PHASE I STUDY OF THE001 (DPPG$_2$-TSL-DOX) COMBINED WITH REGIONAL HYPERTHERMIA IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOFT TISSUE SARCOMA

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OBJECTIVE

Doxorubicin (DOX) remains the most relevant chemotherapy (CTx) for treatment of soft tissue sarcomas (STS). Regional hyperthermia (RHT) was shown to improve survival in locally advanced high-risk STS when combined with DOX-based CTx*. THE001 (DPPG$_2$-TSL-DOX) is an innovative thermosensitive liposomal formulation of DOX, based on phosphatidyldiglycerol as key membrane component. After intravenous administration, THE001 releases DOX in the bloodstream once the temperature in the target area is above 41.5 °C.

The application of THE001 with RHT resulted in preclinical models in up to 15-fold higher DOX concentrations in the tumor and significantly improved antitumor activity compared to conventional DOX.

METHODS

THE001 alone and in combination with RHT is investigated in an open-label adapted 3+3 MAD Phase 1 study in patients with heavily (including DOX-) pretreated locally advanced unresectable or metastatic STS. The study explores three different dose level (DL) of THE001 [DOX: 20, 40, 50 mg/m²] as monotherapy and is applied in six 21-day cycles in the main phase to determine the MTD and RP2D. From cycle 2 onwards, RHT is performed simultaneously. Since all patients are pretreated with conventional DOX, dexrazoxane is supportively given to prevent cardiotoxicity.

Tumor response is determined per RECIST 1.1 and Choi criteria, and safety findings are reviewed by an independent Data Safety Monitoring Board. Intratumoral DOX concentrations are being investigated via sequential tumor biopsies in participants starting from DL2. The study is conducted in Germany at the LMU Klinikum Munich and the Helios Klinikum Berlin-Buch.

Here, we report initial feasibility, safety, pharmacokinetics (PK), and anti-tumor activity results for THE001 combined with RHT in STS.

RESULTS

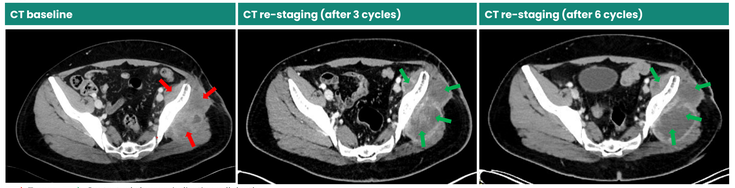
Fig. 1: Baseline Characteristics, Safety and Clinical Activity Overview per Patient (cut-off 30-Oct-2024)

	AGE	GENDER	HISTOLOGY	PRIOR THERAPIES	STAGE AT STUDY ENTRY (AJCC) / ECOG	STUDY STATUS	TREATMENT-RELATED ADVERSE EVENTS ≥ GRADE 2	BOR (RECIST | CHOI)
DOSE LEVEL 1 [THE001: 20 mg/m²]								
Patient 1	60y	female	**Leiomyosarcoma** (retroperitoneal)	6 lines CTx/ITx, 2 surgery, 1 RT	IV / ECOG 2	EoS (PD after C3)	Neutropenia (G3), GGT increase (G3), Fatigue (G3)	PD | PD
Patient 2	45y	female	**Leiomyosarcoma** (retroperitoneal)	8 lines CTx, 3 surgery, 2 RT	IIIa / ECOG 0	EoS (PD after C3)	Anemia (G2)	PD | PD
Patient 3	31y	male	**Malignant peripheral nerve sheath tumor** (extremity / superficial trunk)	3 lines CTx, 4 surgery, 1 RT	IV / ECOG 2	*EoS (PD after C1; no RHT applied)*	-	*NE*
Patient 4	50y	female	**Leiomyosarcoma** (retroperitoneal)	3 lines CTx, 4 surgery, 1 RT	IV / ECOG 0	**EoS (SD after C6)**	-	**SD | SD**
DOSE LEVEL 2 [THE001: 40 mg/m²]								
Patient 5	37y	male	**Undifferentiated Pleomorphic Sarcoma** (extremity / superficial trunk)	5 lines CTx/ITx, 6 surgery, 2 RT	Not evaluable / ECOG 0	**On Study (C12)**	-	**SD | PR**
Patient 6	56y	female	**Leiomyosarcoma** (retroperitoneal)	4 lines CTx, 1 surgery, 1 RT	IV / ECOG 0	On Study (C3)	-	NA | NA
Patient 7	36y	female	**Epitheloid Sarcoma** (retroperitoneal)	3 lines CTx, 4 surgery, 1 RT	IIIa / 0	On Study (C3)	Nausea (G2), Fatigue (G2), Neutropenia (G4)	NA | NA

THE001 is well-tolerated as monotherapy and in combination with RHT in heavily (including DOX-) pretreated locally advanced unresectable or metastatic STS in DL1 [20 mg/m²] and DL2 [40 mg/m²] of the ongoing Phase 1 study (Fig. 1), and dose-escalation to 50 mg/m² is about to start.

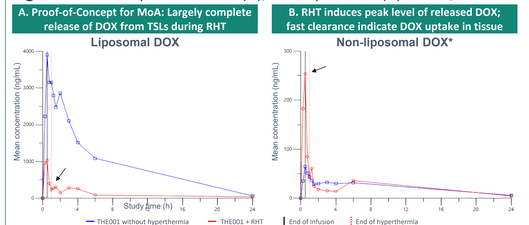
The safety profile pattern observed [cut-off date 30-Oct-2024] is widely expected for DOX. A total number of two SAE (Anemia [G3] and infection [G3]), both unrelated to study treatment, were reported. No SUSAR and DLT were observed, while no adverse events were attributable to the liposomal formulation or the application of RHT. Local disease control of the hyperthermia-targeted lesion has been observed in 3 out of 4 efficacy-evaluable participants and two participants completed the main study phase (6 cycles) in stable disease per RECIST. Patient 5 (DL2) is still on study in the treatment continuation phase in cycle 12 in a durable stable disease per RECIST and with best response of Partial Response per Choi (Fig. 2).

Fig. 2: CT Tumor Assessment in Patient 5 with locally advanced unresectable UPS



From baseline to subsequent tumor assessments: Disease stabilization per RECIST 1.1 and Partial Response per Choi with contextual changes of tumor tissue in CT indicating cell death potentially equal to tumor necrosis.

Fig. 3: PK DL1 – Liposomal DOX (A), Non-liposomal (B) DOX +/- RHT



*Non-liposomal DOX relates to all measured DOX not encapsulated in TSLs (e.g., DOX released from TSL)
Note: Pharmacokinetic (PK) profile summarizes all patients in dose level 1 (DL1); RHT=Regional Hyperthermia

Pharmacokinetic profile analyses for THE001 +/- RHT (analytes: liposomal DOX and non-liposomal DOX) from DL1 (Fig. 3) unequivocally confirm the galenic principle of systemic application of THE001 in combination with RHT to lead to heat-triggered high peak concentrations of DOX and demonstrate that there is a largely complete intentional release of DOX from liposomes, not only supporting the hypothesis of multifold-higher intratumoral DOX concentration but also of a non-inferior systemic exposure of DOX with an AUC comparable to equal-dose of non-liposomal DOX.

CONCLUSIONS

THE001 (DPPG$_2$-TSL-DOX; thermosensitive liposomes encapsulating DOX) + Regional Hyperthermia [RHT]

- is **well-tolerated as monotherapy and in combination with RHT** in DL1 [20 mg/m²] and DL2 [40 mg/m²] in the ongoing Phase 1 study in heavily (including DOX-) pretreated locally advanced unresectable or metastatic STS.
- is a **feasible innovative modality** for **tumor-targeted drug enhancement** in STS with **systemic exposure** assumed non-inferior to equal-dose non-liposomal DOX.
- has shown **encouraging initial signs of clinical activity** with local response and durable disease control in 2 out of 4 efficacy-evaluable patients in DL1 and DL2, with one patient still on treatment in cycle 12.
- represents a **proven galenic principle** of **heat-triggered** immediate and largely complete **release of DOX** from thermosensitive liposomes.

These observations strongly support further dose-escalation in the Phase 1 study and expanded clinical development of **THE001 + RHT** in locally advanced resectable STS as **neoadjuvant treatment** as well as in locally advanced unresectable/metastatic STS, and potentially in other DOX-sensitive solid tumor indications.

ACKNOWLEDGEMENTS

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Our special thank goes to the patients and their families for the participation in the study, and the study teams at the participating sites for their contribution and all their efforts.

** Issels et al., 2010 and 2018;* AUC: Area Under the Curve; BOR: Best Overall Response; C: Cycle; CTx: Chemotherapy; DLT: Dose-Limiting Toxicity; EoS: End of Study; EoT: End of Treatment; G: Grade; ITx: Immunotherapy; MAD: Multiple Ascending Dose; MTD: Maximum Tolerated Dose NA: Not available; NE: Not evaluable; PD: Progressive Disease; PR: Partial Response; RHT: Regional Hyperthermia; RP2D: Recommended Phase 2 Dose; RT: Radiotherapy; SD: Stable Disease; SUSAR: Suspected Unexpected Serious Adverse Reaction; UPS: Undifferentiated Pleomorphic Sarcoma