Value of French early access framework for the health technology assessment in the rare disease space: the example of lanadelumab in patients with hereditary angiœdema

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INTRODUCTION

- **Hereditary angiœdema** (HAE) is a rare, severe, disabling, life-threatening genetic disorder (prevalence ~1/50,000), characterized by occurrence of transient, recurrent subcutaneous/submucosal edema.
- The therapeutic arsenal is based on the **on-demand** treatment of **HAE attacks,** or on the prevention of HAE attacks with a **short-term or long-term prophylaxis (STP/LTP),** including lanadelumab for the latter indication. Lanadelumab, authorized in Europe (Nov. 22, 2018), benefited in France from a nominative Authorization for Temporary Use (ATU) and then from a cohort ATU started on Oct. 8, 2018. Lanadelumab was assessed by the French health technology assessment body, Haute Autorité de Santé (HAS), in 2019. HAS opinions mentioned the need for additional data generation to complement clinical and economical value demonstration:


HAS
HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE
Avis
5 juin 2019

Date d'examen par la Commission : 17 avril 2019

L'avis de la commission de la Transparence adopté le 15 mai 2019 a fait l'objet d'une audition le 5 juin 2019.

lanadelumab

TAKHZYRO 300 mg, solution injectable
B/1 CIP : 34009 301 593 9 (1)

Laboratoire SHIRE FRANCE

Code ATC	B06AC08 (Autres médicaments utilisés dans l'angio-œdème héréditaire)
Motif de l'examen	**Inscription**
Liste concernée	**Collectivités** (CSP, L.5123-2)
Indication concernée	« TAKHZYRO est indiqué pour la prévention des crises récurrentes d'angio-œdème héréditaire (AOH) chez les patients âgés de 12 ans et plus. »

Avis favorable à la prise en charge dans l'indication dans un périmètre restreint

Transparency Opinion – June 5, 2019 (1)

- Expected impact in terms of morbidity
- QoL results of limited scope due to their exploratory nature in clinical trials
- Expected impact on organization of care and on patient's pathway, given the drug's administration route with the possibility of self-injection, despite the absence of data allowing it to be quantified
- Lack of data to estimate the number of patients in the indication

Efficiency Opinion – October 15, 2019 (2)

Studies, including real-world data, are expected to:

- Validate the model's estimate of the number and severity of attacks under lanadelumab
- Corroborate, under real conditions of use, the assumptions that generate the greatest uncertainty,
- Illustrate the actual conditions for dose adjustment


HAS
HAUTE AUTORITÉ DE SANTÉ

AVIS D'EFFICIENCE

TAKHZYRO® (lanadelumab)
Shire France

Date de validation par la CEESP : 15 octobre 2019

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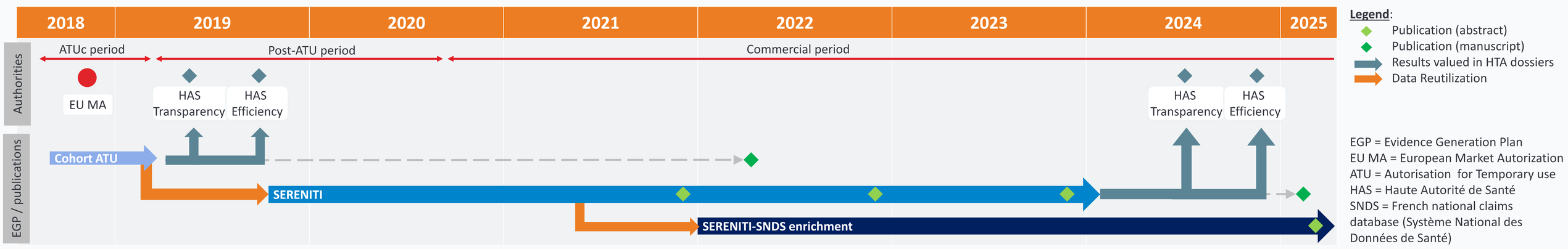
➔ The small number of eligible patients represents a challenge for the development of a conventional Evidence Generation Plan (EGP).

METHOD

- **French Early Access framework** provides a unique opportunity to allow early access of French patients to therapeutic innovations and to collect early real world data to support value demonstration
- **French national claims database SNDS** (Système National des Données de Santé) provides access to unique population-wide, life-time heathcare resource use (HCRU)/cost data, possibly linkable to clinical databases
- An **optimized EGP**, leveraging these components, was built and is evaluated by the number of participants (centers, patients) throughout the enrichment, the execution schedule and the valorization of the results. Success factors and difficulties encountered were discussed.

	Cohort ATU	SERENITI	SERENITI-SNDS enrichment
Design	National multicentre longitudinal cohort (France)	National, multicenter, longitudinal cohort (France)	National, multicenter, longitudinal cohort (France)
Patients	HAE patients included from October 2018 to March 2019	HAE patients from ATU, post-ATU, and post-launch	HAE patients followed from September 2015 to December 2019
Studied treatment	**Initation of lanadelumab after a previous LTP failure**	**Initiation of lanadelumab**	**Initation with lanadelumab**
Comparator	-	-	Patients not treated with lanadelumab during the study period
Outcome	N/A – Descriptive follow-up as part of routine care	Real-World Use, Efficacy, Tolerability and QoL	HCRU, costs
Data Collection	Prospective – follow-up = 6 to 12 months	Ambispective – follow-up = 18 to 50 months	Retrospective – follow-up = up to 50 months

RESULTS



Step 1: Cohort ATU:

- Provided rapid access to treatment (1st in Europe) for **78 French patients**, enrolled within 5 months (Figure 1)
- Provided real-life data on use, efficacy and safety (interim analysis) for HAS initial reviews in 35 patients (16 centers), confirming short-term favorable impact of treatment on attacks reduction in a large sample of French patients, and therefore supporting appraisals (clinical and economical). Effectiveness and safety **results were fully cited in the Transparency opinion**.
- Additional value: Data from early treated French patients could contribute to a multicountry, European chart review study (INTEGRATED), allowing **comparisons between patients from Germany, Austria, Greece, France**.

Step 2: SERENITI study:

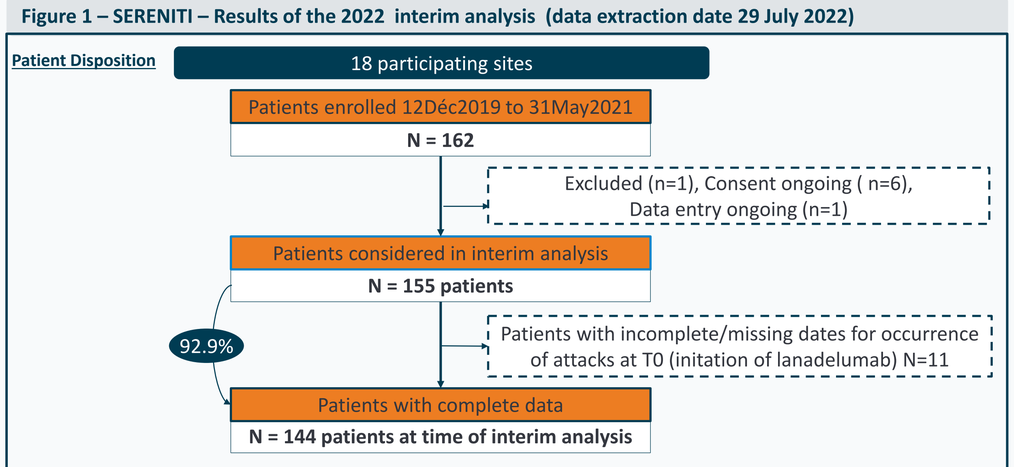
- Data already collected on 62 ATU patients were **enriched with additional follow-up and completed with new patients** initiated during the post-ATU and early commercial periods. A total of 162 patients were enrolled from October 2018 to May 2021 and followed from 18 to 50 months.
- First interim analyses suggest confirmation of the long-term impact of treatment on maintenance of attacks reduction. (Figure 1)

Step 3: SERENITI-SNDS enrichment study (probabilistic linkage):

- **Linkage between clinical and claim data authorised in 5 months** by the external scientific committee (CESREES) in charge of approving access to the SNDS, and by the French Data Privacy body (CNIL).
- **All French patients with identifiable HAE** (managed by a specific HAE treatment) will be extracted from SNDS, **all patients treated with lanadelumab** over the first 4 years of availability (December ≤, 2022) and will **link the 162 SERENITI patients**.

The EGP will help to complete the demonstration of lanadelumab value within the timeframe typically desired by HAS and already resulted in various **scientific publications** including HAS opinions from June 2019 to December 2023 (1,2) and a manuscript for cohort ATU(3). **Data supported HTA/Access process in various countries across the world**.

Figure 1 – SERENITI – Results of the 2022 interim analysis (data extraction date 29 July 2022)



Impact on the average number of attacks/month	n	At initiation of lanadelumab (T0)	At date of interim analysis	P-Value **
Duration of exposure (months), median [Min; Max]	144	-	24,0 [0; 40,2]	
Average number of attacks/month – period 0-6 months	122*	**2.01 ± 1.9**	**0.13 ± 0.4**	<0.001
Average number of attacks/month – period 0-12 months	102*	**2.06 ± 1.9**	**0.10 ± 0.2**	<0.001

** Number of patients with follow-up available; ** Before-After Comparison: P-value (paired Wilcoxon test)*

KEY ACHIEVEMENTS

- France = **1st European country giving access to lanadelumab for patients**, thanks to its Early Access regulatory framework for innovative drugs
- **1st effectiveness data available in Europe**, reused for access worldwide, positioning France as a key player in the field of RWE generation
- **Continuum concept**: Progressive data enrichment to address HTA requests.
- **"Reusing the existing"** = Limitation of the data entry burden for physicians
- Acceleration: recruitment (patients already identified), data already entered and checked
- **Exhaustivity** of SNDS data (patient populations, HRU) linked with clinical data

KEY SUCCESS FACTORS

- Information/education of all partners on the early derogatory access framework
- **Quality** of data collection
- **Collaborative continuum** :
  - With Scientific Committee and investigators - essential to maintain quality
  - With HAS (use of disease –specific effectiveness and QoL measures, project progress and alignment of the assessment calendar)
  - Collaboration among teams (medical, access, regulatory, supply, CRO)

HURDLES / ISSUES

- **Timelines**: short for the ATU and long for the extraction of SNDS data
- Maintenance of **continuity of data collection** between each derogatory access period.
- Anticipation of **patient information**
- Modification of indication at each stage of the access process (ATU, post-ATU, post-launch)
- Risk related to probabilistic linkage

CONCLUSION

- RWE generation is a long and challenging process, especially in rare diseases where patients are few, clinicians are asking for simplified data collection methods, and health authorities are asking for reliable and relevant data to motivate/confirm their decisions.
- An EGP, as a continuum based on the progressive enrichment in patients numbers and follow-up duration of an early access program and maximizing the "re-use of the existing", is possible with high levels of performance (scientific, operational) and acceptability by the health authorities, even if simplification efforts and efficiency gains remain to be found.
- Leveraging French unique resources (early access framework, SNDS database, possible linkage procedures) also provides added value for other countries across the world and positions France as a key partner for early RWE generation programs.

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Disclosures

- N.Schmidely, Dr C. Chatelanaz, C. Strub, Dr T. Marquet and Dr J. Delonca are employed by Takeda France SAS.
- N.Schmidely, Dr C. Chatelanaz, Dr T. Marquet and Dr J. Delonca own Takeda shares
- C.Train is employed by Clinsearch
- Pr L.Bouillet has links of interest with Takeda, CSL Behring, Biocryst, Blueprint, GSK, Astra Zeneca
- Pr O. Fain is a consultant for Takeda, Biocryst and has received a grant from Biocryst

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