## PRIMARY OBJECTIVE

To demonstrate the superiority of mosunetuzumab + lenalidomide combination versus anti-CD20 mAb plus chemotherapy with regards to Progression Free Survival (PFS) in previously untreated patients with FLIPI 2-5 Follicular Lymphoma.

Corresponding endpoint: PFS, assessed by blinded Independent Review Committee (IRC) blind of treatment arms according to the Lugano 2014 criteria.

## ENROLLMENT PROCEDURE

1. Identification of subject -> signature of ICF
2. Verification of inclusion & exclusion criteria and baseline assessments
3. Subject's registration in **Veeva RTSM (IWRS)**

   https://rtsm-prod.veeva.com/MorningLyte

   Investigator's treatment choice for control arm (arm B)

   *Biosimilar products are not permitted in the study.*

4. Subject's randomization in RTSM and treatment arm allocation :
   - Arm A (experimental) : mosunetuzumab + lenalidomide
   - Arm B (control) : G + CHOP
     R + CHOP
     G + bendamustine
     R + bendamustine
5. Study data entry: **Veeva CDMS (eCRF)**

   https://login.veevavault.com/auth/login

## PROPHYLACTIC MEASURES

Refer to section 10.9 of the protocol

## CONCOMITANT TREATMENTS

Refer to section 10.10 of the protocol

## DOSE ADJUSTEMENTS

Refer to section 10.8.2 of the protocol

## PROVISIONAL SCHEDULE

**First Patient Included** = May 2024

**Last Patient Included** = March 2027

**End of treatment** = September 2029

**Last Patient Last Visit** = March 2034

**Enrollment duration** = 34 months

**Study duration** = 10 years



## SAE / Pregnancy / AESI / Special situations

Refer to section 14 of the protocol

**Main Adverse Events reporting rules (section 14.2)**

**All AEs whatever the grade (CTCAE – version 5.0, or ASTCT CRS grading) and AESI (section 14.5 for details regarding grades)**

- *To be reported until 90 days after last treatment administration*
- *Non-serious AE will be reported through eCRF.*
- *When associated to a SAE and regardless of the time of occurrence, the AE must be reported as "Adverse Event" in the appropriate eCRF pages.*
- *Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as "Adverse Event"*

***Main Serious Adverse Events reporting rules (section 14.3)***

- *Any episode of any grade of toxicities, which meets one of the seriousness criteria must be reported as "Serious Adverse Event" in the appropriate SAE form*
- *Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as "Serious Adverse Event".*
- *SPM will be reported as SAE regardless of seriousness criteria: they must be considered as "Important Medical Event" and also as AESI (see section 14.5) even if no other seriousness criteria applies. excepud issum.*

**Abnormal laboratory values reporting rules (section 14.2)**

*If the abnormality is not a part of a diagnosis or syndrome and cannot be reported with a final diagnosis, then the laboratory abnormality itself should be recorded as verbatim (e.g. "alkaline phosphatase increased") in the AE page. In that case, an abnormal laboratory value which is not a component of a diagnosis or syndrome is considered as an AE to report in the EDC, if the abnormality:*

- *is considered as an AESI (see section 14.5); or*
- *results in discontinuation from the study; or*
- *requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or*
- *is judged to be of significant clinical importance.*

**IMMEDIATE REPORTING OF**

**AESI / SAE / PREGNANCY O LYSARC**

To be sent to the LYSARC Pharmacovigilance Department within **24 hours of becoming aware of the event**

**Email: pharmacovigilance@lysarc.org**

**Fax: +33 3 59 11 01 86**

# MORNINGLYTE

**A Phase III randomized, open-label, international, multicenter study evaluating the efficacy and safety of mosunetuzumab plus lenalidomide in comparison to anti-CD20 monoclonal antibody plus chemotherapy in subjects with previously untreated FLIPI 2-5 follicular lymphoma**

EU CT number: 2023-505436-35-00

## CONTACTS

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## MAIN INCLUSION CRITERIA

Refer to section 8.1 of the protocol

1. Patient with histologically proven previously untreated CD20+ follicular lymphoma grade 1, 2, or 3a (including patient watched during up to 10 years after initial diagnosis) as assessed by the investigators according to the WHO 2016 classification12, or classical follicular lymphoma according to the WHO 2022 classification13. Diagnostic tissue must be available for central pathology review, exploratory endpoints and secondary data use.

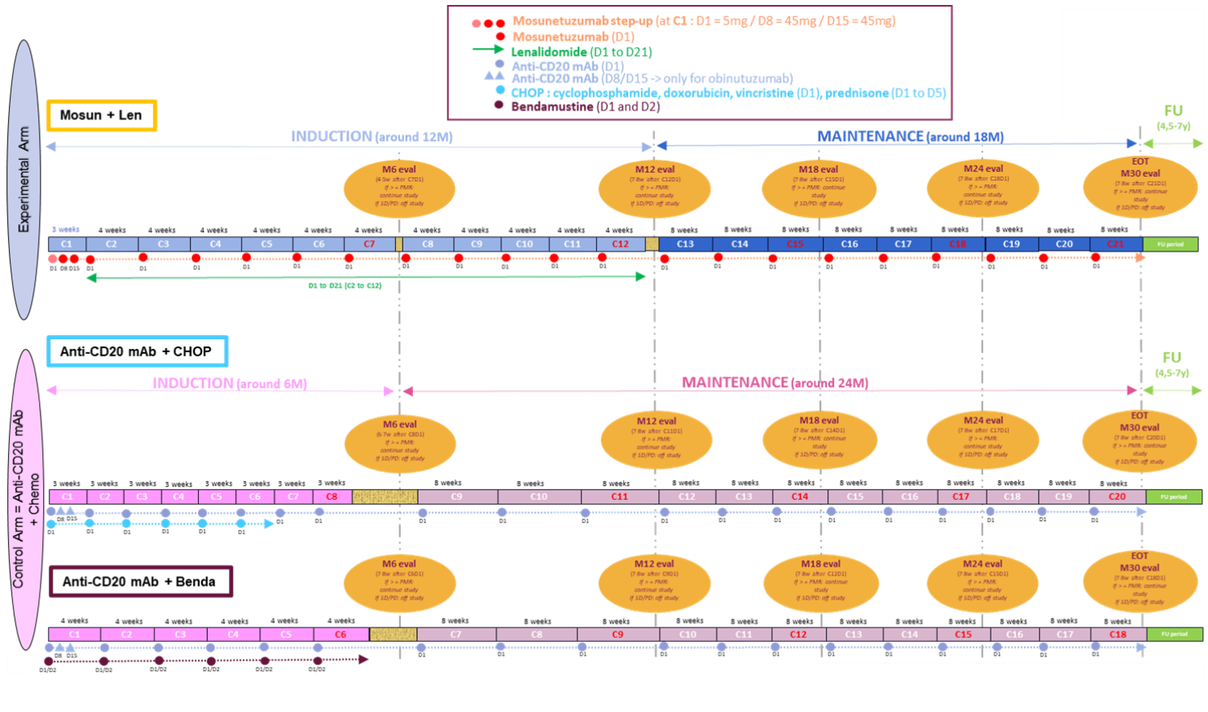
*(Patients with absolute lymphocyte count > 20 G/L must be discussed with the Sponsor before screening/inclusion).*

2. FLIPI 2-5.
3. All Ann Arbor stages (including stage I if FLIPI ≥ 2).
4. Must need treatment as evidenced by at least one of the following criteria:
   - Bulky disease defined as:
     ◊ a nodal or extranodal mass/lesion > 7 cm in its largest diameter
     ◊ involvement of at least 3 nodal or extranodal sites (each with a diameter greater than > 3 cm)
   - Presence of at least one of the following B
   - Symptomatic splenomegaly
   - Any compressive syndrome (for example, but not restricted to- ureteral, orbital, gastrointestinal)
   - Any one of the following cytopenias due to lymphoma:
     ◊ hemoglobin < 10g/dL (6.25 mmol/L)
     ◊ platelets <100 x 109/L, or
     ◊ absolute neutrophil count (ANC) < 1.5 x 109/L
   - Pleural or peritoneal serous effusion (irrespective of cell content)
   - β2microglobulin>ULN or LDH>ULN (item not applicable for Germany)
5. ECOG performance status 0 to 2.

## MAIN EXCLUSION CRITERIA

Refer to section 8.2 of the protocol

1. Grade 3b follicular lymphoma according to the WHO 2016 classification12, or follicular large B-cell lymphoma according to the WHO 2022 classification.
2. Suspicion or clinical evidence of transformed lymphoma at enrollment by investigator assessment (e.g. very high SUV (regarding SUV of other lesions) in at least one lesion that was not biopsied, and discordant with SUV of biopsied lesion, LDH > 2.5 ULN in a context of rapidly progressive disease, etc. *(Please contact the Sponsor to discuss any possible inclusion in borderline cases or any doubt).*
3. Prior localized radiotherapy for the FL.
4. Prior history of another lymphoma.
5. Uncontrolled symptomatic pleural or serous effusion requiring urgent treatment within 48 hours (patients with controlled disease after adequate pleural/serous drainage and/or effective pleurX™ or similar system are eligible).
6. Uncontrolled symptomatic ureterohydronephrosis resulting in renal failure (patients with adequate management i.e. ureteral catheter or double J stent allowing renal failure control are eligible).
7. Symptomatic lymphomatous epidural lesion (patients whose disease is controlled by neurosurgery or short course of steroids are eligible).
8. Use of any standard or experimental anti-cancer drug therapy within 42 days of the start (Day 1) of study treatment.
9. Systemic immunosuppressive medications. Systemic corticosteroid treatment < 20 mg/day of prednisone or equivalent, inhaled corticosteroids and mineralocorticoids for management of orthostatic hypotension is permitted.




## CENTRALIZED IMAGING

- **CT and PET uploading on IMAGYS platform**
  https://lysarc.imagys.com

| | Baseline | M6 | M12 | M18 | M24 | EOT | 1st progression |
|---|---|---|---|---|---|---|---|
| CT | X | X | X | X | X | X | X |
| TEP | X | X | X | | | X | X |

## CENTRAL HISTOLOGICAL REVIEW

- **After randomization:**

⇒ Send pseudonymized pathology report + subject's tumor material & tracking form to the appropriate platform depending on the type of biopsy :

- block / slides FFPE
- block / slides bone marrow biopsy
- samples of core / fine needle biopsy
- tumor cells preparation and freezing in Cryostor®

**Refer to protocol sections 11.2 & 11.4 and the biology manual**

## STUDY ASSESSMENT SCHEDULE

| | Induction phase (-1/+ 3 days) | | | | | Maintenance Phase (+/- 7 days) | | | | FU phase |
|---|---|---|---|---|---|---|---|---|---|---|
| | Screening/ Baseline | C1 (= 3w for exp. arm and mAb-CHOP; = 4w for mAb-Benda) | | | C2-C12 (exp. arm) or C2-C8 (mAb-CHOP) or C2-C6 mAb-Benda) | M6 and M12 evaluations | C13-C21 (exp. arm) or C9-C20 (mAb-CHOP) or C7-C18 (mAb-Benda) - every 8 weeks | M18 and M24 interim evaluations (every 6m from M12 eval) | Evaluation At the end of treatment (EOT) M30 eval | Follow-up, |
| Date (Days, weeks or months) | Within 6 weeks from rando | Day 1 | Day 8 (a) | Day 15 (a) | Day 1 (every 4w for exp. arm and mAb-Benda; every 3w for mAb-CHOP) (b) | M6 (week 28): 4 to 5w after C7 (exp. arm) or 6 to 7w after C8 or 7 to 8w after C6 (control arms) M12 (week 52): 7 to 8w after C12 (exp. arm) or 7 to 8w after C11/C9 (control arms) | Day 1 | M18 (week 76): 7 to 8w after C15 (exp. arm) or 7 to 8w after C14/C12 (control arms) M24 (week 100): 7 to 8w after C18 (exp. arm) or 7 to 8w after C17/C15 (control arms) | M30 (week 125): 7 to 8w after C21 (exp. arm) or 7 to 8w after C20/C18 (control arms), or within 30d following to permanent treatment discontinuation | Every 3m from EOT the first 2y (+/- 14d), then every 6m during the next 3y (+/- 1m), then every year until the end of study (+/- 1m) (v) |
| Mosunetuzumab | | X | X | X | X | | X | | | |
| Lenalidomide | | | | | X (b) | | | | | |
| G-CHOP (b) | | X | X | X | X | | X (G only) | | | |
| R-CHOP (b) | | X | | | X | | X (R only) | | | |
| G-Benda (b) | | X | X | X | X | | X (G only) | | | |
| R-Benda (b) | | X | | | X | | X (R only) | | | |
| Written ICF (+/- Bio/genetic ICF) | X | | | | | | | | | |
| Randomization (within 14d prior to C1D1) | | X | | | | | | | | |
| Patient characteristics (c) | X | | | | | | | | | |
| Clinical examination | X | X | X | X | X | | X | | X | X |
| Weight | X | X | | | X | | X | | X | X |
| Vital signs (d) | X | X | X | X | X | | X | | X | |
| B symptoms | X | X | | | X | | X | | X | X |
| ECOG PS | X | X | | | X | | X | | X | X |
| Complete blood cell count (e) | X | X | X | X | X | | X | | X | X |
| Biochemical tests (f) | X | X | X | X | X | | X | | X | |
| LDH | X | X | | | X | | X | | X | X |
| β2-microglobulin | X | | | | | | | | | |
| TSH | X | X (g) | | | X (g) | | X (g) | | X | X |
| Serum pregnancy test for WOCBP | X | X (h) | | | X | X | X | X | X | |
| Flow cytometry for T/B/NK (optional) | X | | | | | X | | X | X | |
| Serum electrophoresis | X | | | | | X | | | X | |
| SARS-CoV-2 testing (PCR or antigen) | X (h) | | | | | | | | | |
| HIV, HBV, HCV serologies | X | | | | | | | | | |
| EBV and CMV by PCR | X | | | | | | | | | |
| ECG | X | | | | X (i) | | | | X | |
| LVEF assessment | X | | | | | | | | | |
| Neck, thoracic, abdominal and pelvis CT (j) | X | | | | | X | | X | X | X (k) |
| $^{18}$FDG-PET Scan | X | | | | | X | | | X | |
| Tumor biopsy (l) | X | | | | | | | | | |
| Bone marrow biopsy | X (m) | | | | | X (n) | | X (n) | X (n) | |
| QoL questionnaires | | X | | | | X | | X | X | X (o) |
| Serum and plasma PK/ADA samples (exp. arm, 125 pts) | | X | X | X | X (p) | | X (q) | X (q) | X (q) | |
| **Samples for banking and biological studies (r):** | | | | | | | | | | |
| Fresh blood for frozen plasma and cells pellet for MRD and analyses of ROCHE | | X | | | X (s) | X (t) | | X (t) | X | |
| Fresh blood for DNA for MRD | | X | | | X (s) | X (t) | | X (t) | X | |
| Fresh blood for PBMC for biobanking | | X | | | X (s) | X | | | X | |
| Fresh bone marrow aspiration for biobanking | | X | | | | X (M6) (u) | | | X (u) | |
| AE/SAE/AESI | Continuous report, concomitant treatments report, need to monitor concomitant medications at baseline and continuously; warning regarding specific monitoring to perform in case of use of AxMPs (please refer to the SmPC of each AxMP) | | | | | | | | | SPM, related AEs, SAEs, AESI |

(a): **Day 8 and Day 15 of C1**: only for patients randomized in the experimental arm (mosunetuzumab), and in control arms with administration of the anti-CD20 mAb obinutuzumab only (G-CHOP or G-Benda)
(b): **Induction phase: exp. arm**: Len from Day 1 to Day 21, from C2 to C12 ; anti-CD20 mAb-CHOP arm: anti-CD20 mAb at each Day 1 from C1 to C8; CHOP only at each Day 1 from C1 to C6; Bendamustine at Day 1 and Day 2 from C1 to C6
(c): **Patient characteristics**: Age, gender, weight, height, BSA, relevant medical history including COVID-19 vaccination status, history of the NHL and staging (Ann Arbor stage, FLIPI1 and FLIPI2 scores)
(d): **Vital signs**: heart rate, blood pressure and body temperature
(e): **Complete blood cell count**: hemoglobin, platelets, white blood cell count with monocytes, absolute neutrophil count, absolute lymphocyte count, abnormal lymphoma cells
(f): **Biochemical tests**: potassium, magnesium, creatinine, measured creatinine clearance according to MRDR/Cockroft-Gault formula, total and direct bilirubin, AST, ALT, alkaline phosphatases
(g): **TSH**: only if clinically indicated
(h): **Serum pregnancy test**: within 7 days before initiation of study treatment
(i): **ECG**: only at Day 1 of C3 for experimental arm
(j): **CT-scan**: neck only at screening; and if clinically indicated at other evaluations
(k): **CT-scan during follow-up phase**: every 6 months from EOT the first 2 years, then every year until the end of study
(l): **Tumor biopsy**: mandatory within 6 months prior to initiation of treatment; strongly recommended for patients watched for at least 12 months
(m): **Bone marrow biopsy at baseline**: mandatory within 6 months prior to initiation of treatment (even for patients watched for at least 12 months). Bone marrow aspirate will not be acceptable
(n): **Bone marrow biopsy at evaluation**: mandatory only for patients with involved bone marrow at screening, with still involved bone marrow obtained before this assessment, and to confirm CMR at this assessment
(o): **QoL questionnaires**: to be performed once during FU, 6 months after EOT
(p): **Serum and plasma PK/ADA samples**: for Mosun PK/ADA pre-dose at Day 1 of C2, C3, C4, C6, C8, and C12 for experimental arm only. For Len PK, at C2D1, <30 min prior to first dose of len and 2 hrs (+/- 10 min) after the first dose of len.
(q): **Serum and plasma PK/ADA samples**: pre-dose at Day 1 of C13, M18, M24, M30 for experimental arm only
(r): **Samples for biobanking and biological studies**: after patient's signature of specific consent. All samplings must be performed at predose.
(s): **Samples for biobanking and biological studies**: at Day 1 of C2 and C4 only
(t): **Samples for biobanking and biological studies**: at M6, M12, M18, M24
(u): **Fresh bone marrow aspiration for biobanking**: to be performed only for patients with involved bone marrow biopsy at baseline (only if tumor cells were present on the bone marrow biopsy prior to any treatment)
(v): **FU-survival (patients in progression)**: to be performed every 6 months during the first two years, then approximatively every year until the end of study