



**2. SYNOPSIS**

<b>Name of Sponsor/Company:</b> Holostem S.r.l.	
<b>Name of finished product:</b> Holour	
<b>Name of active ingredient:</b> [REDACTED]	
<b>Study title:</b> Prospective, open label, uncontrolled pilot clinical trial to assess the safety and efficacy of [REDACTED] for urethral reconstruction in patients due to hypospadias treatment failure.	
<b>Investigator</b> Prof. [REDACTED] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano Dipartimento di Urologia Pediatrica [REDACTED] [REDACTED] [REDACTED] [REDACTED]	
<b>Study Center</b> Single center	
<b>Study period</b> First patient first visit: 26/11/2021 Last patient last visit: 12/12/2022	<b>Phase of development</b> Phase I/II
<b>Objectives</b> <b>Primary safety objective</b> To demonstrate the safety of HOLOUR in terms of adverse events of special interest (AESIs)—i.e., [REDACTED] —, adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs) at three months and one year after urethral reconstruction treatment in patients suffering from urethral reduced functionality due to hypospadias treatment failure. <b>Primary efficacy objective</b> To evaluate the clinical success of HOLOUR implantation at one year after treatment. <b>Other secondary objectives</b> <ul style="list-style-type: none"> <li>• The efficacy of the treatment with HOLOUR and surgical reconstruction,</li> <li>• The percentage of re-epithelialization in the grafted area,</li> <li>• The clinical stability of the epithelium in the transplanted area,</li> <li>• The presence of scar retraction,</li> <li>• [REDACTED]</li> <li>• [REDACTED]</li> <li>• [REDACTED]</li> <li>• Safety at any time following treatment.</li> </ul> <b>Exploratory objectives</b> <ul style="list-style-type: none"> <li>• The clinical success of treatment based on the Investigator’s judgment,</li> <li>• Improvements in patient’s quality of life following treatment with HOLOUR,</li> <li>• [REDACTED]</li> <li>• [REDACTED]</li> <li>• The presence and severity of symptoms (pain) following the last treatment with HOLOUR,</li> </ul>	

Clinical trial: *Prospective, open label, uncontrolled pilot clinical trial to assess the safety and efficacy of [REDACTED] in patients due to hypospadias treatment failure.*



<ul style="list-style-type: none"> <li>• [REDACTED]</li> <li>• [REDACTED]</li> <li>• [REDACTED]</li> </ul>
<p><b>Methodology</b> Single center, interventional, prospective, open label, uncontrolled, phase I/II, sequential cohort pilot clinical trial.</p>
<p><b>Number of patients</b> Planned: Up to 8 adolescent and pediatric patients. Analyzed: 1 Completed: 0</p>
<p><b>Diagnosis and main criteria for inclusion</b> <b>Inclusion criteria</b> Patients had to meet all the following inclusion criteria to be eligible for enrolment in the study:</p> <ul style="list-style-type: none"> <li>• Written informed consent prior to any study-related procedures (Caregivers); Patients whose parents/legal representatives have been thoroughly informed of the aim of the study procedures and provided signed and dated written informed consent,</li> <li>• Male patients (either pediatrics and adolescents) between [REDACTED]</li> <li>• Need for urethroplasty in failed hypospadias treatment,</li> <li>• [REDACTED]</li> <li>• [REDACTED]</li> <li>• Absence of other clinical contraindications to HOLOUR implantation based on Investigator’s judgement,</li> <li>• A cooperative attitude to follow up the study procedures.</li> </ul> <p><b>Exclusion criteria</b> Patients presenting any of the following conditions were excluded from enrolment in the study:</p> <ul style="list-style-type: none"> <li>• Known or suspected intolerances against anesthesia,</li> <li>• [REDACTED]</li> <li>• Clinical and/or laboratory signs of acute systemic infections and/or severe inflammation at the time of screening. Patient can be re-screened after appropriate treatment,</li> <li>• Severe systemic diseases (i.e., uncompensated diabetes),</li> <li>• [REDACTED]</li> <li>• Allergy, sensitivity or intolerance to drugs or excipients (hypersensitivity to any of the excipients listed in Investigator’s brochure or in this protocol):             <ul style="list-style-type: none"> <li>• [REDACTED]</li> <li>• [REDACTED]</li> </ul> </li> <li>• Contraindications to the post-treatment local or systemic antibiotics and/or corticosteroids,</li> <li>• UTI or urine culture positive require a re-screening of patient,</li> <li>• Contraindications to undergo extensive surgical procedures,</li> <li>• Clinically significant or unstable concurrent disease or other clinical contraindications to stem cell implantation based upon Investigator’s judgment or other concomitant medical conditions affecting grafting procedure,</li> <li>• Patients and parents/tutor unlikely to comply with the study protocol or unable to understand the nature and scope of the study or the possible benefits or unwanted effects of the study procedures and treatments,</li> <li>• Participation in another clinical trial where conventional investigational drug was received less than 1 month prior to screening visit,</li> </ul>

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- Patient who received surgical procedure in the same area within 6 months prior to screening visit,
- Anesthesia or severe hypoesthesia of the area,
- Diagnosis of local or systemic neoplastic disease.

**Test product, dose, and mode of administration**

[REDACTED]

- 1. [REDACTED]
- 2. [REDACTED]
- 3. [REDACTED]
- 4. [REDACTED]
- 5. [REDACTED]
- 6. [REDACTED]
- 7. [REDACTED]
- 8. [REDACTED]
- 9. [REDACTED]
- 10. [REDACTED]
- 11. [REDACTED]
- 12. [REDACTED]
- 13. [REDACTED]
- 14. [REDACTED]
- 15. [REDACTED]
- 16. [REDACTED]
- 17. [REDACTED]
- 18. [REDACTED]
- 19. [REDACTED]
- 20. [REDACTED]
- 21. [REDACTED]
- 22. [REDACTED]
- 23. [REDACTED]
- 24. [REDACTED]
- 25. [REDACTED]
- 26. [REDACTED]
- 27. [REDACTED]
- 28. [REDACTED]
- 29. [REDACTED]
- 30. [REDACTED]
- 31. [REDACTED]
- 32. [REDACTED]
- 33. [REDACTED]
- 34. [REDACTED]
- 35. [REDACTED]
- 36. [REDACTED]
- 37. [REDACTED]
- 38. [REDACTED]
- 39. [REDACTED]
- 40. [REDACTED]
- 41. [REDACTED]
- 42. [REDACTED]
- 43. [REDACTED]
- 44. [REDACTED]
- 45. [REDACTED]
- 46. [REDACTED]
- 47. [REDACTED]
- 48. [REDACTED]
- 49. [REDACTED]
- 50. [REDACTED]
- 51. [REDACTED]
- 52. [REDACTED]
- 53. [REDACTED]
- 54. [REDACTED]
- 55. [REDACTED]
- 56. [REDACTED]
- 57. [REDACTED]
- 58. [REDACTED]
- 59. [REDACTED]
- 60. [REDACTED]
- 61. [REDACTED]
- 62. [REDACTED]
- 63. [REDACTED]
- 64. [REDACTED]
- 65. [REDACTED]
- 66. [REDACTED]
- 67. [REDACTED]
- 68. [REDACTED]
- 69. [REDACTED]
- 70. [REDACTED]
- 71. [REDACTED]
- 72. [REDACTED]
- 73. [REDACTED]
- 74. [REDACTED]
- 75. [REDACTED]
- 76. [REDACTED]
- 77. [REDACTED]
- 78. [REDACTED]
- 79. [REDACTED]
- 80. [REDACTED]
- 81. [REDACTED]
- 82. [REDACTED]
- 83. [REDACTED]
- 84. [REDACTED]
- 85. [REDACTED]
- 86. [REDACTED]
- 87. [REDACTED]
- 88. [REDACTED]
- 89. [REDACTED]
- 90. [REDACTED]
- 91. [REDACTED]
- 92. [REDACTED]
- 93. [REDACTED]
- 94. [REDACTED]
- 95. [REDACTED]
- 96. [REDACTED]
- 97. [REDACTED]
- 98. [REDACTED]
- 99. [REDACTED]
- 100. [REDACTED]

**Duration of treatment**

The planned duration of treatment included a first-stage surgery (HOLOUR implantation) on day [REDACTED], followed by a follow-up period until the second-stage surgery [REDACTED] on day [REDACTED] and continued follow-up through one year post-first implantation.

**Criteria for evaluation**

Safety and efficacy assessments were scheduled to occur approximately at [REDACTED] and [REDACTED] days, and at [REDACTED] months after grafting, based on the Investigator’s judgment at the treatment site. At three months post-implantation, the clinical outcome was to be evaluated by the Investigator.

**Primary safety variable**

Safety was assessed as number and percentages of patients experiencing AESIs (i.e., persistent fever and infection), ADRs, SAEs, and SADR at three and 12 month after HOLOUR engraftment.

**Other safety variables**

- The following events were collected during the study, from [REDACTED]
- Adverse events (AE), treatment emergent adverse events (TEAEs), and ADRs.
  - AESIs, i.e., [REDACTED]
  - Long-term safety evaluation,
  - Safety after repeated treatments with HOLOUR,
  - Vital signs, i.e., blood pressure, ECOG status, weight, temperature, pulse rate and respiratory rate,
  - Hematology and blood chemistry parameters at baseline, and at the three- and 12-months following treatments with HOLOUR.

**Primary efficacy variable**

The primary efficacy variable was the percentage of patients with implantation success at [REDACTED] months following HOLOUR treatment. Implantation success was defined clinically by [REDACTED]. The degree of epithelial stability was evaluated [REDACTED].

**Secondary variables**

Other secondary variables of the study were as follows:

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<ul style="list-style-type: none"> <li>• [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> </ul> <p><b>Exploratory variables</b></p> <ul style="list-style-type: none"> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> <li>■ [REDACTED]</li> </ul>
<p><b>Summary and conclusions</b></p> <p>The study was prematurely terminated in 2024 following the liquidation of Holostem Therapie Avanzate. The only patient enrolled, discontinued early the study following an adverse event “Retraction” that occurred after the second implantation of HOLOUR, classified as moderate and considered related to study treatment and surgical procedure. Due to early study termination and limited data, efficacy and overall safety profile of HOLOUR could not be analyzed in this study.</p> <p><b>Efficacy results</b></p> <p>The first HOLOUR implantation of the patient was assessed as a treatment failure as per Investigator judgment. [REDACTED] No retractions were identified at visual inspection, and the epithelium was evaluated as stable overall. Based on the Investigator’s judgement, the patient was considered as eligible for urethroplasty.</p> <p><b>Safety results</b></p> <p>The patient enrolled in the study experienced two non-serious adverse events following the study procedure. “Infection” (from October 12 to October 25, 2022), and “Retraction” (on December 12, 2022), both of moderate severity, and assessed as related to study treatment and surgical procedure. Infection required specific therapy before recovering. Retraction led to the patient’s discontinuation from the study; no specific medical action was undertaken, and the event resolved with sequelae of retraction, which means, according to the PI, that the subject returned to the initial conditions before the transplant.</p> <p><b>Date of report: 01/12/2025</b></p>

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