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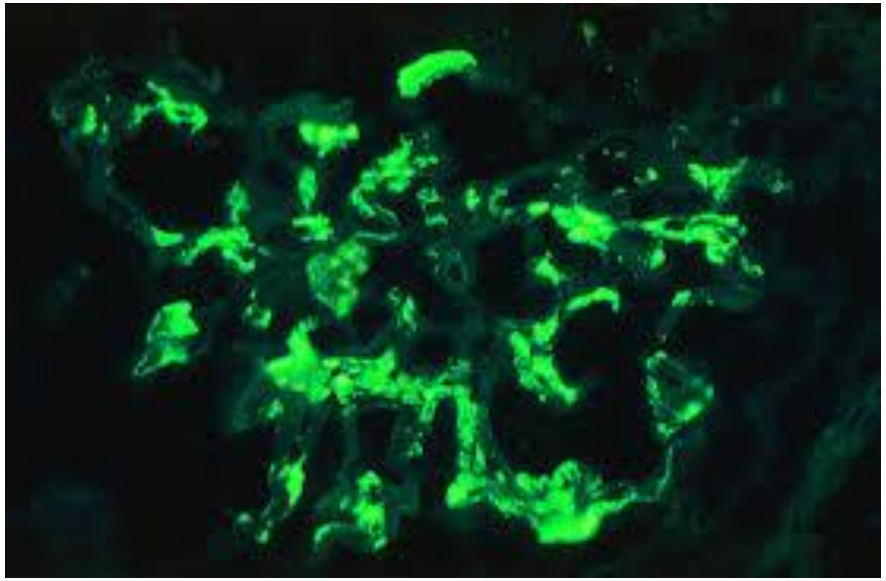

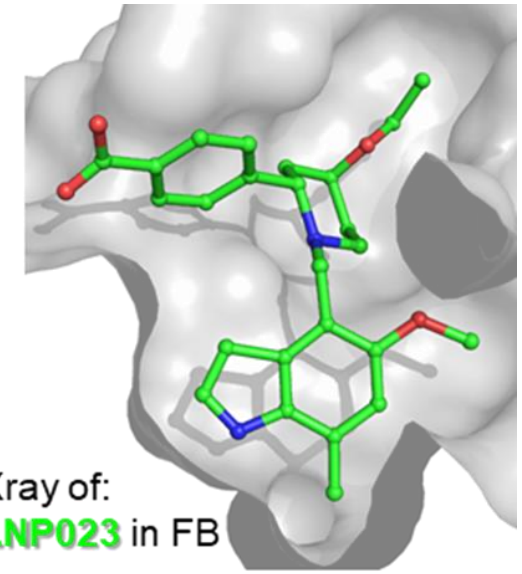

LNP023: a novel oral complement alternative pathway factor B inhibitor for the treatment of glomerular disease

Webb NJA, Haraldsson B, Schubart A, Milojevic J, End P, Holbro T, Junge G

EDTA-ERA 2020 meeting | 8-Jun-2020

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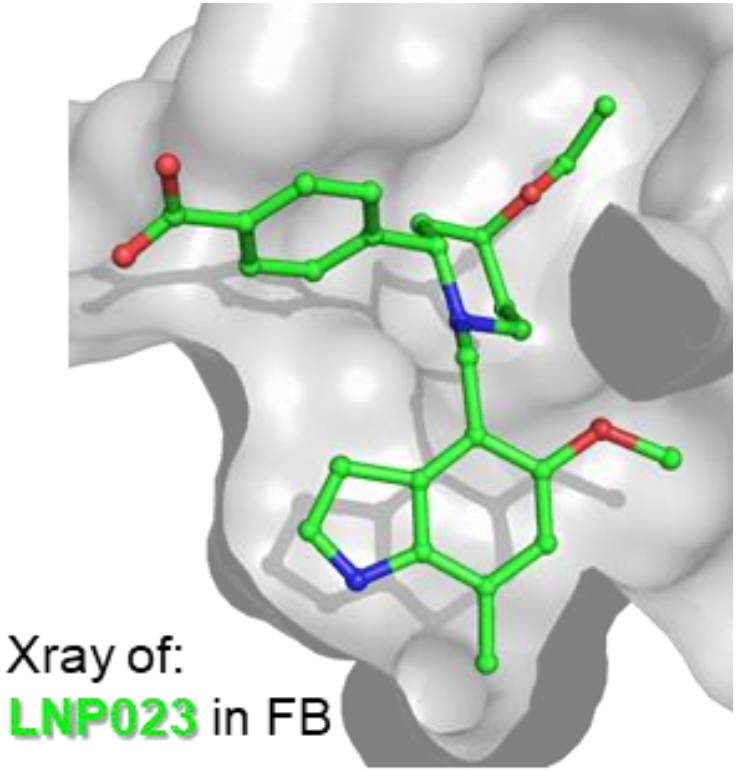
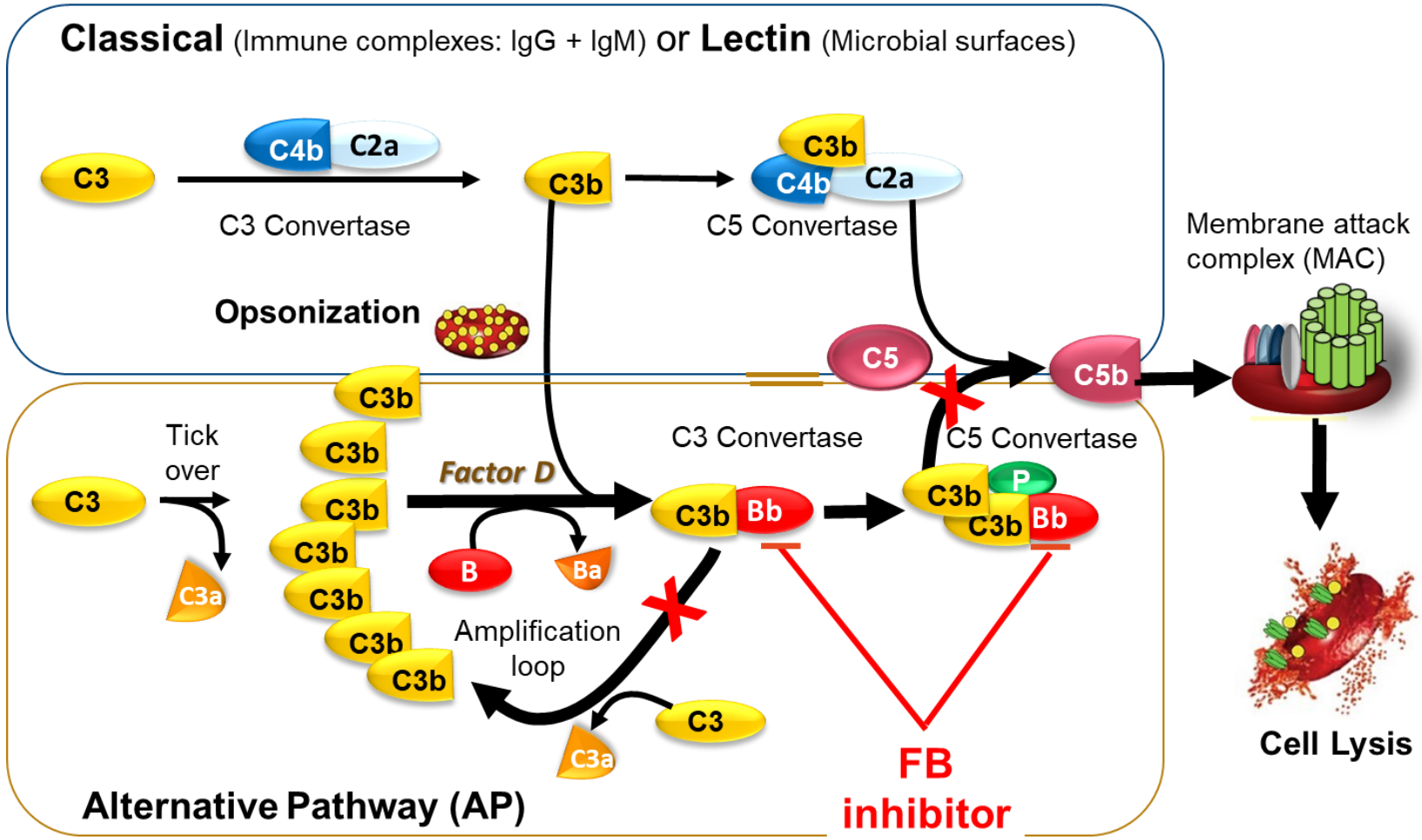
Disclosures

- Authors are Novartis employees
- All studies to be discussed are funded by Novartis
- The investigational use of LNP023 for the treatment of IgA nephropathy, C3 glomerulopathy and idiopathic membranous nephropathy will be discussed

LNP023: oral low molecular weight Factor B inhibitor





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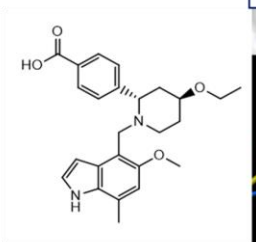
LNP023: oral low molecular weight Factor B inhibitor

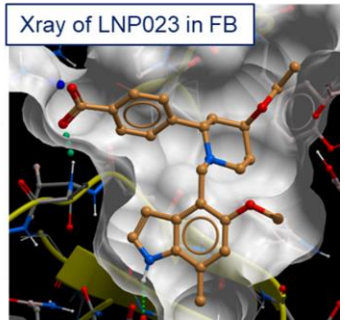
- Potent and selective FB inhibitor that inhibits ex vivo stimulated Membrane Attack Complex (MAC) formation in serum and whole blood
- Inhibits C3 deposition and hemolysis of PNH-like erythrocytes
- Dose dependent and sustained inhibition of AP activation and activation-dependent products (Ba, C3d) in vivo (mouse LPS)
- No safety flags in vitro identified to date
- Good solubility and no food effect
- BCS type I/III (high solubility / moderate permeability), low Q+ developability risk
- Good DDI profile with no/minimal inhibition of CYP & uptake transporters
- PK profile allows for complete AP inhibition in a bid and potentially qd dosing regimen

LNP023 $IC_{50/90}$

	LNP023
Human FB IC_{50} ng/mL	4
Human MAC formation $IC_{50/90}$ 50% serum, ng/mL	52 / 190
Hemolysis of human PNH-like erythrocytes $IC_{50/90}$ 95% serum, ng/mL	50 / 340
Mouse MAC formation $IC_{50/90}$ 50% serum, ng/mL	50 / 150
Mouse LPS model $EC_{50/90}$ ng/mL	240 / 470

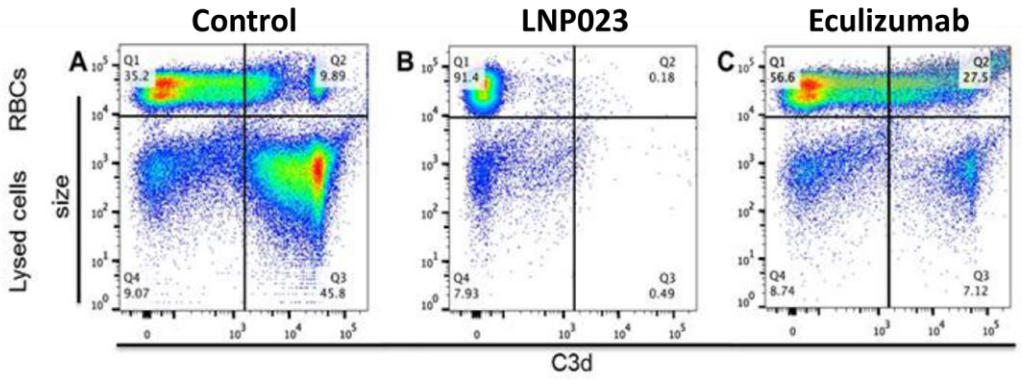
LNP023 Structure





Pharmacodynamics

LNP023 blocks complement-induced hemolysis and C3d opsonization (whereas eculizumab only does the former)



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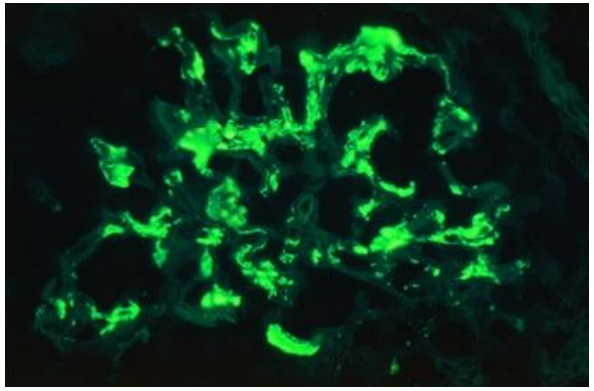
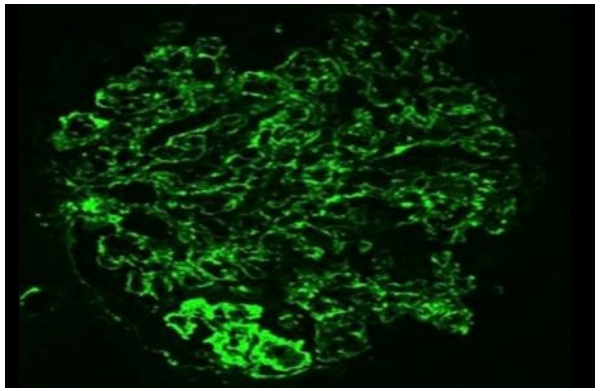
Scientific evidence supports role of alternative complement pathway in targeted renal diseases



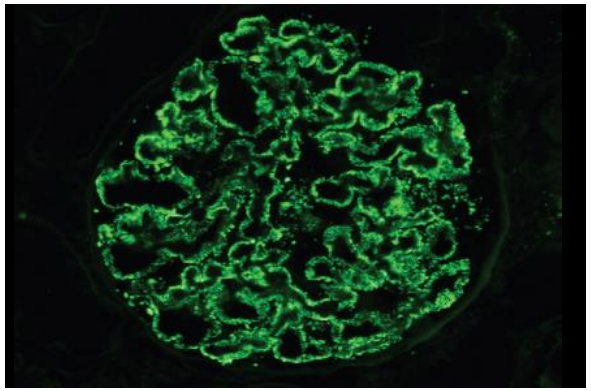
IgA Nephropathy

- GWAS data: CFHR1/3 gene deletions are protective
- Kidney biopsies stain positive for AP (not CP, less often LP)
- Patients have increased levels of serum C3 fragments and FD



C3 Glomerulopathy

- Some patients with loss/gain of function in AP genes (e.g., FH)
- Some patients with auto-Abs leading to AP activation
- Kidney biopsies stain positive for AP (not CP, not LP)



Membranous Nephropathy

- Kidney biopsies stain positive for AP and LP (no CP)
- Patients have increased levels of serum FD
- Some patients have elevated C5b9 and C3dg in urine

Abbr.: A/C/LP = Alternative/Classical/Lectin (complement) Pathway; FD/H = Factor D/H; GWAS = Genome-Wide Association Study

LNP023 First in Human Study: EudraCT no. 2015-005567-16

Primary Objective

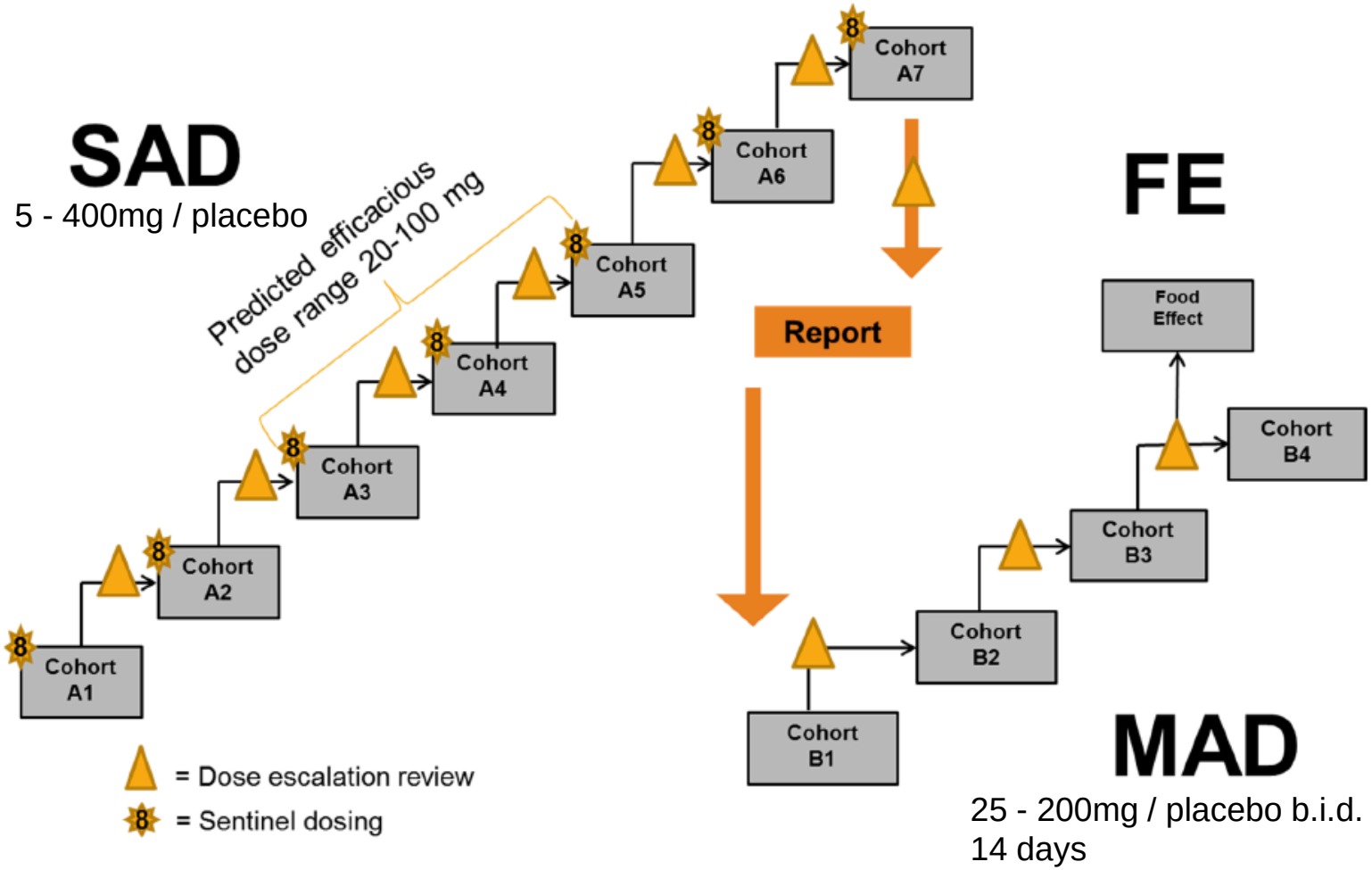
- Safety and tolerability of LNP023
- Maximum tolerated dose of LNP023 after single oral doses

Key Secondary Objectives

- PK of ascending single and multiple oral doses of LNP023
- PK of single LNP023 dose under fed and fasted conditions

Exploratory Objectives soluble biomarkers

- PK/PD relationship between LNP023 systemic exposure and selected PD markers
- Effect of single or multiple doses of LNP023 on complement pathway components as potential PD / MoA markers



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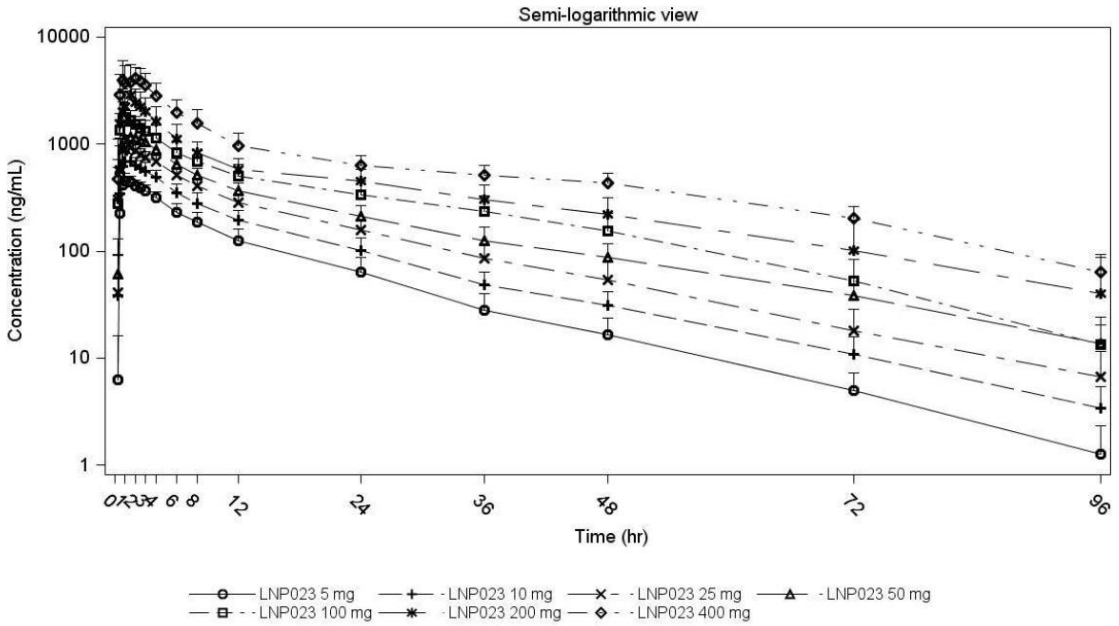
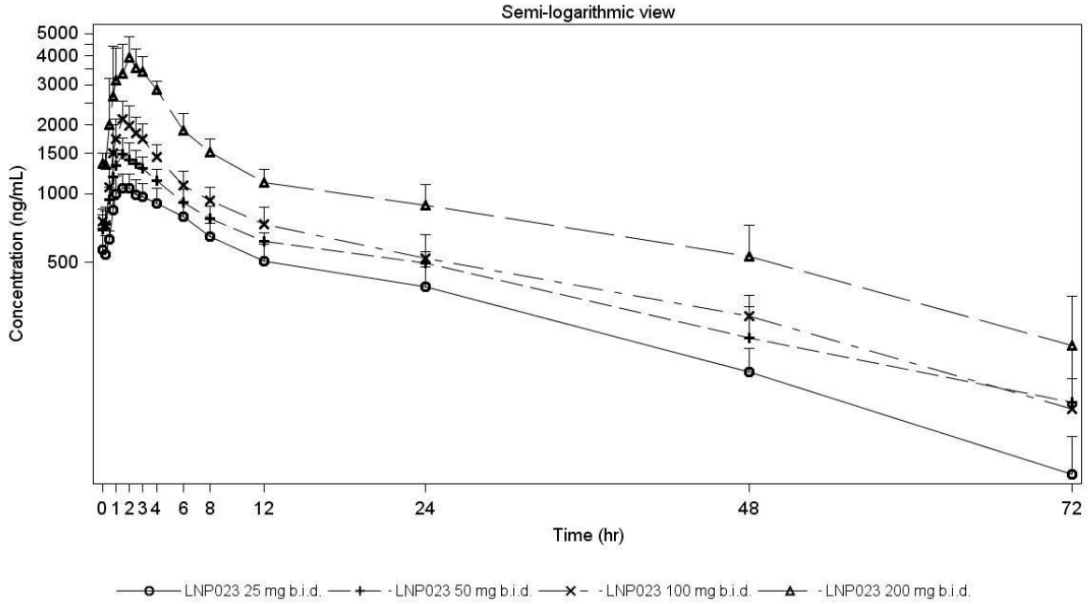
Pharmacokinetic profiles of LNP023 after single oral and multiple dose administration

Arithmetic means of PK profiles from single ascending doses of 5 to 400 mg (qd)



Arithmetic means of PK profiles from multiple ascending doses of 25 to 200 mg (bid)



Calculated half-lives amounts to ~20 hrs across doses

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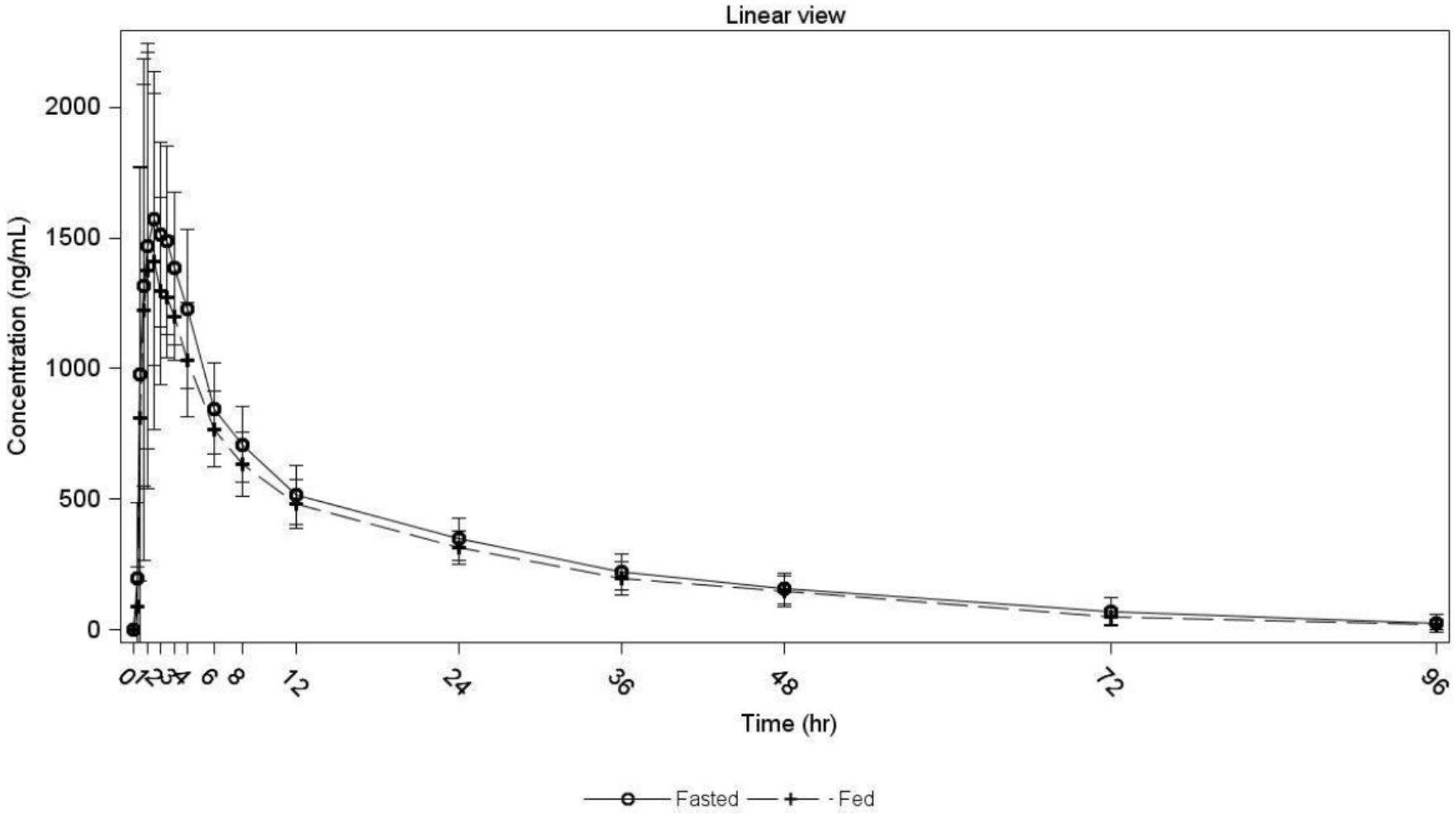
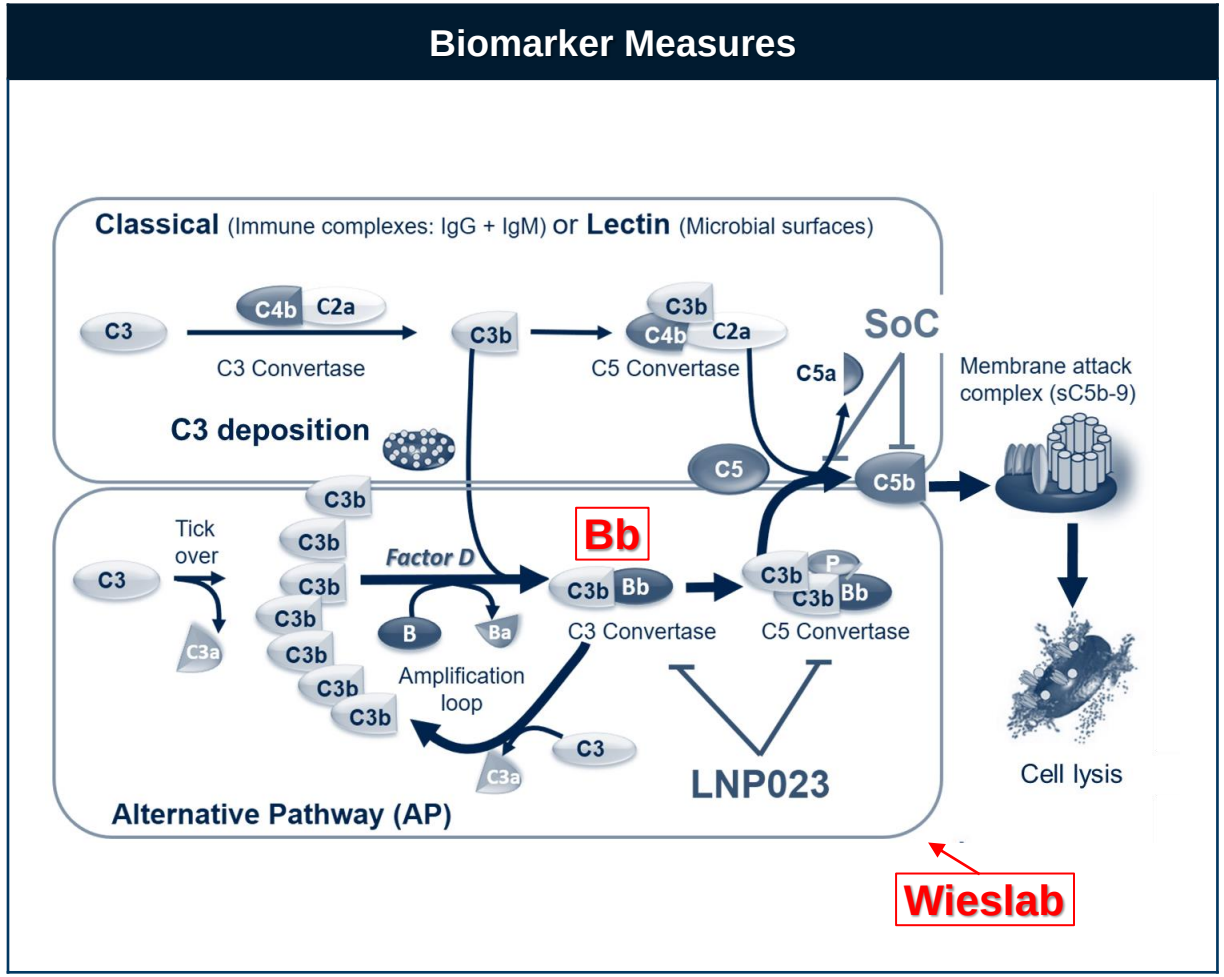
Pharmacokinetic profiles of LNP023 after a single dose of 100 mg at fasted versus fed condition



Safety results

- Overall, no deaths, SAE, or AE leading to study drug discontinuation observed in subjects treated with LNP023
- AE incidence rates and AE profiles were generally similar in the total LNP023 and placebo groups
  - SAD: 14.3% LNP023 vs. 14.3% placebo
  - MAD: 62.5% LNP023 vs. 62.5% placebo
- Across LNP023 treatment arms, no meaningful dose-effect pattern for AE could be identified

Biomarker measures

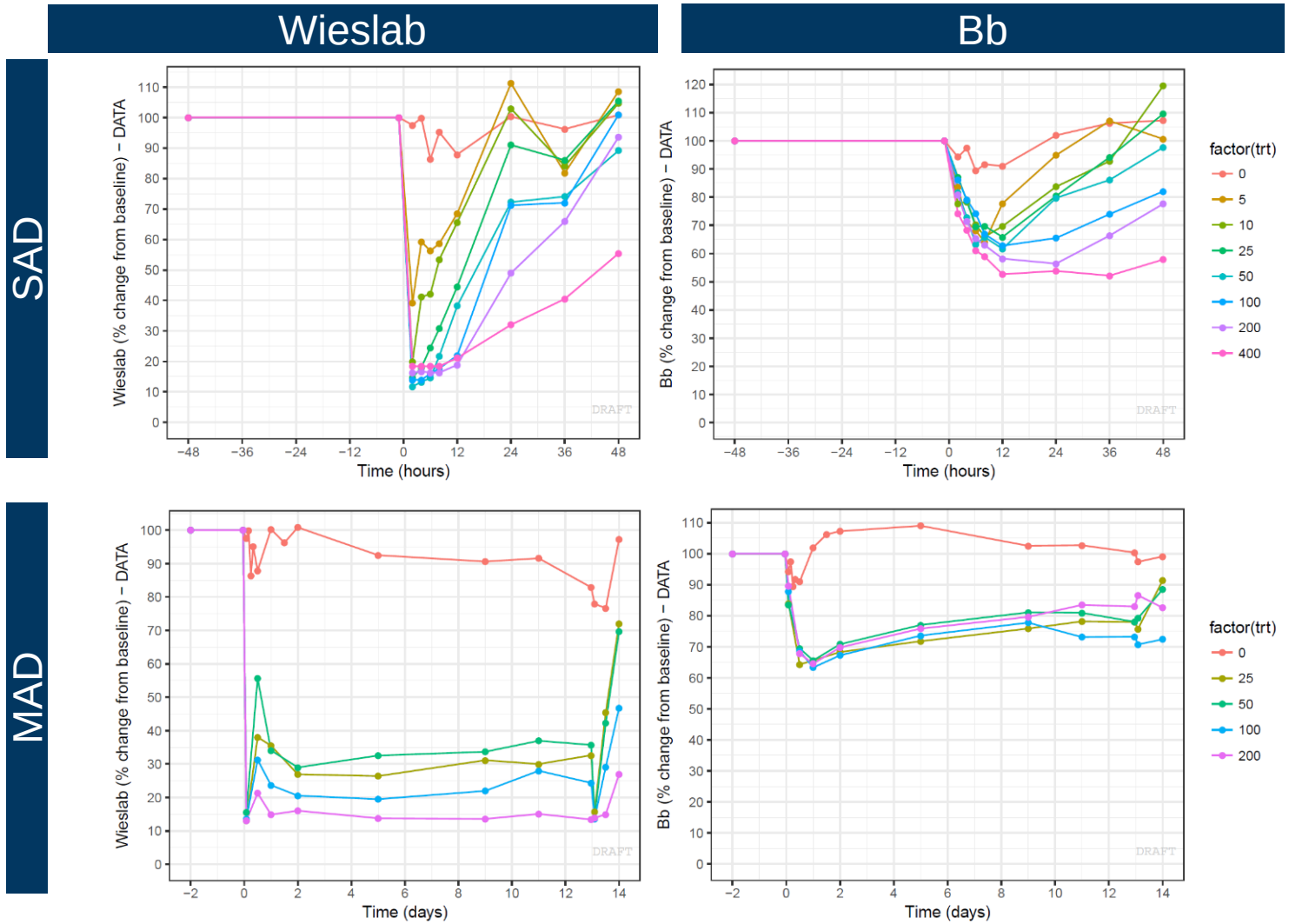


Complement alternative pathway

- **Wieslab**® is an assay measuring the functional alternative complement pathway activation upon *ex vivo* stimulation.

- Alternative pathway complement activation generates the active complement breakdown fragment **Bb**.

Dose-dependent inhibition of complement alternative pathway



Error bars omitted for clarity.

Single ascending dose:

- Maximal inhibition 2h post-dose
- > 80% Wieslab inhibition achieved at 10 mg dose or higher
- 30 – 50% reduction of circulating Bb levels (5 mg dose or higher)
- Dose-dependent duration of inhibition

Multiple ascending dose:

- Persistent pathway inhibition
- Dose-dependent magnitude of inhibition based on Wieslab (but not Bb)
- >80% of maximal inhibition achieved between 25 mg (based on Bb) to 100 mg bid (based on Wieslab)

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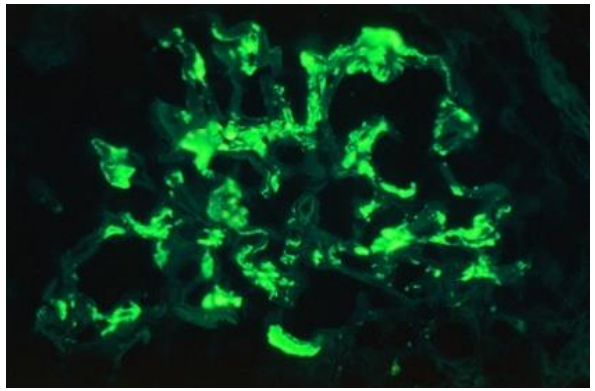
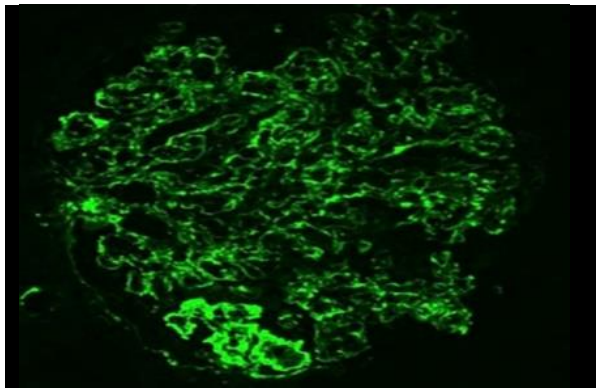
Clinical trials of LNP023 in renal disease associated with complement dysregulation

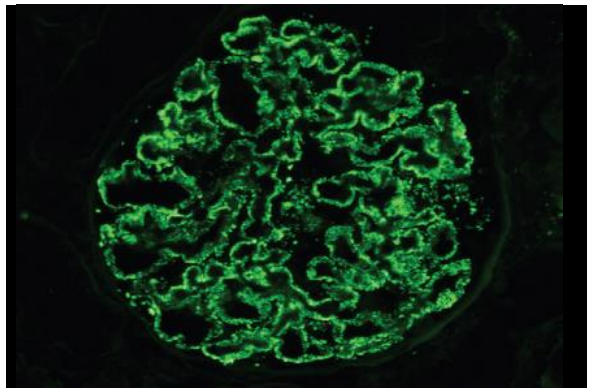
IgA nephropathy



C3 glomerulopathy



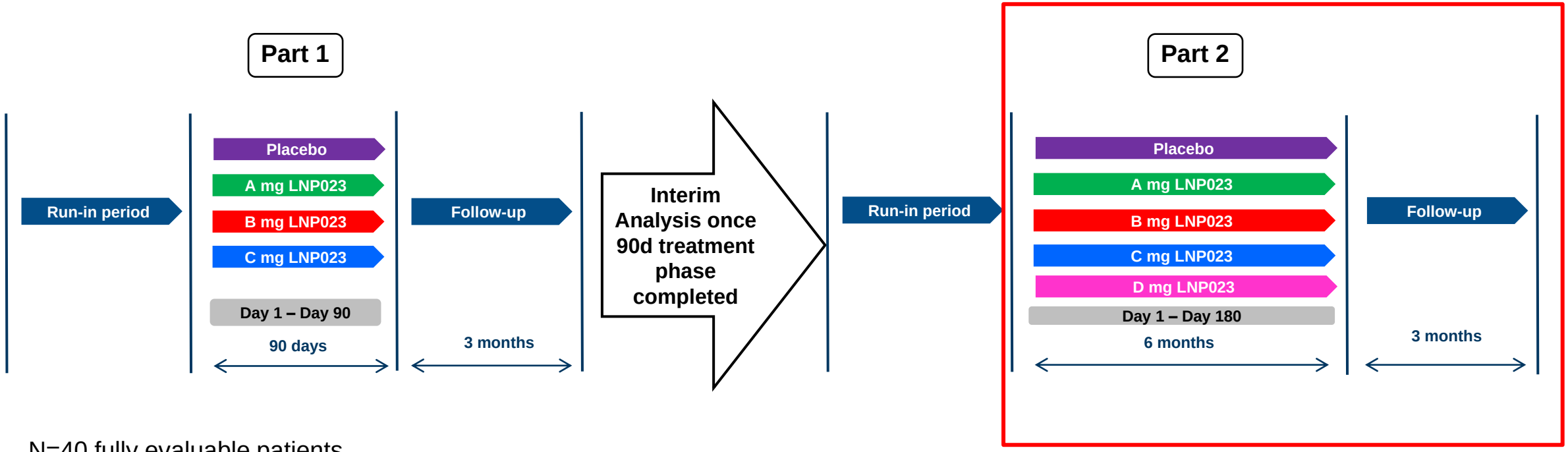
Membranous nephropathy



CLNP023X2203: IgA nephropathy

ClinicalTrials.gov Identifier NCT03373461

Independent DMC approved



N=40 fully evaluable patients

Primary EP: Dose response relationship of LNP023 on the reduction in proteinuria versus placebo after 90 days of treatment

Biopsy proven IgAN, eGFR ≥30ml/min/1.73m^2, Proteinuria ≥0.75g/24h, max tolerated ACE/ARB

Decision to proceed to Part 2 study (lack of futility), sample size and choice of doses determined by interim analysis

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Safety: Serious adverse events by preferred term

- No deaths
- No treatment discontinuations due to SAEs
- 5 patients (10.9%) had a total of 6 SAEs: only one was treatment-emergent

Serious Adverse Event	Number
Screening period	
IgA nephropathy	1
Localised infection	1
Inflammatory reaction	1
Treatment period	
Respiratory fume inhalation disorder	1
Follow-up period	
Influenza (45d post last dose)	1
IgA nephropathy (85d post last dose)	1

Localised infection and respiratory fume inhalation disorder occurred in same patient

Preferred term ‘IgA nephropathy’ refers to flare of native disease following infection with rise in proteinuria and / or deterioration in renal function

No cases of proven bacterial infection

CLNP023X2202: C3 glomerulopathy

ClinicalTrials.gov Identifier NCT03832114

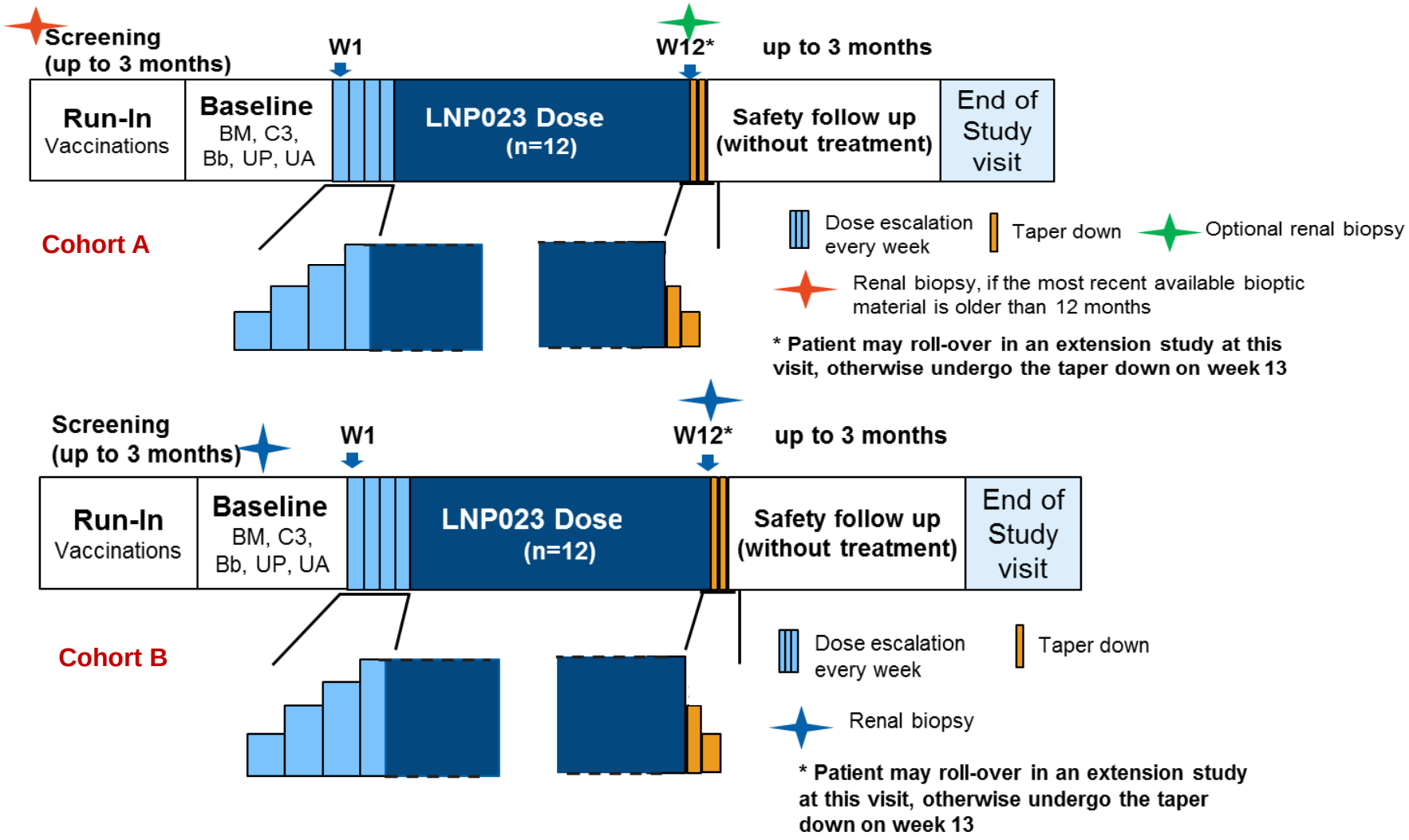
Key inclusion criteria

- Biopsy-proven C3G
- eGFR ≥30 mL/min/1.73m2
- Max ACEi or ARB
- Proteinuria ≥1 g/24h or UPCR >100mg/mmol
- Vaccinated total urinary protein excretion from 24h collection during run-in period
- Stable immunosuppression and no acute rejection for Tx patients

Primary objectives

Cohort A: To evaluate reduction in proteinuria at 12w compared with baseline

Cohort B: To assess histopathological changes (C3 deposit score) at 12w compared with baseline



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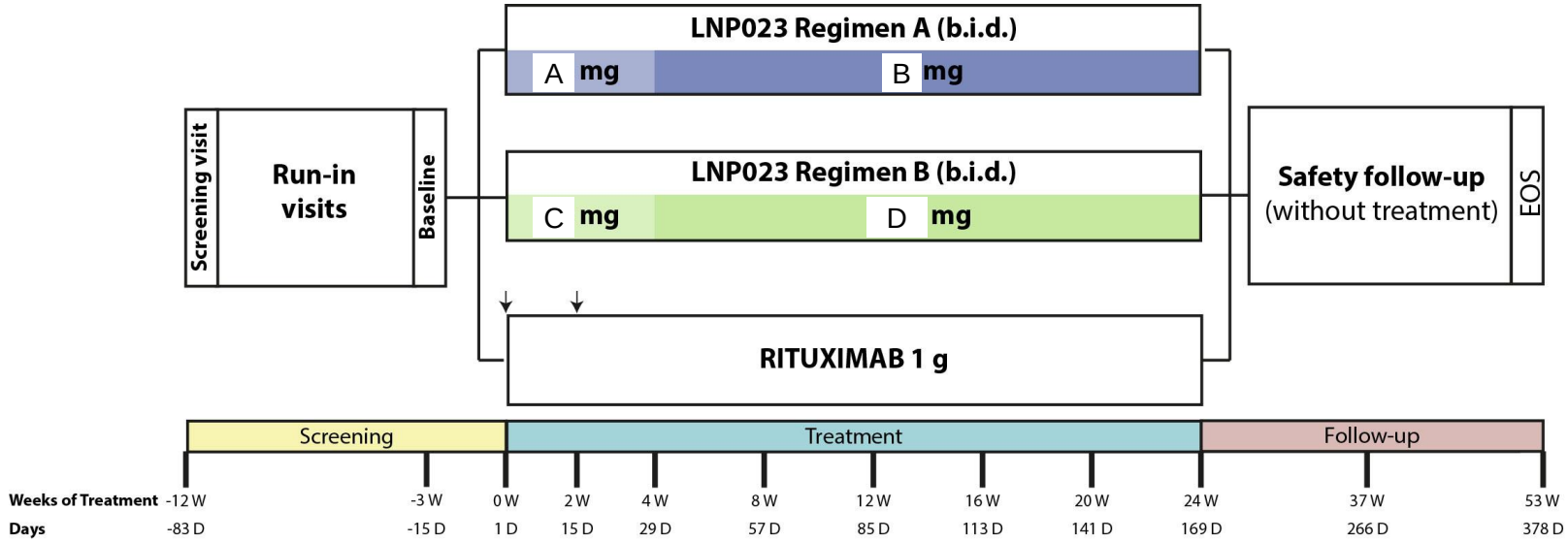
CLNP023D12201: Membranous nephropathy

ClinicalTrials.gov Identifier NCT04154787



- **Inclusion criteria:**
  - Biopsy-proven PLA2R positive membranous nephropathy diagnosed in past 24m
  - eGFR >40 ml/min
  - proteinuria >3.5g/24h
  - Anti-PLA2R ab >100u/ml
  - Stable maximally tolerated diuretic, ACEi, ARB and adequate BP control
  - Vaccinated

- **Primary endpoint:**
  - Ratio to baseline of UPCR from 24h collection at 6m
- **Secondary endpoints:**
  - Complete remission, Partial remission,
  - ΔGFR at end of study, PK, safety

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Summary

- LNP023 first in human studies showed benign safety profile
- PK studies demonstrated rapid drug absorption with no food effect
- LNP023 terminal drug half-life is around 20h. Only 20% of clearance is renal
- Biomarker studies (Wieslab and Bb) demonstrated dose-dependent inhibition of complement alternative pathway
- Ongoing clinical studies of LNP023 in IgAN, C3G, MN and PNH
  - IgAN Part 1 study has confirmed excellent patient safety. Based on efficacy and safety, independent DMC has approved progression to Part 2 study
  - Full read-outs of all three studies expected in 2020-2021. All include dose finding elements to enable direct transition to Phase 3