HT4) receptor agonist	IBS-C	7/24/2002	no - "no significant [systemic] accumulation (~10%) of tegaserod"	No	N
Senna	Many	stimulant laxative	occasional constipation	Not approved	no - "Minimal absorption following oral administration."	No	N
Polyethylene glycol (Miralax)	BAYER HEALTHCARE LLC; ANI PHARMS;	osmotic laxative	occasional constipation	10/6/2006	no - "Minimal absorption"	No	N
Docusate	Many	stool softener	occasional constipation	*Not approved* 1993 Proposed	no - "limited systemic absorption"	**Not in humans** (FDA became aware of information in animal	(1) A star three-ge reproduc
Lactulose	AUROBINDO PHARMA LTD; CHARTWELL RX;	osmotic laxative	occasional constipation	11/14/1996	no - "systemic absorption limited"	No	N

Project 2: Comprehensive Analysis of FDA PMR/PMC Database for Pregnancy-Related Studies



E	R	S	W	X	Y	Z	AA
CMT_DESC	APPLICANT	PRODUCT	Pregnancy Related (Y/N)	Condition Treated	Pregnancy Specific Disease State (Y/	Vaccine (Y/N)	Time Duration
PMR 4019-1: Conduct a worldwide study that collects prospective and retrospective data in women exposed to Evkeeza (evinacumab) during pregnancy to assess the risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years. Results will be analyzed and reported descriptively. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.	Regeneron Pharmaceuticals, Inc.	Evkeeza (evinacumab-dgnb)	Yes	Homozygous Familial Hypercholesterolemia (HoFH)	No	No	10 years
PMR 4026-1: Conduct a worldwide, descriptive safety study that collects data in women and their offspring who are exposed to Nexviazyme (avalglucosidase alfa-ngpt) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Outcomes of exposed infants, including growth and development, will be assessed through at least the first year of life. The study will collect information for 10 years.	Genzyme Corporation	Nexviazyme (avalglucosidase alfa-ngpt)	Yes	Pompe disease	No	No	10 years
PMR 4202-1: Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Vyvgart (efgartigimod) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.	Argenx BV	Vyvgart (Efgartigimod alfa)	Yes	Generalized Myasthenia Gravis (gMG)	No	No	?
PMR 4427-1: Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to rozanolixizumab-noli during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the							

MOTEGRITY® PMR Pregnancy Safety Studies Projects

Project Objectives:

- Gain a thorough understanding of **MOTEGRITY's drug profile**
- Comprehend the **purpose** and **rationale** behind FDA-requested **PMR/PMCs**
- Identify the **challenges** associated with post-marketing **pregnancy safety studies** and explore potential solutions
- Review **historical and ongoing** PMC/PMR studies to understand approaches taken by **competitors**
- Gather supporting evidence to help the team develop a **strategic response** to the **FDA**

Requirement/Commitment Number: 3

Required Under:	FDAAA Section 505(o)(3)
Original Projected Completion Date:	06/30/2026
Description:	PMR 3529-3: A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Motegrity (prucalopride) during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.
Current Status:	Ongoing

Requirement/Commitment Number: 4

Required Under:	FDAAA Section 505(o)(3)
Original Projected Completion Date:	06/30/2026
Description:	PMR 3529-4: An additional pregnancy study that uses a different design from the Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to Motegrity (prucalopride) during pregnancy compared to an unexposed control population.
Current Status:	Ongoing

Requirement/Commitment Number: 5

Required Under:	FDAAA Section 505(o)(3)
Original Projected Completion Date:	08/31/2024
Description:	PMR 3529-5: Perform a milk only lactation trial in lactating women who have received therapeutic doses of Motegrity (prucalopride) using a validated assay to assess concentrations of prucalopride in breast milk and the effects on the breastfed infant.
Current Status:	Ongoing

MOTEGRITY® PMR Pregnancy Safety Studies – Project #1

List of Prescription and OTC IBS-C/CIC Drugs

Compile a list of drugs currently available for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) and/or chronic constipation

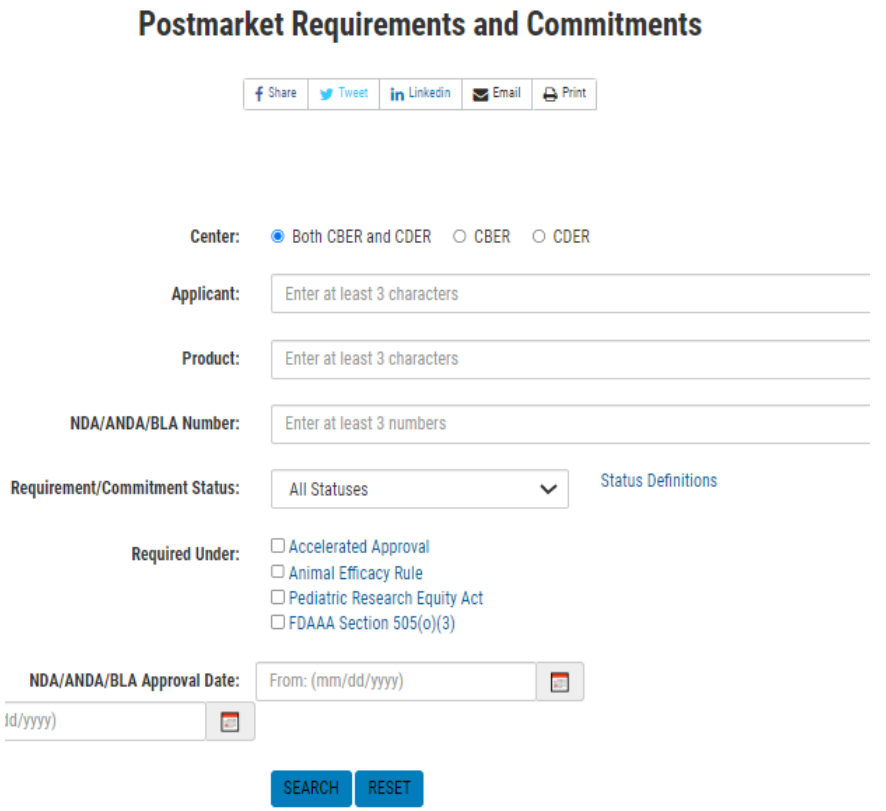
Gather relevant information from the drug labels, including:

- Manufacturers
- Drug class
- Indications
- Initial approval date
- Is the drug systemically absorbed?

Investigate whether there are any PMC/PMRs for these drugs

- Determine if a pregnancy study was requested, specifying the type of study and its status
- Utilize the FDA's PMC/PMR search tool: FDA PMC Index

Identify publications pertaining to pregnancy exposure in relation to these drugs



MOTEGRITY® PMR Pregnancy Safety Studies – Project #1

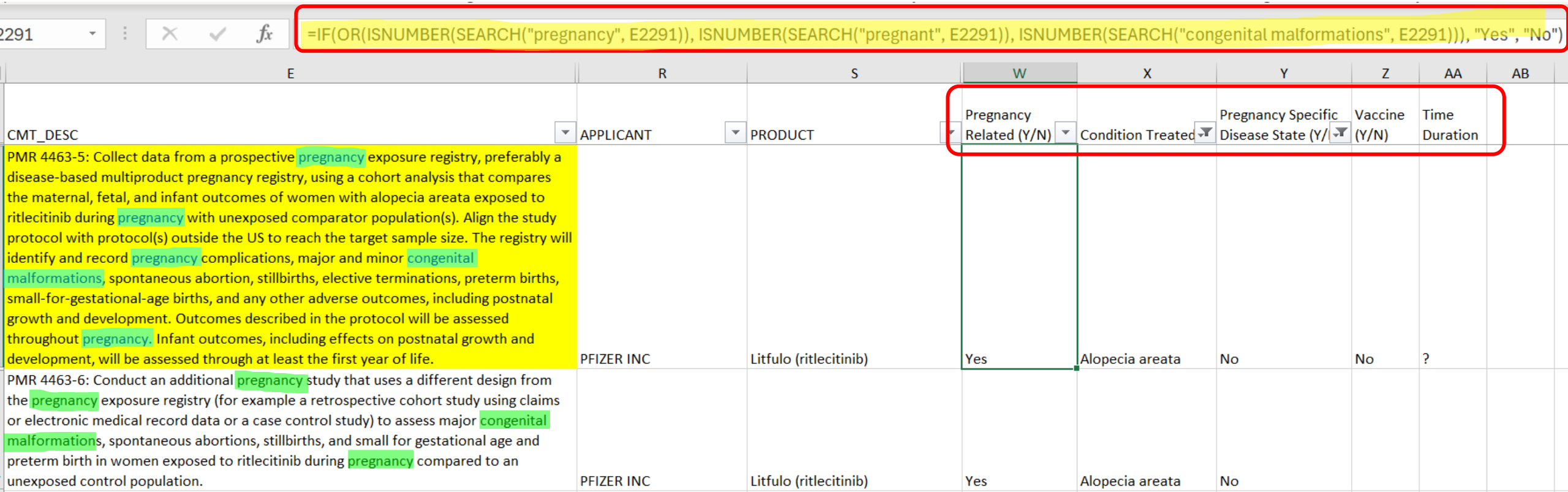
List of Prescription and OTC IBS-C/CIC Drugs

Drug Name	Manufacturer(s)	Class	Indication	Initial Approval	Systemic Absorption?	Was a Pregnancy Study Requested?	Type of Study Requested	Pregnancy Study Findings	Status of the Requested Study	Related Publications	Publication Findings	Pregnancy Summary
Linaclotide (Linzess)	AbbVie and Ironwood	guanylate cyclase-C agonist	IBS-C and CIC	8/30/2012	no - "negligibly absorbed systemically"	No	N/A	N/A	N/A	None	None	Should be used during pregnancy only if the potential benefit
Lubiprostone (Amitiza)	Sucampo	chloride channel activator	IBS-C and CIC	1/31/2006	no - "low systemic availability"	No	N/A	N/A	N/A	None	None	Should be used during pregnancy only if the potential benefit
Plecanatide (Trulance)	Salix	guanylate cyclase-C agonist	IBS-C and CIC	1/19/2017	no - "negligibly absorbed systemically"	No	N/A	N/A	N/A	None	None	Should be used during pregnancy only if the potential benefit
Tegaserod (Zelnorm) DISCONTINUED	Alfasigma	serotonin-4 (5-HT4) receptor agonist	IBS-C	7/24/2002	no - "no significant [systemic] accumulation (~10%) of tegaserod"	No	N/A	N/A	N/A	None	None	Should be used during pregnancy only if the potential benefit
Senna	Many	stimulant laxative	occasional constipation	Not approved	no - "Minimal absorption following oral administration."	No	N/A	N/A	N/A	Acs N, Banhidy F, Puho EH, Czeizel AE. Senna treatment in	Our data did not show any association	Avoid long term use during pregnancy; may cause electrolyte
Polyethylene glycol (Miralax)	BAYER HEALTHCARE LLC; ANI PHARMS;	osmotic laxative	occasional constipation	10/6/2006	no - "Minimal absorption"	No	N/A	N/A	N/A	Mahadevan U, Kane S. American Gastroenterological	PEG (pregnancy category C) is negligibly absorbed	Negligibly absorbed; likely to be safe in pregnancy
Docusate	Many	stool softener	occasional constipation	*Not approved* 1993 Proposed	no - "limited systemic absorption"	**Not in humans** (FDA became aware of information in animal	(1) A standard FDA three-generation reproductive study	In 1993, the FDA completed evaluation of animal studies and	Closed	Jick H, Holmes LB, Hunter JR, et al. First-trimester drug use	Of these pregnant women, 473 of them received docusate	No demonstrated association with fetal malformations; one
Lactulose	AUROBINDO PHARMA LTD; CHARTWELL RX;	osmotic laxative	occasional constipation	11/14/1996	no - "systemic absorption limited"	No	N/A	N/A	N/A	Li H, Zhang P, Xue Y. A comparison of the safety and efficacy	In a randomized study comparing PEG to lactulose in	Recommendation is only use in pregnancy when need is clearly

MOTEGRITY® PMR Pregnancy Safety Studies – Project #2

Comprehensive Analysis of FDA PMR/PMC Database for Pregnancy-Related Studies

- Analyze FDA's PMR/PMC database of 2632 PMR/PMC studies and search for the PMR/PMCs that contain the word "pregnancy" and/or "pregnant" to identify some examples from other disease areas
  - Once identified as a pregnancy study then investigate those that were extended and for how long
  - Identify if the drug is being used for a pregnancy specific condition



2291

=IF(OR(ISNUMBER(SEARCH("pregnancy", E2291)), ISNUMBER(SEARCH("pregnant", E2291)), ISNUMBER(SEARCH("congenital malformations", E2291))), "Yes", "No")

	E	R	S	W	X	Y	Z	AA	AB
	CMT_DESC	APPLICANT	PRODUCT	Pregnancy Related (Y/N)	Condition Treated	Pregnancy Specific Disease State (Y/	Vaccine (Y/N)	Time Duration	
	PMR 4463-5: Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women with alopecia areata exposed to ritlecitinib during pregnancy with unexposed comparator population(s). Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.	PFIZER INC	Litfulo (ritlecitinib)	Yes	Alopecia areata	No	No	?	
	PMR 4463-6: Conduct an additional pregnancy study that uses a different design from the pregnancy exposure registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to ritlecitinib during pregnancy compared to an unexposed control population.	PFIZER INC	Litfulo (ritlecitinib)	Yes	Alopecia areata	No			

MOTEGRITY® PMR Pregnancy Safety Studies

Impact:

- Narrowed the list of 2,632 PMC/PMR studies to 227 that specifically involve pregnancy
- Provided the team with a historical understanding of pregnancy-related PMC/PMR requests
- Equips the team with a comprehensive overview of the competitive landscape
- Facilitates comparison and benchmarking of MOTEGRITY's profile against existing treatments and supports strategic positioning
- Helped the team grasp the scope and timeline of similar studies, supporting arguments about the practicality and burden of conducting extended studies

Key Takeaways:

- Pregnancy studies present unique challenges due to difficulties in participant recruitment, especially for voluntary studies.
- Analyzing past scenarios is advantageous for developing effective strategies to address the current situation.
- Given that this scenario is unprecedented at Takeda, examining other disease areas and competitor approaches can yield valuable insights.
- When brainstorming, it is crucial to consider the perspectives of each contributor's functional team.
- Incorporating diverse perspectives fosters a comprehensive and multifaceted team discussion.
- Engaging with the FDA necessitates a meticulous, step-by-step strategy supported by robust data-driven arguments.

Other Clinical Science Contributions

Other Clinical Science Contributions

Observe IQVIA feasibility assessment for Motegrity registry in pregnant patients with constipation	Observe strategic plan of FDA-facing futility argument to support Motegrity PMR release request	Read TAK-555-5002 Interim Report	TAK-555-4006/5001/5002 Study Execution Team Meeting
Read FDA Guidance - Post Approval Pregnancy Safety Studies	Attend MIT DHIVE program lectures	Gain background overview of pediatric drug development and regulations	Understand the legal, ethical, regulatory and policy issues for pregnant and lactating patient research
Support TAK-555-4006 Motegrity Breastfeeding/Lactation Study	Understand the process of breastmilk development	TAK-555-5002 Interim Report Pre-Draft Review	Comprehend the rationale behind the implementation of a higher safety standard for vaccines

Other Involvements

Other Involvements

- MPD RWD/RWE Learning Series
- MPD DE&I Ambassadors
- GRA CMC Intern Seminar
- MPD FUN-Raising Walk
- ADHD Programs: GPT Meeting
- PPI GPT Cluster Meeting
- Met with functional team representatives to connect and understand their contributions and how it collectively drives team success

Key Takeaways

Key Takeaways

Everything applies to **PTRB**

Prioritizing efficiency in all areas ensures our commitment to putting patients first by delivering the highest quality in the shortest possible timelines

Deepened Knowledge of Industry Pharmacy

- Gained an in-depth understanding of the pharmaceutical industry, including post market drug monitoring, regulatory requirements, and market dynamics

Balancing Technical Knowledge and Soft Skills

- Developed skills in process improvement
- Worked closely with teams across different departments, practicing the collaborative and integrated environment at Takeda

Legal and Regulatory Understanding

- Understanding the legal landscape of the pharmaceutical industry has emphasized the need for compliance and ethical practices in research and development

If it is not documented, it never happened

- Keeping meticulous records and clear documentation has proven vital for tracking progress and ensuring compliance

Developed the ability to prioritize tasks effectively, balancing urgent and important responsibilities

Developing good relationships has improved communication, making it easier to share ideas, provide feedback, and resolve conflicts

Recognize and respect varying time zones and cultural holidays to ensure inclusivity and collaboration within our global team.

Future Plans and Goals

Future Plans and Goals

Expected graduation date: May 2026

Post graduation plans: Fellowship (hopefully at Takeda)!

Pursue a fellowship, leveraging the skills and knowledge gained during my internship

Thank you!