

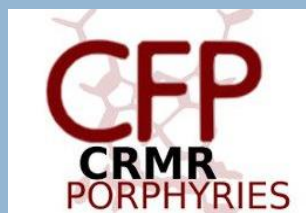
# GIVOSIRAN IN ACUTE INTERMITTENT PORPHYRIA

ASSEMBLÉE GÉNÉRALE G2M

31/03/2023



Antoine Poli



# CONFLICT OF INTEREST

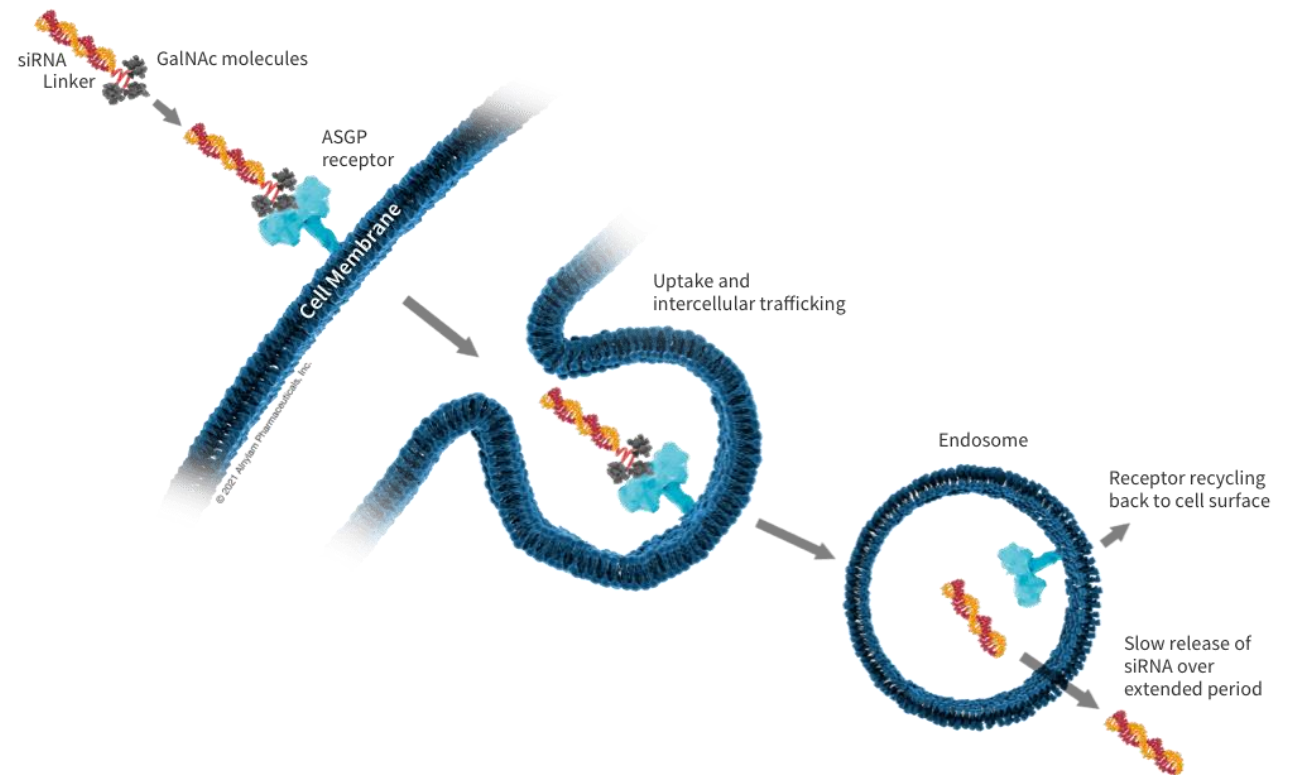
- None

# ACUTE INTERMITTENT PORPHYRIA (AIP)

- PBGD deficiency, third enzyme of heme biosynthesis pathway
- Autosomal dominant, low penetrance
- Accumulation of heme precursors, ALA and PBG, triggered by precipitating factors (alcohol, fasting, infections, medications, menstrual cycle...)
- Attack: severe and long lasting abdominal pain + other digestive symptoms + possible neurological involvement
- Recurring attacks in less than 5% of patients

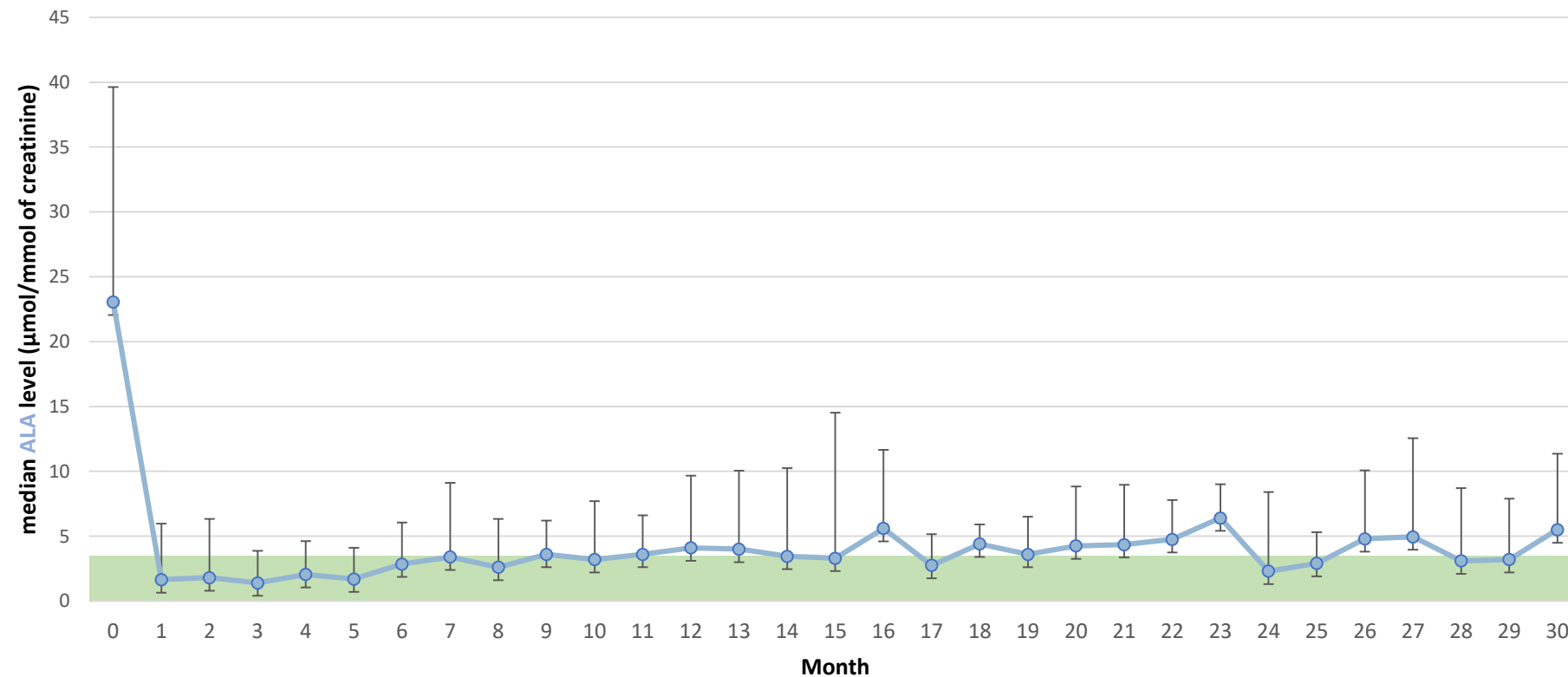
# GIVOSIRAN

- siRNA targeting ALAS1 mRNA, first enzyme of heme biosynthesis pathway in the liver
- Reduced ALAS1 activity
- Decrease in ALA and PBG levels



# MEDIAN LEVELS OF URINARY DELTA-AMINOLEVULINIC ACID

Median percent reduction in ALA level = 89.9%



Median levels of urinary delta-aminolevulinic acid (ALA). Bars indicate the interquartile range. Green area indicates ALA normal range (0 to 3  $\mu\text{mol}/\text{mmol}$  of creatinine)

# CLINICAL EFFECTIVENESS

- Major clinical effectiveness: 96% of the patients were attack-free at the time of the study
- Patients with a profound and stable decrease in ALA level (and no acute symptoms) : 10/24 (42%)
- Patients with moderate and/or unstable decrease in ALA level (and no acute symptoms) : 14/24 (58%)
- Mean time since disease onset between patients on follow-up and patients treated every three months or more frequently 6.7 years vs. 19.6 years,  $p=0.0009$

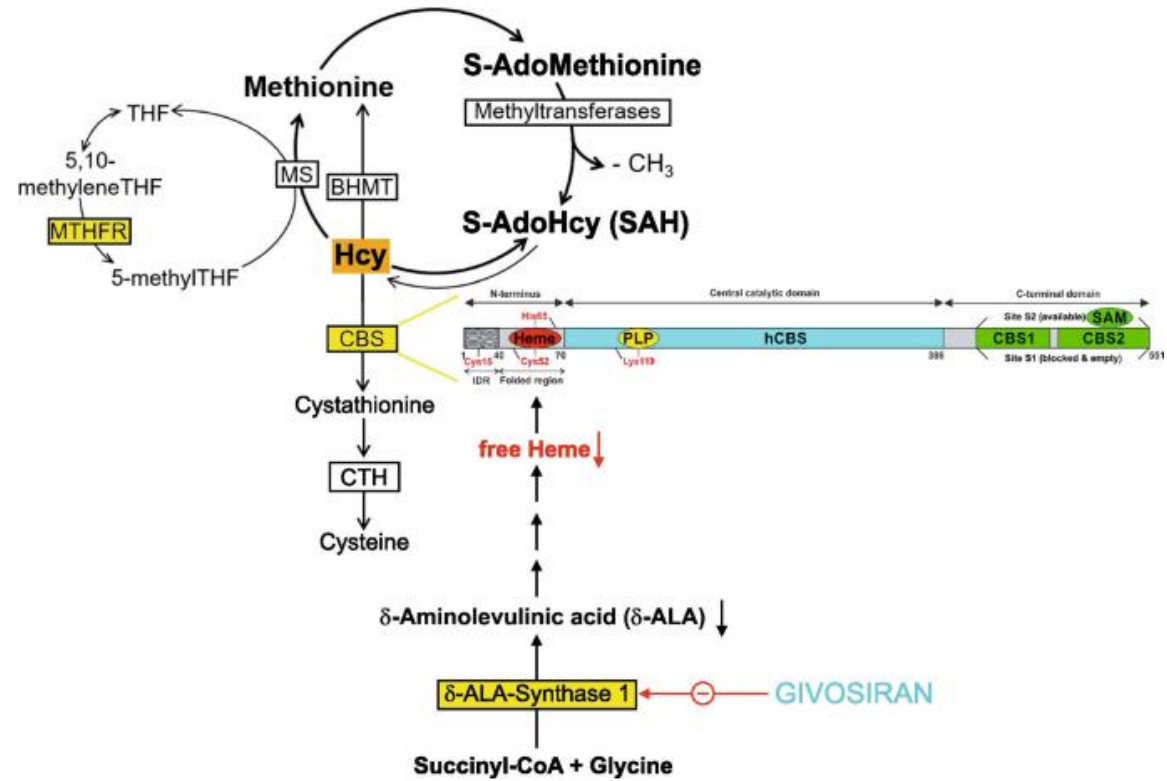
➡ Givosiran was more effective if given early in the disease course

# ADVERSE EVENTS

	no. of patients	%
Any adverse event	25/25	100
Serious adverse event	6/25	24
Any adverse event leading to treatment discontinuation	1/25	4
Acute pancreatitis	1/25	4
Pulmonary embolism	1/25	4
Nausea	10/25	40
Fatigue	17/25	68
Myoclonus/tremors	3/25	12
Injection site reaction/rash	6/25	24
Increased hair loss and/or spontaneous nail loss	6/25	24
Hyperhomocysteinemia	23/23	100
Increased ALT	8/25	32
Increased lipase level	5/25	20
Decreased eGFR	2/22	9
Transient increase in serum creatinine	20/22	91

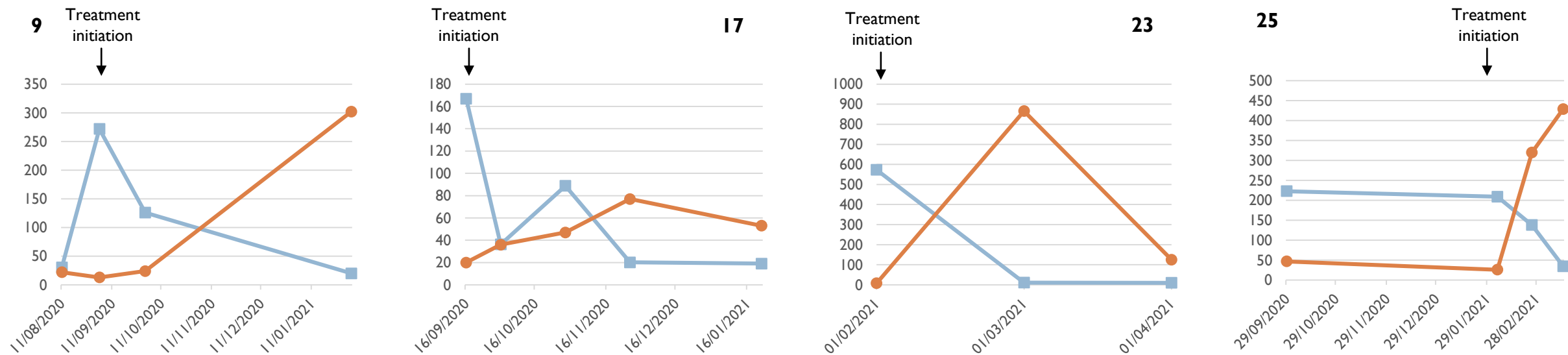
ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate.

# HYPERHOMOCYSTEINEMIA



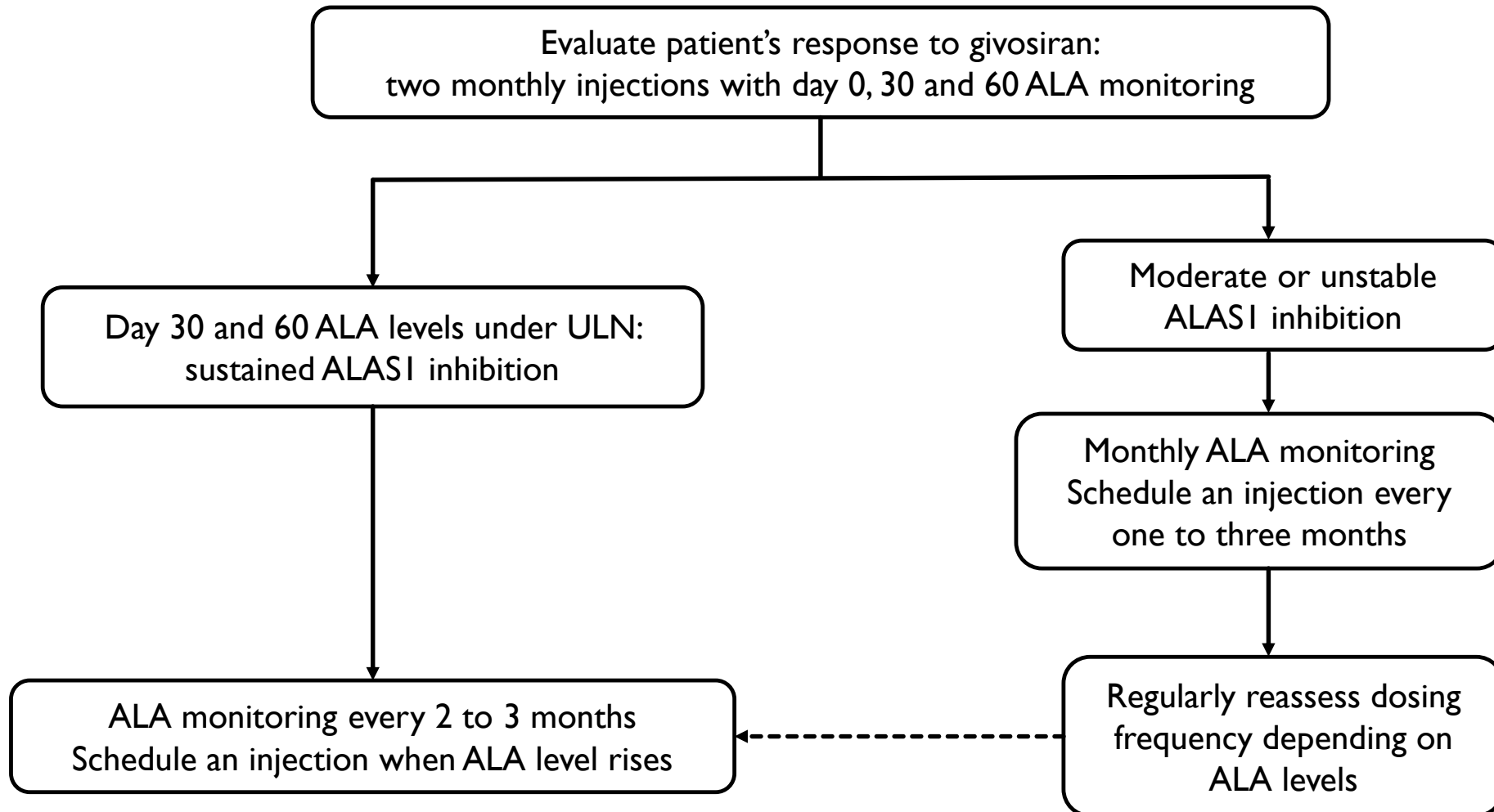


# B6 TREATMENT & HOMOCYSTEINE

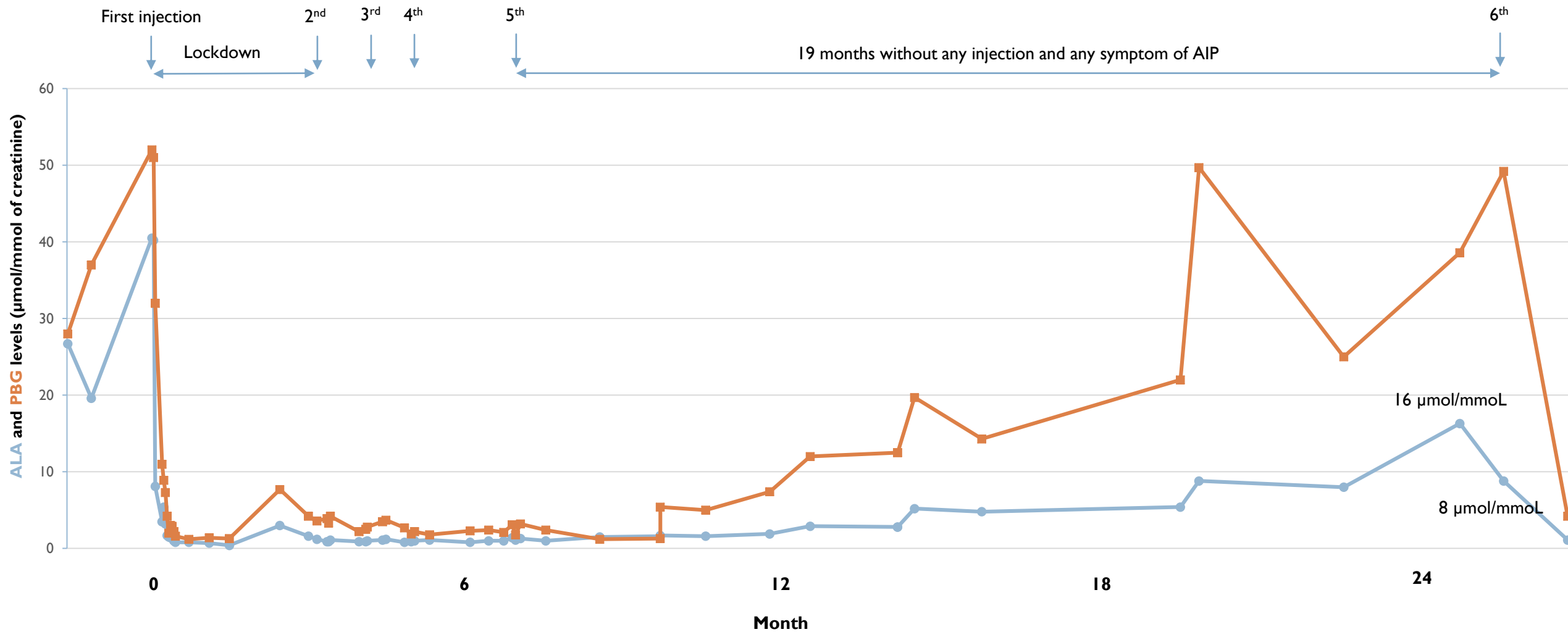


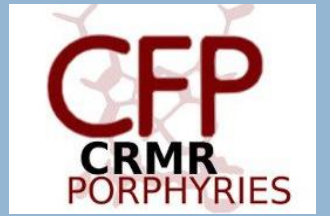
Hcy (µmol/L, blue squares) and B6 (nmol/L, orange dots) levels in patients 9, 17, 23 and 25, treated with vitamin B6 250 mg each day. Arrows indicate vitamin B6 treatment initiation.

# PATIENTS' TREATMENT AND MONITORING ALGORITHM: TOWARDS A PERSONALIZED MEDICINE APPROACH



# LONG-TERM OUTCOME





***Medical staff***

- **Laurent Gouya**
- **Hervé Puy**
- **Caroline Schmitt**
- **Thibaud Lefebvre**
- **Neila Talbi**
- **Boualem Moulouel**
- **Jean-Charles Deybach**
- **Antoine Poli**

***Genetic counselor***

- **Arienne Mirmiran**

***Laboratory technicians***

- **Andrea Araujo**
- **Corinne Culerier**
- **Lorena Chappuis**
- **Nathalie Dessendier**
- **Catherine Guesdon**

***Secretaries***

- **Laurence Champroux Beaufiles**
- **Valérie Monie-Joyes**

***Research team***

- **Valeria Fiorentino**
- **Hana Manceau**
- **Gaël Nicolas**
- **Katell Peoc'h**

***Molecular biology laboratory***

- **Jérôme Lamoril**
- **Dimitri Tchernitchko**