

# IIT Global Areas of Interest

Cardiovascular, Renal & Metabolism

## **Inclisiran (Leqvio®)**

Studies within the label population

- Long-term safety and tolerability
- Health-related quality of life (HrQoL)
- Implementation science and/or quality system improvement programs (ex. clinical care pathways)
- Early post-event implementation
- Stroke
- PAD
- LDL-C lowering in under-represented population
- Adherence vs. other LLTs

Mechanistic Studies in secondary prevention

- Remodeling, fibrosis, inflammation
- Plaque burden regression/modification
- CABG graft remodeling

Mechanistic Studies in primary prevention and/or patients with statin-intolerance

- Remodeling, fibrosis, inflammation
- Plaque burden regression/modification
- Assessment techniques (IVUS, echo, CCTA, OTC, MRI) must be guidelines validated (pending vascular bed assessment)

Out of scope:

- Studies in off-label populations (with respect to geographies)
- Efficacy, safety and tolerability studies with inclisiran in pediatric population (<18 y)
- Studies in adults with HoFH and/or different populations than ASCVD and ASCVD equivalent
- CVOT trials
- Head-to-head efficacy/safety studies with other lipid lowering therapies
- Pre-Clinical Proposals (separate process)

Studies involving drug for any indication(s) currently in clinical development and not yet approved

## **Iptacopan (LNP023)\***

### **With Drug**

1. Mechanistic studies in IgAN, C3G, aHUS
2. Subgroups of patients that are included in the overall study population in indications pursued with iptacopan (IgAN, C3G, aHUS)

## Without Drug

1. Role of complement system in complement-mediated kidney diseases
2. Additional ways to foster diagnosis of glomerulopathies beyond biopsy
3. Studies which attempt to clarify the histopathologic complexity/equipoise of C3G
4. Identification of approaches that lead to better characterization, management or correlation with outcomes in IgAN, C3G, aHUS, MN, LN – e.g. identification of biomarkers, genetic analysis or biopsy-based studies
5. Burden of disease (clinical, economic, and/or humanistic burden) - IgAN, C3G, aHUS, MN, LN
6. Epidemiology studies (incl. registries) - IgAN, C3G, aHUS, MN, LN

Out of scope:

- Pediatric studies (with drug)
- Studies exploring different dosing regimens as currently investigated
- Any study, which combines iptacopan with immunosuppressant
- Head-to-head comparisons
- Studies including patients with CKD stages 4 and 5

\* Strategic areas of interest for iptacopan (PNH), please also refer to the Oncology section

## Pelacarsen

Without drug

- Epidemiology associated with elevated Lp(a)
  - Patient characterization, identification, and genetic risk across sub-groups
  - Plaque characteristics and differences across patient sub-groups
  - Association & impact on different types of CVD (ischemic stroke, CAVS, PAD), various vascular beds, and other diseases (e.g., AF, kidney disease, diabetes)
- Distinct and unique pathophysiology of Lp(a)
  - Insights on the pro-inflammatory or pro-thrombotic mechanisms impacted by Lp(a)
  - Unique features of Lp(a)
- Quantification of Lp(a) role in CV risk assessment tools
  - Quantification of Lp(a) contribution to global CV risk and in light of other CV risk factors
  - Risk score calculators incorporating Lp(a)
  - Patient perception on contribution of Lp(a) to CVD and CV risk
- Lp(a) testing and global CV risk management
  - Implementation of Lp(a) testing in CVD management pathways
  - Clinical and economic value of Lp(a) testing
  - Guidance on management of currently modifiable risk factors in the setting of elevated Lp(a)

Out of scope:

- Comparison / association with LDL-C
- Studies involving drug for any indication(s) currently in clinical development and not yet approved

## Sacubitril/Valsartan (Entresto)

### Heart Failure

- RWE or Implementation Science studies on improvements of HF care through increase in GDMT

- RWE studies with sac/val in Chronic Heart Failure with reduced EF
- RWE studies with sac/val in Chronic Heart Failure with mildly-reduced or preserved EF - in geographies where it is in-label
- RWE studies with sac/val in HTN - in geographies where it is in-label

Out of scope:

- Comparative effectiveness studies vs other MoA, e.g. SGLT2i, MRA, BB
- Studies in non-cardiovascular disease
- Studies in patients with valvular disorders not related to HF
- Studies in children (<18 years)
- Mechanistic Studies in HF including but not limited to those looking at:
  - Remodeling, fibrosis, inflammation
  - Cardiac function (including diastolic function)
  - Cardiac biomarkers
- Studies in populations with specific, less well studied / documented HF etiologies, e.g. chemotherapy /toxicity induced HF

Gene Therapies

## **Zolgensma IV**

### **Areas of interest by product**

- Demonstrating or validating care needs for SMA populations post OAV101 Treatment-safety related items
- Expansion of treatment with OAV101 to patient populations not included in clinical trials (e.g. older/heavier, 4 copies, switch therapy, ambulatory)
- Value of OAV101: Cost of care, Quality of life, and Caregiver Burden-Cost effectiveness
- Methods/Processes to assess the efficacy and durability of OAV101 (e.g. bulbar function)
- Biomarkers for efficacy

### **Out of scope**

- Clinical Trials involving OAV 101 re-dosing
- Study of OAV101 alternative doses/maximum dose
- Head-to-head comparison with other therapies and combination with other MDT
- Basic Science research that request use of OAV101

## **OAV101 IT**

### **Areas of interest by product**

- Interventional Studies of OAV IT in patients not included in clinical trials (e.g. ambulant SMA patients, severe scoliosis)
- Non-interventional Studies of OAV IT assessing sleep, bulbar function, scoliosis and respiratory function, head steadiness and independence.
- Studies on biomarkers assessing clinical response to OAV IT

### **Out of scope**

- Clinical Trials involving OAV 101 re-dosing
- Study of OAV101 alternative doses/maximum dose

- Head-to-head comparison with other therapies and combination with other MDT
- Basic Science research that request use of OAV101

## Global Health

### **Adakveo, Ryverna (Crizanlizumab, SEG101)**

- Studies with crizanlizumab in sickle cell disease and related complications
  - e.g- renal, leg ulcer, stroke, AVN, adolescents with SCD, priapism, splenic sequestration, VOCs
- Mechanistic studies with crizanlizumab
- Predictors of response to crizanlizumab
- SCD biomarkers

#### Out of scope:

- IIT requests from countries outside of US, SSA, Brazil
- IIT requests in non-SCD indications

### **HU, HU-FCT (Hydroxyurea)**

- Studies with HU in sickle cell disease and organ protection
  - e.g., spleen, lungs, kidneys
- Societal and economic impact of HU/HU-FCT on LMIC
- Studies with HU-FCT looking at treatment/stroke prevention in LMIC
- HU-FCT preference by caregivers

#### Out of scope

- IIT requests from countries outside of SSA, Brazil and India
- IIT requests in non-SCD indications

## Immunology

### **Secukinumab (Cosentyx)**

### **Indications: axSpA (axial spondyloarthritis), incl. r-axSpA (radiographic) and nr-axSpA (non-radiographic)**

#### **Clinical data, outcomes & RWE:**

- Long term RWE studies on clinical efficacy, structural progression & safety of secukinumab
- Clinical outcomes with Secukinumab across different manifestations of axSpA , by gender and race

#### **Implementation Science/HCS research.**

- Identification of Predictors of structural progression and treatment algorithm related to structural progression
- Impact of early intervention and treat-to-target on patient outcomes
- impact of Secukinumab on prevention or reduction of Comorbidities
- Research Use of Novel imaging modalities for early diagnosis, pathogenesis of disease and monitoring of Secukinumab response
- Evaluate the impact of Secukinumab and treatment strategy to reduce Fatigue and pain

#### **Exploratory/ mechanistic studies:**

- New classification criteria of AxSpA and differences in pathogenesis of axSpA vs. axial PsA.
- Role of IL-17A in the pathogenesis of axial, peripheral manifestations and comorbidities of AxSpA
- Role of IL-17A across the spectrum of spondyloarthritides (SpA)

### **Out of scope**

- Studies on safety topics e.g. infections (tuberculosis, HIV, viral hepatitis), high-risk patients
  - Studies with combination biologics
  - Clinical comparative studies with other treatments
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## **Indications: Psoriatic arthritis (PsA)**

### **Clinical data, outcomes and RWE:**

- Long term RWE studies on clinical efficacy, inhibition of structural progression & safety of secukinumab
- Long term RWE studies on efficacy, safety and treatment strategy in juvenile PsA (JPsA) and enthesitis-related arthritis (ERA)
- Clinical outcomes with Secukinumab in key manifestations of PsA, by gender, race, ethnic minorities and access to health care systems
- Clinical outcomes with Secukinumab in specific phenotypes (Axial PsA, skin predominant, nail/dactylitis, Oligoarticular predominant)

**Implementation Science/HCS research:** cost-effectiveness, resource utilization and guideline implementation

- Impact of early treatment and treat-to-target on patient outcomes and resource utilization
- Impact of Secukinumab on prevention or reduction of Comorbidities (e.g. CV, metabolic)
- Research studies on Novel imaging for early diagnosis and monitoring of Secukinumab response
- Evaluate the impact of Secukinumab to reduce Fatigue and pain

### **Exploratory/ mechanistic studies:**

- Role of IL-17A in the pathogenesis of Axial PsA and differences with pathogenesis of axial PsA vs axSpA
- Roles of different cytokine pathways in the key manifestations of PsA notably axial disease, enthesitis, nail-dactylitis

### **Out of scope**

- Studies on safety topics e.g. infections (tuberculosis, HIV, viral hepatitis), high-risk patients
  - Studies with combination of other biologics
  - Comparative studies with other treatments
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## **Indications: Psoriasis (PsO)**

### **Clinical data, outcomes and RWE:**

- Long term RWE studies on clinical efficacy, & safety of secukinumab, risk factors and prevention of the transition period of PsO to PsA
- Clinical outcomes with Secukinumab by gender, race, skin of colors, ethnic minorities and access to

health care systems

- Long term RWE studies on efficacy, safety and treatment strategy in pediatric PsO

#### **Implementation Science/HCS research:**

- Impact of early intervention strategy on disease modification in PSO and resource utilization
- Research program designed for early diagnosis and characterization of PSO patients at risk of PsA : disease burden, risk factors, screening tools/app, novel imaging

#### **Exploratory/ mechanistic studies:**

- role of IL-17A in the pathogenesis of the transition period PsO to PsA
- Mechanistic study of Secukinumab in Early PsO

#### **Out of scope**

- Studies on safety topics e.g. infections (tuberculosis, HIV, viral hepatitis), high-risk patients
  - Studies with combination other biologics
  - Comparative studies with other treatments
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### **Indications: Hidradenitis Suppurativa**

#### **Clinical data, outcomes and RWE:**

- Early intervention with Sec and impact on disease progression (including imaging techniques, such as ultrasound)
- Clinical outcomes in subpopulations (e.g. disease phenotypes, Black / African American, super-responders,..)
- Integrating surgical procedures with the administration of Secukinumab for the treatment of HS. (effectiveness and Safety)
- HS comorbidities (Mental Health, Obesity, CV)
- Effects of lifestyle intervention on HS treatment with Secukinumab

#### **Implementation Science / HCS research:**

- Quality of care, cost-effectiveness, resource utilization, and guidelines implementation
- AI/ML algorithms and big data approach to improve diagnosis and treatment of HS
- Development and validation of scoring tools / PROs

#### **Exploratory/ mechanistic studies:**

- Translational research on pathophysiology - role of IL-17A and other pathways in HS over the course of the disease , and in specific aspects of the disease e.g., Fistula/tunnel development"
- Biomarkers to predict disease and treatment outcomes

#### **Out of scope**

- Comparative studies with other treatments
- Combination studies for Secukinumab with other biologic agents
- IV dosing for HS

### **Indications: GCA and PMR**

## **Pathophysiology and biomarkers**

- Biomarkers to monitor subclinical disease activity, predict prognosis and treatment outcomes
- Effects of a mechanism-based approach to therapy
- Pathways involved in refractory/flare GCA
- Biomarkers to predict drug/GC toxicity

## **Diagnosis and classification**

- Standardization of clinical trial endpoints
- Validation of the definition of remission, response, relapse and disease subtypes of importance
- Use of the different imaging techniques for vascular activity, damage assessment and follow-up

## **Treatment and treatment outcomes**

- Implementation Science/HCS research: quality of care, cost-effectiveness, resource utilization, and guidelines implementation
- Disease characteristics and clinical outcomes in patients with skin of color, ethnic minorities, or populations so far underrepresented in clinical trials. Gender related differences
- Assessment of prognosis by demographic, clinical and histological data
- Predictors of response, remission or relapse
- Validation of patient-reported outcomes
- Predictive models for IL-17A inhibition responses across disease phenotypes
- Effect of secukinumab on the development of future vascular complications

## **Out of scope**

- Effect of secukinumab on the development of future vascular complications
- Combination studies of secukinumab with other biologic agents
- The role of ultrasound for guiding temporal artery biopsy, specific treatment of organ complications

## **Neuroscience**

### **Ofatumumab (Kesimpta) and siponimod (Mayzent) - Multiple sclerosis (MS)**

- Focus on prognosis and diligent monitoring of patients with MS (including data and digital):
  - Markers for disease prognosis, disease monitoring, and/or risk mitigation
  - New or improved quantitative outcome measures in MS, including next-generation technology and patient assessment technologies
  - Integration of markers/outcome measures to establish disease stability or disease control, disease progression
- Mechanistic studies looking at differentiating Novartis compounds from other DMTs

## **Remibrutinib in RMS**

**Disease:** Relapsing Multiple Sclerosis

**Product:** Remibrutinib

## **Areas of interest by product**

### Follow the science

- Impact on the immune system in and outside the CNS – clinical and preclinical studies

- Direct CNS effects (i.e. microglial activity, synaptogenesis, neuronal function) and correlation with clinical outcomes beyond relapses (e.g. PIRA, disability improvement) and with some patient outcomes (e.g. cognition, fatigue)
- Impact on chronic inflammation and correlation with linked clinical and paraclinical outcomes (disability measures, such as EDSS/MSFC, imaging measures, fluid biomarkers)

#### Safety related:

- BTKi – vaccine response
- Pregnancy registries (in line with initiatives already in place)

#### Identify unmet need under current DMTs:

- Patient preference
- Tolerability and safety concerns (what, when, to whom – patient profile-)
- Effectiveness gaps under HET (what, when, to whom – patient profile -)

#### **Out of scope**

*Progressive phenotypes of MS (naSPMS or PPMS); hepatotoxicity*

#### **Remibrutinib in CU**

**Disease:** Chronic Urticaria – CSU (chronic spontaneous urticaria) and CindU (chronic inducible urticaria)

**Product:** Remibrutinib

#### **Areas of interest by product**

##### Disease Related Research:

- Population-based epidemiology studies; studies investigating the impact of urticaria on patients; comorbidities; studies of real-world treatment patterns (incl. e.g. overuse of corticosteroids, impact on sleep)
- Studies investigating biomarkers in urticaria aiming to identify predictors of chronic urticaria in patients with acute episodes, biomarkers predictive of treatment response, biomarkers correlating with the time-course of CSU, biomarkers of permanent remission or relapse, including with remibrutinib
- Studies employing digital technology e.g. *in silico* models, machine learning techniques, telemedicine etc. to predict disease trajectories, treatment response, disease modification, etc.
- Studies investigating innovative tools to support urticaria management, e.g. digital applications, sleep related
- Long-term CSU observational registries and secondary use of data
- Studies investigating patient preference

##### Clinical Studies:

- Studies with remibrutinib in CindU
- Studies with remibrutinib focusing on angioedema only

##### Mechanistic Studies

- Mechanistic studies assessing the effects of remibrutinib on mast cells, basophils, B-cells *in vitro* or *ex vivo*



- Studies investigating the disease modifying potential of remibrutinib, including pre-clinical *in vitro* or *ex vivo* research

## Out of scope

- Head-to-head comparisons of remibrutinib with other active treatments
- Studies investigating remibrutinib in combination with biologics
- Alternative dosing regimens to 25 mg b.i.d developed in the CSU phase 3 clinical program

## Oncology

### Asciminib (Scemblix)

Studies in adult patients Chronic Myeloid Leukemia in Chronic Phase (CML-CP) in early treatment lines, investigating:

- Long-term safety and tolerability
- Clinical efficacy and safety in real-world setting
- Treatment sequencing
- Patient-reported outcomes (PROs) and Quality of Life (QoL)
- Patients with CML-CP and additional T315I mutation
- Response to asciminib in patients with pre-existing mutations other than T315I or treatment approaches in patients with emerging mutations under asciminib, including compound mutations

Studies exploring additional high-need patient populations other than CML-CP:

- Patients with Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL)
- Exploratory high risk CML populations such as patients with additional genomic alterations
- CML-AP/BC

Studies in Treatment Free Remission (TFR)

- Studies aiming to improve deep molecular responses, increase the eligibility for TFR attempts or reduce the risk of relapse after treatment discontinuation
- Combination approaches of asciminib with non-ATP-TKI compounds

Studies providing insight into mechanistical action of asciminib, potential on- and off target effects and its use against additional mutations in patients with CML.

Out of scope:

- Use of asciminib in ABL-independent diseases

### Iptacopan (LNP023)\*\*

#### With Drug

1. Mechanistic studies in Paroxysmal Nocturnal Hemoglobinuria (PNH);
2. Studies evaluating factors associated with or predictive of treatment outcome in PNH;
3. Studies exploring preferences in oral treatment administration approaches in PNH

#### Without Drug

1. Role of complement system in complement-mediated PNH, Immune Thrombocytopenia Purpura (ITP) and Cold Agglutinin Disease (CAD);

2. Approaches to facilitating and expediting diagnosis of PNH and CAD;
3. Identification of biomarkers that leads to better characterization, management or correlation with outcomes in PNH, ITP and CAD;
4. Burden of disease (clinical, economic, and/or humanistic burden) – PNH and CAD;
5. Epidemiology studies (incl. registries) – PNH and CAD

Out of scope:

- Pediatric studies
- Studies exploring different dosing regimens as currently investigated
- Any study, which combines iptacopan with immunosuppressant and anti-C5 treatments
- Head-to-head comparisons
- Studies in other hematology diseases

\*\* Strategic areas of interest for iptacopan (IgAN, C3G, aHUS, MN, LN), please also refer to the Cardiovascular, Renal & Metabolism section

### **[177Lu] Lu-DOTA-TATE (Lutathera®)**

- Studies (other than prospective design) describing optimal timing and sequence of treatment in advanced or metastatic GEP-NET patients
- Studies of Lutathera in advanced or metastatic NET patients in combination with other anti-cancer treatments, including chemotherapy (also bolus 1L), immuno-oncology therapies, tyrosine kinase inhibitors (TKIs), PARP-inhibitors, CDK4/6 inhibitors, or other upcoming treatments (if supported by MoA rationale)
- Retrospective studies describing long-term safety or health economic aspects
- Studies on biomarkers to predict and prognosticate treatment in GEP-NET

### **[177Lu] Lu-PSMA-617 (Pluvicto®)**

**Indication:** Prostate Cancer

- Sequential use of different radioligand therapies (alpha- or beta-emitter)
- Efficacy and safety of <sup>177</sup>Lu-PSMA-617 combinations to overcome resistance and to improve efficacy outcomes / Efficacy and safety of <sup>225</sup>Ac-PSMA-617/R2 combinations (any disease stage)
- Efficacy and safety of <sup>177</sup>Lu-PSMA-617 in low volume disease (*mHSPC*, *OMPC*)
- Adaptive and alternative treatment regimens with <sup>177</sup>Lu-PSMA-617 monotherapy or in combinations (*mHSPC*, *mCRPC*)
- Efficacy and safety of radioligand therapy (alpha- or beta-emitter) in neoadjuvant setting (HRLPC)
- Impact of <sup>177</sup>Lu-PSMA-617 efficacy and safety in patient populations with sub-optimal outcomes, including patients distinct mutations (e.g., PTEN-loss, AKT, DDR), patients CNS mets, liver mets etc. (*mHSPC*, *mCRPC*)
- Retrospective analysis to predict long-term safety events (*mCRPC*)
- Treatment effect on disease biology (HRLPC, *mHSPC*, 1L-2L *mCRPC*)
- Understanding PSMA expression in different stages of prostate cancer (HRLPC, *mHSPC*, 1L-2L *mCRPC*)

### **Beyond GU**

- Brain Metastasis (secondary malignancies)
- Ovarian Ca

- NSCLC
- GBM: microenvironment and translational research (MoA deeper understanding)
- GBM: Other mode of administration in GBM (not IV)
- Hepatocellular Carcinoma
- High grade gliomas
- Others PSMA-expressing/PET-avid tumors
- Imaging studies
- Pediatric indications

### **Ribociclib (Kisqali)**

- HR+/HER2- studies in breast cancer
  - Exploring data on CDK4/6 inhibitor rechallenge
  - Exploring ribociclib with novel/emergent compounds
  - Utilizing real world data and/or digital health technologies
  - Utilizing patient reported outcomes (PRO)

Out of scope:

- Any area outside HR+/HER2- breast cancer
- Any study in overlap with ongoing Novartis-sponsored/supported studies

### **(RAG) $^{225}\text{Ac}$ -PSMA-617 in Prostate Cancer**

**Disease:** Prostate Cancer

**Product:** RAG)  $^{225}\text{Ac}$ -PSMA-617

#### **Areas of interest by product:**

- Combinations (taxane based chemotherapy, PARPi with or without ARPI, Combination in DDR+ vs DDRwt patients, others)
- Retreatment or rechallenge or extension of treatment
- Safety: protecting salivary gland or preventing xerostomia.
- Tandem dosing schedule between  $^{117}\text{Lu}$ -PSMA-617 and  $^{225}\text{Ac}$ -PSMA-617
- Head-to-Head  $^{225}\text{Ac}$ -PSMA-617 vs PARPi +/- ARPI in BRCA2mut vs ITT
- Head-to-Head  $^{225}\text{Ac}$ -PSMA-617 vs  $^{117}\text{Lu}$ -PSMA-617
- Impact of prior ARPI exposure on  $^{225}\text{Ac}$ -PSMA-617 combination with ARPI (ARPI resistant vs sensitive)
- Impact of prior treatment on Dosimetry and Adaptive dosing

#### **For consideration:**

- Concordance rate of PSMA positivity/negativity between different PSMA PET imaging agents
- Define new categories of volume of disease/burden of disease in mHSPC based on PSMA – PET based imaging
- Metachronous Oligometastatic CRPC detected by PSMA-PET but being non-metastatic by conventional imaging
- Prospective study to correlate PET parameters with treatment outcomes.
- Biomarker correlation of acquired resistance and response to  $^{225}\text{Ac}$ -PSMA-617
- Evaluation Method of Intra-tumoral Heterogeneity by PET Imaging and Molecular expression analysis

**Out of scope:**

- Outside prostate cancer.

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**List of links present in page**

1. <https://prod1.novartis.com/node/662876>
2. <https://prod1.novartis.com/node/662876/printable/print>
3. <https://prod1.novartis.com/node/662876/printable/pdf>