Challenges with conducting pediatric trials in pJIA

Industry Perspective:

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FDA/UMD CERSI pJIA Drug Development Workshop

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FDA Approved Drugs for pJIA and Actively Recruiting Interventional Clinical Trials in pJIA (CT.GOV*)

- FDA Approved drugs
  - Methotrexate
  - Enbrel (etanercept), May 1999
  - Humira (adalimumab), February 2008
  - Orencia (abatacept), April 2008
  - Actemra (tocilizumab), April 2013

- Actively recruiting interventional clinical trials
  - Tofacitinib
  - Upadacitinib
  - Barcitinib
  - VSL#3 (probiotic)

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*Accessed 27 Aug 2019

Sarilumab Pediatric Post Marketing Requirement

Sarilumab (Kevzara) approved by US FDA for the treatment of adult patients with moderate to severe active RA in May 2017

Postmarket Requirements and Commitments

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Applicant:	sanofi-aventis U.S. LLC
Product:	Kevzara (Sarilumab)
NDA/BLA Number:	761037
NDA/BLA Approval Date:	05/22/2017
Annual Report Due Date: (must be submitted within 60 days of this date)	05/22/2019
Annual Report Received:	07/20/2018

Requirement/Commitment Number: 1

Required Under:	Pediatric Research Equity Act
Original Projected Completion Date:	12/31/2018
Description:	A study to assess the pharmacokinetic and pharmacodynamics (PK/PD) parameters and dosing of sarilumab in children ages greater than or equal to 2 years to 17 years with polyarticular juvenile idiopathic arthritis (pJIA) (study DRI3925).
Current Status:	Submitted
Explanation of Status:	The final report was submitted to FDA on 12/17/2018.

Requirement/Commitment Number: 2

Required Under:	Pediatric Research Equity Act
Original Projected Completion Date:	01/31/2023
Description:	A study to assess the efficacy and safety of sarilumab in children ages greater than or equal to 2 years to 17 years with polyarticular JIA (study EFC11783).
Current Status:	Delayed
Explanation of Status:	The final protocol is delayed pending results from 3218-1 which is ongoing.

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Sarilumab pJIA Dose-Finding Study Design: DRI13925

- An Open-label, Sequential, Ascending, Repeated Dose-finding Study of Sarilumab, Administered with Subcutaneous (SC) Injection, in Children and Adolescents, Aged 2 to 17 Years, with Polyarticular-course Juvenile Idiopathic Arthritis (pcJIA) followed by an Extension Phase
- 12-week treatment part and 92-week extension part
- 3 ascending doses evaluated in 2 weight groups
- Total 36 patients projected to be enrolled in16 countries; 45 sites

Sarilumab pJIA Confirmatory Efficacy and Safety Study design: EFC11783

- A randomized, double-blind, placebo-controlled withdrawal study of sarilumab administered subcutaneously (SC) in children and adolescents, aged 2 to 17, with polyarticular-course juvenile idiopathic arthritis (pcJIA)
- 16 week open label phase followed by a 24 week double-blind withdrawal phase
- At least 270 patients anticipated to be enrolled with ~ 220 randomized to DB withdrawal phase

Enrollment Timelines - DRI13925 (Dose-finding Portion – 12 week core phase) Projected and Actual

	Planned (Initial)	Actual
Number of patients	36	42
Number of sites selected	30 / 40	45
Number of countries selected	10-20	16
First Patient In	Jun-16	03-Oct-16
Last Patient In	05-Jul-17	16-May-18
Last Patient Last Visit	27-Sep-17	08-Aug-18

Multiple timeline revisions made over the course of the 12 week core phase enrollment period due to recruitment challenges

Enrollment – DRI13925

- US recruitment
  - Multiple sites targeted for participation
    - 3 sites participated; no patients enrolled

- Ex-US recruitment – 20 sites enrolled 42 patients.

  20 sites enrolled at least 1 patient, in 11 countries (Argentina, Chile, Czech Republic, France, Germany, Italy, Mexico, Netherlands, Poland, Russia, and Spain).

Key Challenges in Enrollment – DRI13925

- Rare disease
- Parents not consenting
- Availability of alternative therapies
- Finding patients with active disease
- Study Design
  - **Frequent PK sampling within the first 2 weeks of the study**
  - **Frequent visits**
  - **Management of recruitment across countries and sites due to:**
    - dose-finding study design: enrollment by cohort, dose escalation process, pause in the recruitment between cohorts for DMC/DEC activities
    - recruitment more difficult in lower weight patients
    - keeping sites motivated while monitoring the staggered recruitment

Mitigation Strategies – DRI13925

- Targeted pediatric-rheumatology sites familiar with clinical trials and PK trials
- Dynamic monitoring of recruitment (number of patients per dose and group) across countries and sites
- Proactive communication to maintain site commitment
- Increased number of qualified sites in select countries

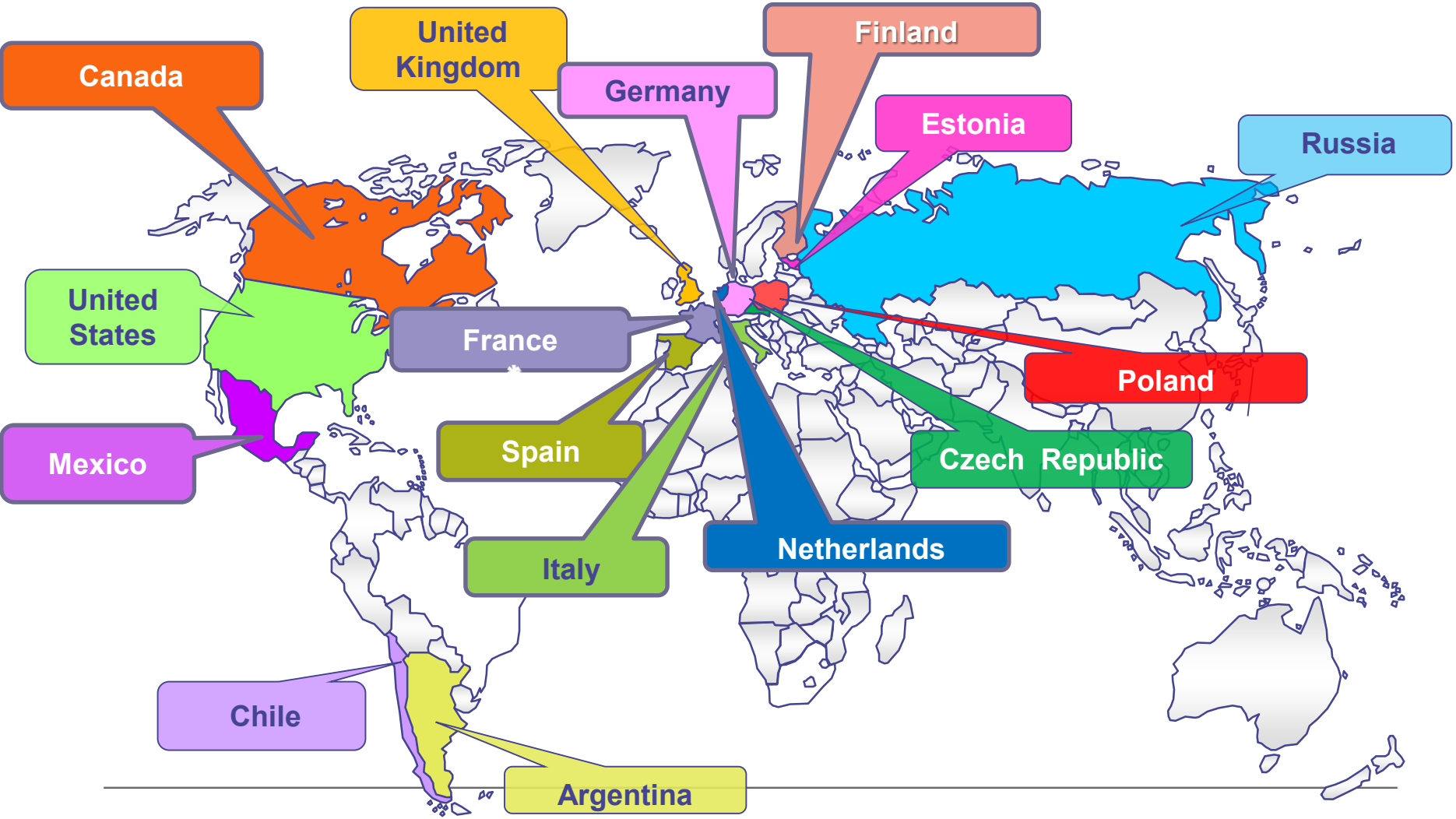
Conclusion

- Challenging enrollment for dose-finding study
  - pJIA rare disease
  - Several approved treatments available
  - Treat to target objective in pediatric patients
  - Competing clinical trials
- Sponsor revising strategy to fulfill PMR given challenges for conducting a study in this disease

Back up Slides

DRI13925

16 Participating countries – 45 sites



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