# Thalassemia NEWS 2026

A quarterly newsletter keeping the medical and patient community in touch with thalassemia developments

## IN THIS EDITION



## IN-PROFILE

**An in-depth view of an organization or individual involved in thalassemia**

In this issue, we bring you insights from Prof. Khaled Musallam of the Center for Research on Rare Blood Disorders and Thalassemia & Sickle Cell Center, Burjeel Cancer Institute, Burjeel Medical City, Abu Dhabi, UAE, and Prof. Aurelio Maggio of the Campus of Haematology Franco and Piera Cutino, UOC Ematologia per le Malattie Rare Del Sangue e degli Organi Ematopoietici, Palermo, Italy, on their de-LIGHT (longitudinal investigation of genetic and hematologic determinants of outcomes in β-thalassemia) cohort study collaboration (for more details on recent de-LIGHT publications, see page 2).

### What were the key aims of your collaboration?

We collected standardized clinical data on >500 patients with β-thalassemia, from diagnosis until December 2020. The unique nature of the data was the longitudinal collection of variables over the years from medical records that date back as early as diagnosis - this has allowed us to evaluate the relationship between several laboratory and clinical risk factors and morbidity and mortality outcomes over the patients' lifetime.

### What are the key findings so far?

What we have published to date primarily examines the relationship between hematological parameters and clinical outcomes. This has confirmed that disease severity varies greatly by treatment adequacy, and the effectiveness of anemia and iron control across phenotypes directly correlates with morbidity and mortality.

### What can we look forward to next, for de-LIGHT?

The other major aim of the study is to identify genetic markers that influence disease phenotype, as we have also analyzed genetic samples from around 450 patients included in the cohort.

We hope to be able to identify and stratify genetic signatures by clinical phenotype; this would potentially enable the development of an algorithm to help guide treatment selection, implementing, even in thalassemia, a model of precision medicine crucial for detecting the ideal candidates for innovative treatments.

It will keep us both busy for a number of years!

## KEY DATES

European Hematology Association Congress
Stockholm, June 11-14

Dutch Hemoglobinopathies Symposium
Amsterdam, June 19

24th World Hematology Congress
Berlin, August 10-11

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THA-ALL-0266 May 2026

The longitudinal investigation of genetic and hematologic determinants of outcomes in β-thalassemia (de-LIGHT) was a retrospective cohort study conducted at six participating centers in Italy and Greece. More than 500 patients were followed from diagnosis for a median of 38 years, and this comprehensive, longitudinal dataset was recently interrogated in order to address important knowledge gaps by examining the relationship between anemia and iron with outcomes. Data included in these analyses were from patients with a confirmed diagnosis of a clinically significant form of β-thalassemia, with medical records dating back to diagnosis, and with archived DNA samples[1-3]. This has given rise to the three publications summarized below, with further publications anticipated.

## Relationship Between Lifetime Anemia and Iron Control on Outcomes in β-thalassemia[1]

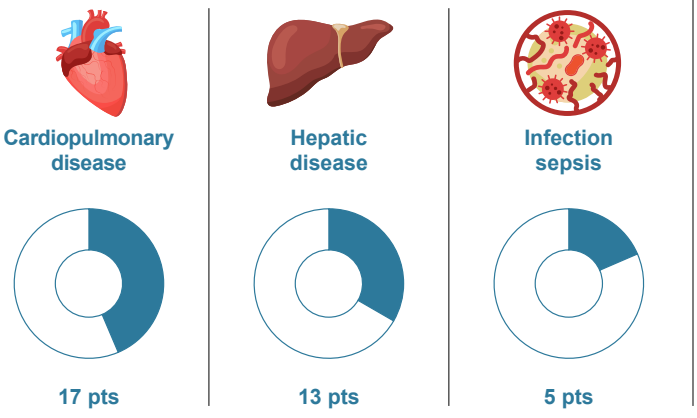
***Objective:*** Evaluate the associations between lifetime anemia and iron control with long-term morbidity and mortality outcomes in β- thalassemia.

Patients were characterized by lifetime exposure to transfusion therapy, calculated as the percentage of time spent on transfusion therapy throughout the observation period. A lifetime anemia and iron control index (LAICI) was also calculated for each patient using the formula (lifetime Hb level/ lifetime ferritin level) x 1000. Study outcomes were mortality and morbidity.

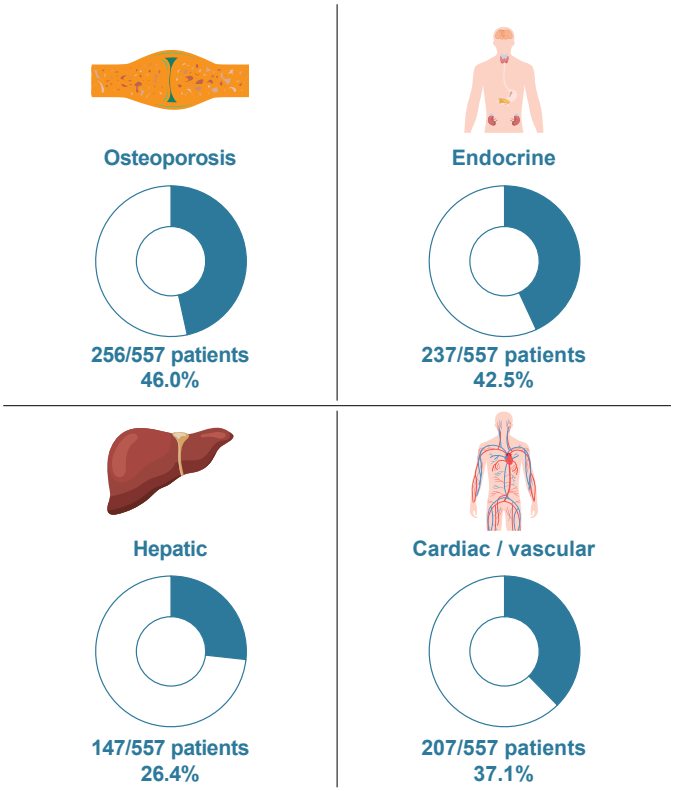
The analysis included data from 557 patients (53.5% female) followed for a median of 38.0 years and with a median age at last follow up of 40.6 years.

- 301/557 patients (54%) were splenectomized at a median of 10.3 years
- 210/557 patients (37.7%) had acquired HCV
- 532/557 patients (95.6%) had received transfusions for all or part of their lifetime, with a median lifetime proportion on transfusion of 95% (IQR: 65–100, range: 0–100)
- Median lifetime Hb level was 9.6 g/dL (IQR: 9.2–9.9, range: 6.5–12.1)
- Median lifetime serum ferritin level was 1150 ng/mL (IQR: 690–1828, range: 16–8000)
- Median LAICI 7.4 (IQR: 5.0–11.5, range: 1.5–513)

The crude incidence of thalassemia-related mortality was 7.0% (95% CI 5.0-9.5), with deaths occurring at a median age of 55.0 years. The most common causes of death were:




75.9% patients (423/557) had at least 1 morbidity, with 308 patients (55.3%) experiencing two or more. The most common morbidities included;




There was a significant association between the lifetime proportion spent on transfusion and thalassemia- related mortality that remained significant when adjusted for confounding factors (adjusted hazard ratios (HR) 0.987, 95% CI 0.977-0.997 for each 1- percent increase in lifetime proportion spent on transfusion, p=0.014). ROC analysis identified a 70% lifetime proportion on transfusion as the best predictor of thalassemia-related mortality (AUC: 0.748, 95% CI 0.661-0.834, p<0.001); the threshold of ≥70% was therefore selected to delineate between TDT vs. NTDT. Using this threshold:

- Cumulative 50-year survival rates were 51% for NTDT vs. 93% for TDT (log-rank test 17.410, p<0.001)
- Adjusted HR for thalassemia-related mortality was 0.224 (95% CI 0.100-0.497, p<0.001) for TDT vs. NTDT
- In both TDT and NTDT there was a significant association between LAICI and mortality
  - NTDT: adjusted HR 0.916 for each 1- point increase (95% CI 0.852-0.984, p=0.017)
  - TDT: adjusted HR 0.672 for each 1-point increase (95% CI 0.472-0.955, p=0.027)



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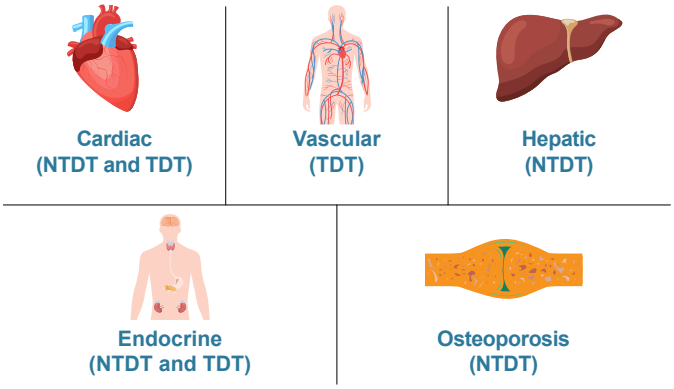
THA-ALL-0266 / Date of preparation May 2026

## Impact of Lifetime Anemia and Iron Control (LAICI) on Outcomes

- In both TDT and NTDT, survival was significantly lower in patients with suboptimal vs. optimal LAICI (suboptimal control: LAICI ≤12.5 in NTDT and ≤3.8 in TDT; optimal: LAICI >12.5 in NTDT and >3.8 in TDT – values driven from Thalassaemia International Federation guidelines for target hemoglobin and serum ferritin values)
  - NTDT: adjusted HR 0.395, p=0.046; TDT: adjusted HR 0.205, p=0.020 for optimal vs. suboptimal LAICI
- Patients with optimal LAICI had significantly lower odds of morbidities including;




In summary, this paper demonstrated that patients who spent most of their lifetime on transfusions had improved survival compared to patients who did not, highlighting a need to reconsider management strategies, especially for untreated NTDT patients. However, it also illustrated that the introduction of transfusion therapy by itself cannot guarantee a favorable disease course, since suboptimal anemia and iron control are associated with poor mortality and morbidity outcomes in both patients with TDT and NTDT. The authors concluded that optimal anemia and iron control throughout a patient's entire disease course are essential to reduce morbidity and mortality in all patients with β-thalassemia.

## Relationship Between Lifetime Transfusion Burden and Morbidities in β-thalassemia[2]

***Objective:*** Quantify the relationship between magnitude of transfusion burden (volume of transfused blood) and the development of morbidity in patients with transfusion-dependent β-thalassemia.

Eligible patients were transfusion-dependent (defined as a lifetime proportion on transfusion >70% [Definition for TDT from the de-LIGHT impact of lifetime anemia publication[2]] and were followed from their date of diagnosis to death, loss of follow up, or Dec 31 2020, whichever was earlier. Patients had to be optimally transfused according to Thalassaemia International Federation (TIF) Guidelines, with a lifetime median pre-transfusion Hb of ≥9.5 g/dL; this was to exclude the confounding impact of anemia on morbidity development.

Data on demographics, splenectomy status, average annual red cell transfusion volume over the entire observation period (expressed as mL/kg), and morbidities, were analyzed.

275 patients (51.6% female), with a median follow up of 37.0 years, and a median age at last follow up of 38.2 years, were included in the analysis. 134/275 patients (48.7%) were splenectomized. The mean ± SD of annual red cell transfusion volume was 172.1±38.3 mL/kg (median:164.9, IQR:146.5–197.2, Range:53.3–299.3).

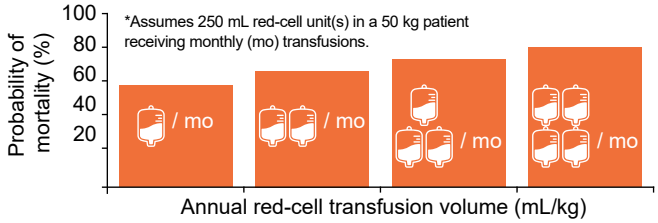
192/275 patients (69.8%) developed at least one morbidity at a median age of 22.4 years.

Cox regression analysis demonstrated a 54% increased risk of morbidity per 100 mL/kg increase in annual red cell transfusion volume (HR 1.542, 95% CI 1.047-2.272, p=0.028) that remained significant after adjusting for sex and splenectomy status (adjusted HR 1.616, 95% CI 1.047-2.495, p=0.030).

Stratifying the analysis by median serum ferritin during the observation period revealed that the independent effect of transfusion burden on morbidity development was lower at higher iron overload thresholds. Since an independent effect of transfusion burden on morbidity development was no longer evident at higher iron levels, this suggests the effect of transfusion burden on morbidity development was largely mediated by uncontrolled secondary iron overload:

- Serum ferritin <1000 ng/mL (70/275) adjusted HR per 100 mL/kg increase in red cell transfusion volume 2.319 (95% CI 0.972-5.5333, p=0.058)
- Serum ferritin 1000-2500 ng/mL (171/275) adjusted HR 1.689 (95% CI 0.958-2.976, p=0.070)
- Serum ferritin >2500 ng/mL (34/275) adjusted HR 1.312 (95% CI 0.374-4.597, p=0.672)

Figure 1. Probability of Morbidity According to Annual Red-cell Transfusion Volume




The authors noted these data support the development of therapeutic approaches that aim to reduce transfusion requirements while maintaining adequate Hb as a potential mechanism to reduce morbidity risk.

## Lifetime Risk of Liver Disease in Patients with β-thalassemia[3]

***Objective:*** Establish the lifetime incidence of liver disease among patients with β-thalassemia, and to quantify the risk factors for liver disease, including viral hepatitis and iron overload.

Data on demographics, splenectomy status, hepatitis C virus (HCV) history and treatment, transfusion history, hemoglobin (Hb) and serum ferritin were evaluated, in addition to alanine aminotransferase (ALT) levels for each 5-year interval of observation. Data on development of heart failure, hypothyroidism, and diabetes mellitus were also included.

In order to interrogate results based on patient's overall transfusion exposure, the percentage of time spent receiving transfusions throughout the observation period was calculated



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for each patient. Lifetime values for Hb, ferritin and ALT were calculated as the mean for all values.

557 patients (53.5% female) were included in the analysis, with a median follow up of 38.0 years, and a median age at last follow up of 40.6 years.

During the observation period, 46 patients died, with liver disease as the primary cause in 13 patients (28.3%).

The overall crude incidence of liver disease was 26.4% and occurred at a median age of 34.4 years:

- Fibrosis/cirrhosis occurred in 24.2% patients (136/557, 95% CI 20.9-28.2) at a median age of 34.4 years
- Hepatocellular carcinoma (HCC) occurred in 2.3% patients (13/557, 95% CI 1.3-4.0) at a median age of 45.4 yrs. 5 of these 13 patients had no preceding cirrhosis
- Other liver disease occurred in 1.8% patients (10/557, 95% CI 0.9-3.3) at a median age of 40.6 years

Table 1. Significant risk factors for liver disease in β-thalassemia

| Risk Factor | Liver disease NO (n=410) | Liver disease YES (n=147) | P value |
|---|---|---|---|
| Follow up duration in years, median (IQR) | 34.0 (23.0-42.0) | 29.9 (18.0-38.3) | <0.001 |
| Splenectomy, n (%) | 194 (47.3) | 94 (63.3) | 0.001 |
| HCV infection, n (%) | 97 (23.7) | 90 (61.2) | <0.001 |
| Anti-HCV treatment, n/N (%) | 23/97 (23.7) | 10/90 (11.1) | 0.034 |
| Lifetime proportion on transfusion | | | 0.010 |
| ≤ 10% | 22 (5.4) | 5 (3.4) | |
| >10 to <90% | 133 (32.4) | 68 (46.3) | |
| ≥ 90% | 255 (62.2) | 74 (50.3) | |
| Lifetime Hb level, g/dL, median (IQR) | 9.6 (9.2-10.0) | 9.5 (9.0-9.7) | 0.003 |
| Lifetime serum ferritin level, ng/mL, median (IQR) | 1306 (799-1919) | 1616 (1011-2443) | 0.001 |

IQR, interquartile range

Independent risk factors for the development of liver disease identified by multivariate Cox regression analysis were HCV (adjusted HR 2.195 95% CI 1.503-3.205, p<0.001) and lifetime serum ferritin (adjusted HR per 100 ng/mL increase 1.030, 95% CI 1.020-1.041, p<0.001).

The cumulative 20- and 40-year liver-disease- free survival rates were 82% and 44% in patients **with** a history of HCV, versus 83% and 79% in patients **without** (Log-rank test 12.273, p<0.001).

The cumulative 20- and 40-year liver-disease- free survival rates were 82% and 44% in patients with a lifetime serum ferritin level >1500 ng/mL, versus 83% and 79% in patients with a lifetime serum ferritin level ≤1500 ng/mL (Log-rank test 17.729, p<0.001).

Importantly, liver-disease-free-survival was significantly shorter in patients with a history of HCV **AND** lifetime serum ferritin >1500 ng/mL, versus either risk factor alone; and in patients with neither risk factor (Log-rank test 34.476, p<0.001).

From the overall population, 248 patients had ALT levels recorded. The crude incidence of liver disease in this subgroup was within the 95% CI of the overall cohort, with a median lifetime ALT level of 28 IU/L (IQR 18-50, range 8.5-317). There was a significantly increased risk (hazard ratio [HR]) of liver disease with increasing median lifetime ALT levels:

- HR 1.537 (95% CI 0.905-2.609, p=112) in patients with mild ALT elevation (< 2x ULN)
- HR 1.871 (95% CI 0.871-4.021, p=0.108) in patients with moderate ALT elevation (> 2x ULN)
- HR 9.096 (95% CI 3.544-23.346, p<0.001) in patients with severe ALT elevation (> 3x ULN)

The authors concluded that patients with β-thalassemia have a considerable increased lifetime risk for the development of liver disease, primarily driven by HCV infection and/or uncontrolled iron overload (serum ferritin >1500 ng/mL), especially in the 4-5$^{th}$ decades of life. Close monitoring of these patients to identify liver disease, and early intervention, is vitally important.

## Take home messages for patients with β-thalassemia

- These analyses provide important new information on the relationship between anemia and iron overload with long-term outcomes in β-thalassemia[1-3]
- There was a significant association between the lifetime proportion spent on transfusion and thalassemia-related mortality - survival was better for patients who had spent most of their lifetime on transfusions compared to patients who did not[1]
- Outcomes were dependent on optimal anemia and iron control throughout a patients' entire disease course, which are essential to reduce morbidity and mortality in both NTDT and TDT patients[1]
- In patients with β-thalassemia, longitudinal data showed ~76% of patients had at least one morbidity, with 55% patients experiencing two or more morbidities[1]
- Patients have a considerable increased lifetime risk for the development of liver disease, primarily driven by HCV infection and/or uncontrolled iron overload[3]
- Close patient monitoring to identify liver disease, and early intervention, is vitally important[3]

## References


1. Musallam KM, Vitrano A, Inzerillo A, et al. Impact of lifetime anaemia and iron control on outcomes in β-thalassaemia: Data from the longitudinal de-LIGHT study. Br J Haematol. 2025;00:1-11. DOI: 10.1111/bjh.70047.
2. Musallam KM, Vitrano A, Inzerillo A, et al. Quantifying Morbidity Risk Attributed to Red-Cell Transfusion Volume in Optimally Transfused Patients With β-Thalassemia. Am J Hematol. 2025;0:1-3. https://doi.org/10.1002/ajh.70100.
3. Musallam KM, Vitrano A, Inzerliio A, et al. Lifetime Risk of Liver Disease in Patients With β-Thalassemia: Data From the de-LIGHT Retrospective Cohort Study. Eur J Haematol. 2025; 115:278-286. https://doi.org/10.1111/ejh.14446.




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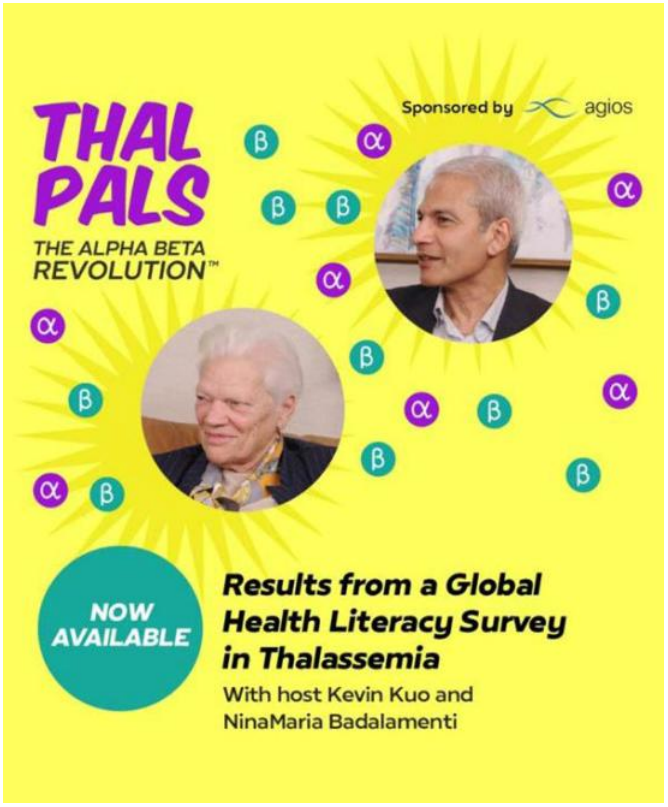
THA-ALL-0266 / Date of preparation May 2026

## COMMUNITY RESOURCES

**Discover new resources for thalassemia healthcare providers, patients, and their caregivers**

### Thal Pals Podcasts – Episode 36 now available!

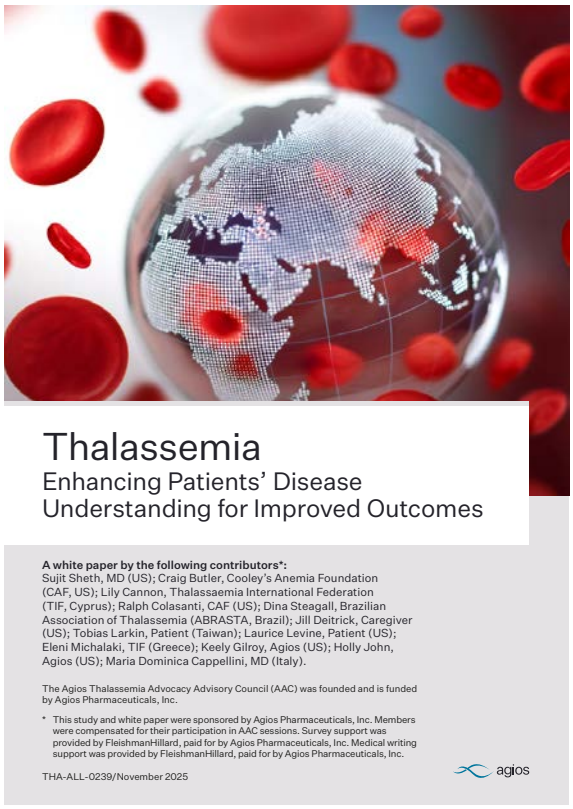
The thalassemia podcasts Thal Pals:  The Alpha Beta Revolution™ aims to facilitate ongoing collaboration between patients, caregivers, and medical experts. The monthly broadcasts feature members of the thalassemia community from around the world discussing currents topics relevant to both α- and β-thalassemia.




**36 episodes are available and can be accessed here:**
https://www.bloodstreammedia.com/thal-pals-the-alpha-beta-revolution

### A White Paper on Health Literacy in Thalassemia

Results and insights from a global health literacy survey in thalassemia are captured in this White Paper. Having identified that health literacy was a critical unmet need in patients with thalassemia, the White Paper was developed in collaboration with patients, caregivers, patient advocates and physicians by the Thalassemia Advocacy Advisory Council (AAC).




**You can access and download the White Paper here:**
https://twotenstudio.github.io/agios-thal-aac-whitepaper/

## EDITORIAL POLICIES & TEAM

The objective of this newsletter is to provide updates on new scientific information, resources, and activities of interest to the thalassemia medical and patient community. The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals. All of these experts serve as paid consultants for Agios Pharmaceuticals.

The following experts are involved in this initiative

| | | | |
|---|---|---|---|
| Khaled Musallam, MD, PhD | Thomas Coates, MD | Ali Taher, MD, PhD | Kevin Kuo, MD |
| Sujit Sheth, MD | Vip Viprakasit, MD, DPhil | Hanny Al-Samkari, MD | Maria Dominica Cappellini, MD |

**Contact: ThalassemiaNews@agios.com**



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The overall objective of this study is to build the evidence base for disease course, risk factors and treatment outcomes in α-thalassemia. Until relatively recently α-thalassemia was managed as a subtype of thalassemia, rather than the distinct condition it is now recognized to be[1]. Consequently, clinical data specific to α-thalassemia are extremely limited and treatment recommendations are typically based on expert opinion or extrapolations from β-thalassemia. Furthermore, the low incidence of α-thalassemia combined with its broad spectrum of phenotypes and non-specific symptomatology, make diagnosis and treatment extremely challenging. To obtain evidence-based data that will inform effective diagnostic and treatment decisions, a global cohort study of α-thalassemia has just been approved.

This retrospective observational study will analyze pooled data for patients with a confirmed diagnosis of α-thalassemia with three gene deletions/mutations (hemoglobin H disease) registered at centers across the globe. The analysis will include clinical data collected from source documents at each participating center, from birth through December 2025.

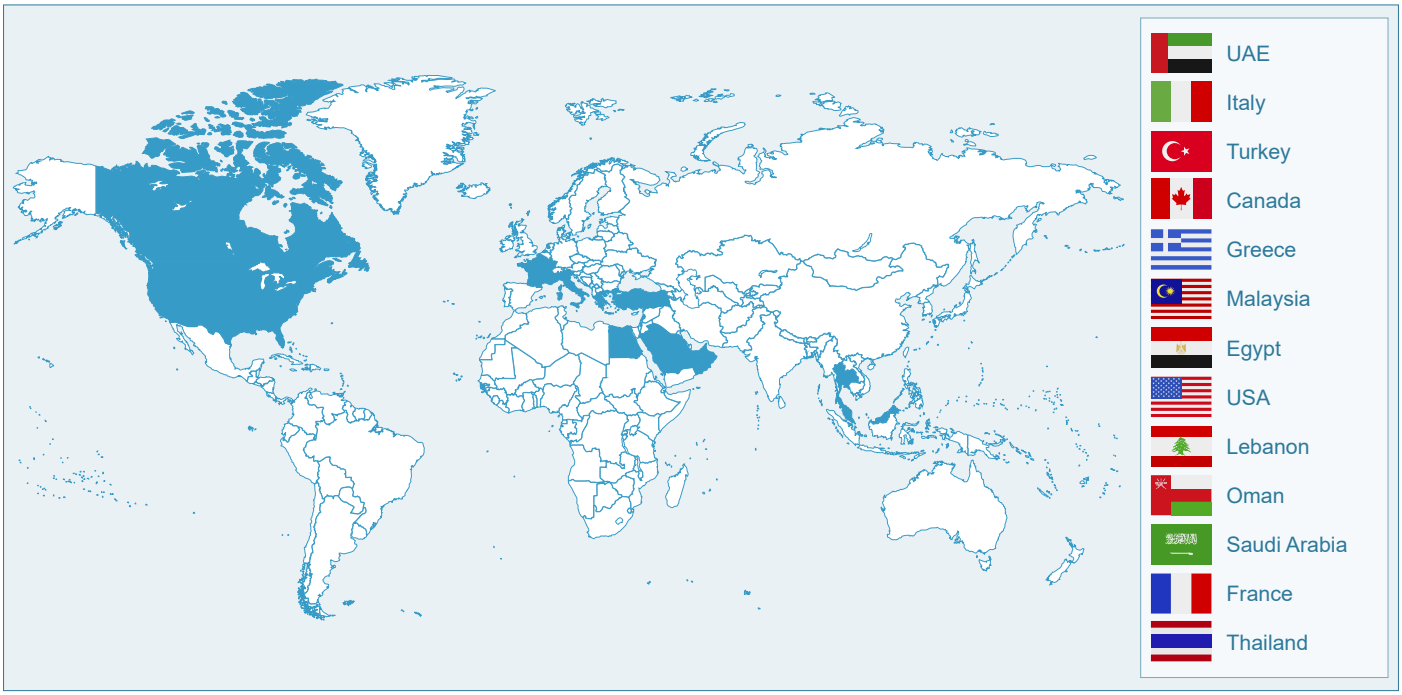
Some of the key endpoint assessments are shown below.

| Objective | Endpoints |
|---|---|
| Describe morbidity and mortality | • Prevalence of morbidities<br>• Survival rate<br>• Morbidity-free survival<br>• Age and cause of death |
| Evaluate anemia course | • Change in levels of hemoglobin, lactate dehydrogenase, and bilirubin over time |
| Evaluate course of iron overload | • Iron distribution in serum, heart and liver<br>• Longitudinal changes in serum ferritin level, liver iron concentration and cardiac T2* MRI |
| Evaluate management strategies in clinical practice | • Treatments received |
| Evaluate healthcare resource utilization | • Number and cause of emergency room visits<br>• Frequency and cause of hospitalisation |

## UPDATE: STILL ACTIVELY RECRUITING!

Further details of the study can be obtained from the Principal Investigator Khaled M Musallam by e-mailing

khaled.musallam@burjeelholdings.com




## References

1. Thalassaemia International Federation. Guidelines for the Management of α-thalassaemia. 2023. Eds. Amid A, Lal A, Coates TD, Fucharoen S. ISBN 978·9963-717-28-6



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