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Horizon Project IMPORTANT

IMPlementing geriatric assessment for dose Optimization of CDK 4/6-inhibitors in older bReasT cAncer patieNTs

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Project Partners

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Revision History

Date	Ver.	Author(s)	Summary of main changes
15.01.2025	1.1	Fountzila, Papapavlou, Sofou, Drougka	Additional information on process in sections 2, 3, 5
17.01.2025	1.2	Valachis	Additional information in section 4
30.01.2025	1.3	Drougka, Papapavlou, Valachis	Minor revisions in sections 2 and 3

Contents

1. Executive Summary

This deliverable includes an overview of the number of recruited participants, any problems in recruitment and any mitigating strategies applied to compensate for any incurred delays as well as the impact of specific mitigating strategies to inclusion rate.

2. Strategies to assess accrual and dropout rates

During the Task 4.3, the process for assessing and monitoring the patient recruitment process as well as dropout rates both cumulatively and for each clinical site was defined.

Specifically, PHAZE (IMPORTANT study's CRO and partner of the IMPORTANT consortium) provides information to HECOG (Task 4.3 leader) with the number of patients that entered or withdrew from the study for each clinical site at a monthly basis. This information is used to compare actual recruitment against site feasibility projections, to monitor the recruitment process and pinpoint any delays in the participating sites. Subsequently, all clinical sites receive monthly updates from HECOG on patient recruitment and dropout rates for each site. The overall results of accrual and dropout rates for IMPORTANT study per month are discussed in Trial Steering Committee (TSC) meeting (held monthly). TSC meeting is responsible for recommending appropriate mitigating strategies as needed.

HECOG has also developed a feedback questionnaire (Appendix 1) to be sent to all clinical sites every three months to identify the root causes of delays in recruitment. This survey will gather detailed insights on recruitment challenges, reasons for patient withdrawals, and potential strategies for improving recruitment efficiency. By analyzing this feedback, the HECOG team aims to develop targeted action plans to address specific site issues.

3. Actual and predicted accrual and dropout rates in IMPORTANT

3.1 Actual and predicted accrual rates

The planned and actual accrual rates in IMPORTANT study until December 2024 is shown in Figure 1. Until December 2024, five sites (ORB, HUS, AHU, RUL, FCRB) from four European countries (Finland, Norway, Spain, Sweden) are recruiting patients whereas the process for study site initiation is ongoing for the remaining eight sites (two in Italy: UNIFI, LHUTC; six in Greece; parts of the HECOG research network) and is expected to be completed during the first quarter of 2025. A small delay in inclusion rate is observed, although the fact that several study sites are not recruiting patients could explain this discrepancy in actual and planned accrual.

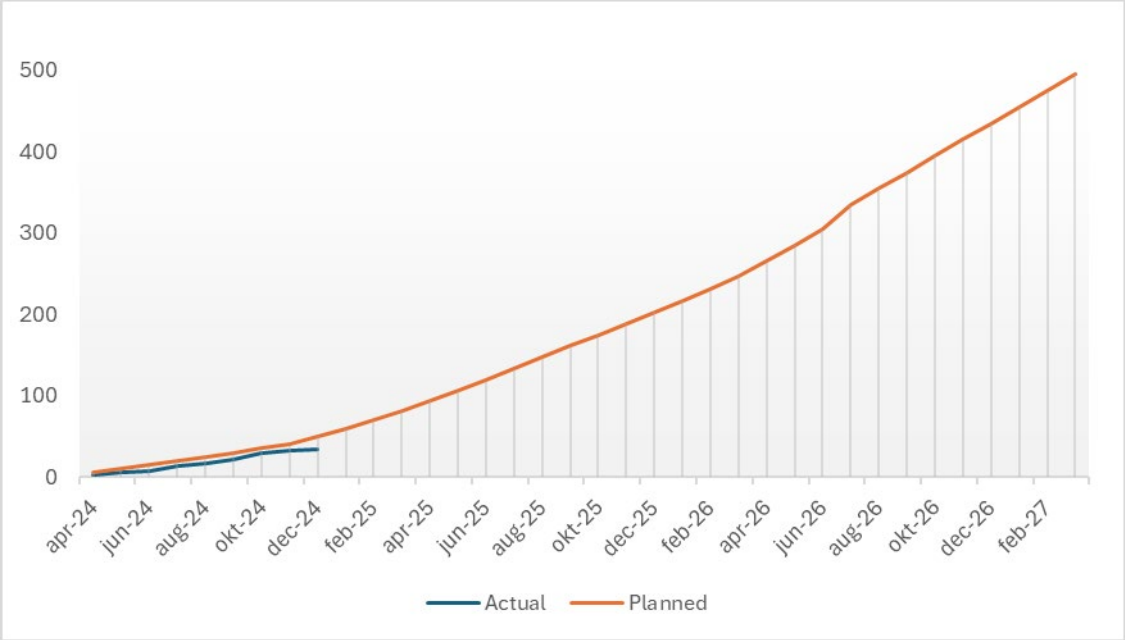
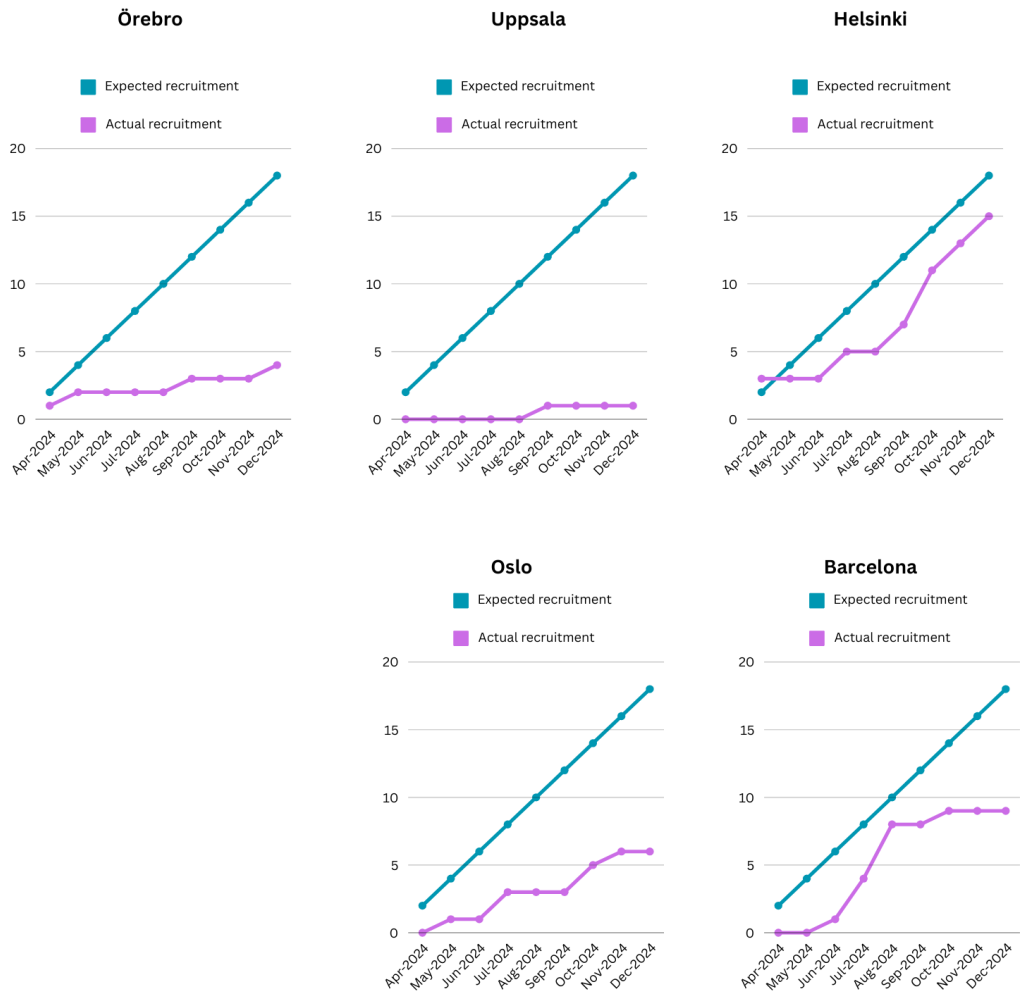


Figure 1. Planned and actual patient enrollment in IMPORTANT trial (update: December 2024)

A detailed assessment of actual and planned accruals per study site (including only study sites that includes patients) is shown in Figure 2.



3.2 Dropout rates

We define dropout as the complete withdrawal of patient consent from all aspects of the trial, including follow-up, or in cases of loss to follow-up.

Until December 2024, no dropouts have been observed among included patients. Dropout rates will continue to be monitored as described in Section 2. The sample size calculation for IMPORTANT study accepts an up to 10% dropout rate throughout the study period. Higher dropout rates as anticipated will result in discussing mitigating strategies through TSC meetings.

4. Mitigating strategies

Extension of patient inclusion period

The IMPORTANT study was initially planned to start patient recruitment in November 2023 with a recruitment of 30 months that would give us the opportunity to present our results (including minimum 24-month follow-up for every included patient) before the end of the IMPORTANT project in May 2028. However, we faced some difficulties with regulatory approvals in all countries due to the pragmatic nature of the project. This delay is associated with the fact that pragmatic trials do not fit the Clinical Trial Regulation and regulatory authorities have difficulties in assessing this type of clinical trial.

Our patient enrolment was, therefore, initiated in April 2024 with only a few clinical sites, and we are still in the process of opening new sites after regulatory approvals. This delay impacts on our ability to include the planned number of patients during a 30-month period.

The TSC has discussed extending the inclusion period from 30 to 36 months (from April 2024 to April 2027). This would enable us to reach the patient target (see Figure 1 for more details).

Expansion of patient inclusion to satellite clinical sites in Sweden

During the first assessment of study site-specific accrual rates, the two study sites from Sweden had the largest discrepancy between planned and actual accruals. The lack of adequate number of patients eligible for IMPORTANT study was discussed as a potential source of this discrepancy in the TSC. As a mitigating strategy, expansion of patient inclusion through referrals from other nearby hospitals utilizing them as satellite sites was proposed. This strategy was deemed feasible for Sweden as Departments of Oncology in Mid-Sweden healthcare region (where both Uppsala and Örebro University Hospitals belong) are already a part of a research network and have previously been collaborated as main and satellite sites for other clinical trials within breast cancer.

The legal and ethical aspects of satellite sites have been thoroughly explored by the IMPORTANT's Privacy and Ethics Committee. A substantial amendment has been submitted via CTIS and ethical approval is expected before proceeding with this mitigating strategy.

5. Follow-up and outcome of mitigating strategies

A systematic follow-up process of all mitigating strategies will be implemented, as described in Section 2. TSC plays a central role is monitoring the impact of mitigating strategies on accrual rates.

Considering the delays in initiating patient inclusion (see Section 3), the final version of D4.3 will also have to be delayed until the accrual period is mature enough to present reliable results on mitigating strategies and their impact.

6. Conclusion

This preliminary version of D4.3 provides an overview of the established process for monitoring and assessing the accrual and dropout rates of IMPORTANT study. Following the monthly assessment of accrual rates and the proposed mitigating strategies by the TSC, the derivable will be able to present the impact of specific mitigating strategies on accruals.

The delay in patient inclusion impacts the timeline of this deliverable. Its final version will be ready when the patient inclusion status is mature enough for suitable analyses.

Appendix A. Questionnaire for assessing study site-specific delays