STATISTICAL CONSIDERATIONS

The aim of this management study is to demonstrate that in patients with a first unprovoked VTE a combination of a prediction rule based on D-dimer and low-dose DOAC in those at higher recurrence risk result in a recurrence risk comparable to the population of patients with provoked VTE.

Assumptions
based on the results of the DULCIS study[10], approximately 45% of all eligible patients are expected to discontinue anticoagulation, with an annual rate of recurrent VTE events around 3% (95% 2.0 to 4.4%).
In the remaining 55% of patients who will be encouraged to use apixaban, based on the results of the Amplify Extension study the expected rate of recurrent VTE is around 1.7% after the first year of treatment.
Based on the metanalysis[12] the annual recurrence risk in patients with provoked VTE is 3.3%

Based on these assumptions, we expect the recurrence rate at 12 months to be:

$$0.45*0.03+0.55*0.017=2.2\%$$

Sample size: With an expected annual recurrence rate of 2.2% in the APIDULCIS population, we calculated the sample size to demonstrate, with an 80% power, that the 95% CI is below 3.5% according to Shen [12]. The required sample size is 1148 patients to be recruited for the purpose of the APIDULCIS study.

Kaplan–Meier survival curves will be plotted to estimate the cumulative incidence of symptomatic recurrent VTE; hazard ratios (HR) and their 95% confidence intervals (CI) will be calculated for subgroup analyses.

Safety end-points and interim analysis

Based on a 2.2% annual event rate, a total sample size around 1150 patients and 18 months of follow-up, we expect around 38 recurrences and 2 major bleeding in our study. Since low-dose apixaban may be considered as the treatment gold-standard at the time of release of the study protocol, we plan an interim analysis when 20 primary endpoints are registered. The study will be interrupted if the relative risk of primary endpoints (HR) in the observational non-treatment arm will be >3 HR, with a p value <0.0001.