

## **SAGES 2022 ANNUAL MEETING THE NEXT BIG THING (FORMERLY EMERGING TECHNOLOGY) ABSTRACT SUBMISSION INFORMATION**

**Title: D-PLEX<sub>100</sub>, a novel doxycycline formulation that provides high, local concentrations of antibiotic activity for approximately four weeks to reduce Surgical Site Infections**

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**Objective:** Despite significant advances in infection control guidelines and practices, surgical site infections (SSIs) remain a substantial cause of morbidity, prolonged hospitalization, and mortality among patients undergoing both elective and emergent surgeries.<sup>1-4</sup> Even with the most robust adherence to currently accepted preventive measures, up to 60% of SSIs are still deemed preventable.<sup>5</sup> We developed a drug delivery platform to address the major deficiencies of available local drug delivery systems, including the uncontrolled and large initial release of antibiotic, risk of dangerously high early systemic drug levels, and lack of prolonged drug release necessary to achieve therapeutic efficacy in SSI reduction.<sup>6-8</sup>

**Technology:** D-PLEX<sub>100</sub> is a novel drug product which pairs the PLEX platform with the broad-spectrum antibiotic, doxycycline (DOX).<sup>6,9</sup> By selectively matching chosen lipids with biodegradable polymers, the resulting Polymer-Lipid Encapsulation matrix (PLEX) fully integrates doxycycline and allows for a preprogrammed, zero-order kinetics release rate for a period determined by the chosen polymer-lipid composition.<sup>6,9</sup> The PLEX composition is confirmed via several methods, including differential scanning calorimetry (DSC), scanning electron microscope (SEM), and X-ray diffraction.<sup>10</sup> D-PLEX<sub>100</sub> is designed to provide local, prolonged, and high concentration anti-bacterial activity of DOX directly at the surgical incision site for a period of approximately four weeks.<sup>6,9</sup> The localized, high concentrations of antimicrobial activity effectively treat many of the common pathogens associated with SSIs, including frequently encountered antimicrobial-resistant pathogens.<sup>3,6,11-12</sup>

**Preliminary data:** The product was evaluated in a double-blind phase 2 clinical trial.<sup>13</sup> Patients undergoing elective colorectal surgery were randomized 1:1 to D-PLEX<sub>100</sub>+ Standard of Care (SOC) or SOC alone (ClinicalTrials.gov identifier NCT03633123). All patients received IV antibiotic prophylaxis 30-60 minutes prior to surgery.<sup>13-14</sup> Patients randomized to the investigational arm received D-PLEX<sub>100</sub> at the time of closure based on the length of surgical incision (5-10 cm = 5g D-PLEX<sub>100</sub> (5g D-PLEX<sub>100</sub> contains 54.6 mg doxycycline), 11-20 cm = 10g D-Plex<sub>100</sub>, >20cm = 15g D-Plex<sub>100</sub>).<sup>15-16</sup> The SSI rate within 30 days post-index surgery revealed a 64% relative risk reduction in SSI rate in the D-PLEX<sub>100</sub> plus SOC group (N=7/88 [7.9%]) vs SOC alone (N=20/91 [21.9%]);<sup>17-18</sup> p<0.05, with minimal systemic doxycycline levels<sup>16</sup>.

**Conclusions:** These data demonstrate that the addition of D-PLEX<sub>100</sub> to the SSI SOC prophylaxis regimen in elective colorectal surgery reduces the SSI rate. D-PLEX<sub>100</sub> may be a promising addition to established SSI bundles and is currently being evaluated in two Phase 3 clinical trials (ClinicalTrials.gov Identifier: NCT04411199; NCT04233424) and in prevention of SSI in bone tissue (sternal wound) (NCT03558984). This may have additional implications in other high risk surgical procedures.

#### Reference List:

1. Anderson DJ, Podgorny K, Berríos-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol.* 2014;35(6):605-627. doi:10.1086/676022
2. Lawson EH, Hall BL, Ko CY. Risk Factors for Superficial vs Deep/Organ-Space Surgical Site Infections: Implications for Quality Improvement Initiatives. *JAMA Surg.* 2013;148(9):849–858. doi:10.1001/jamasurg.2013.2925
3. Weiner-Lastinger, L., Abner, S., Edwards, J., Kallen, A., Karlsson, M., Magill, S., . . . Dudeck, M. (2020). Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015–2017. *Infection Control & Hospital Epidemiology*, 41(1), 1-18. doi:10.1017/ice.2019.296
4. Yamamoto T, Morimoto T, Kita R, et al. The preventive surgical site infection bundle in patients with colorectal perforation. *BMC Surg.* 2015;15:128. Published 2015 Dec 18. doi:10.1186/s12893-015-0115-0

5. Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE, Itani KM, Dellinger EP, Ko CY, Duane TM. American College of Surgeons and Surgical Infection Society: Surgical Site Infection Guidelines, 2016 Update. *J Am Coll Surg*. 2017 Jan;224(1):59-74. doi: 10.1016/j.jamcollsurg.2016.10.029. Epub 2016 Nov 30. PMID: 27915053.
6. Metsemakers WJ, Emanuel N, Cohen O, Reichart M, Potapova I, Schmid T, Segal D, Riool M, Kwakman PH, de Boer L, de Breij A, Nibbering PH, Richards RG, Zaat SA, Moriarty TF. A doxycycline-loaded polymer-lipid encapsulation matrix coating for the prevention of implant-related osteomyelitis due to doxycycline-resistant methicillin-resistant *Staphylococcus aureus*. *J Control Release*. 2015 Jul 10;209:47-56. doi: 10.1016/j.jconrel.2015.04.022. Epub 2015 Apr 21. PMID: 25910578.
7. Kachel E, Moshkovitz Y, Sternik L, Sahar G, Grosman-Rimon L, Belotserkovsky O, Reichart M, Stark Y, Emanuel N. Local prolonged release of antibiotic for prevention of sternal wound infections postcardiac surgery-A novel technology. *J Card Surg*. 2020 Oct;35(10):2695-2703. doi: 10.1111/jocs.14890. Epub 2020 Aug 2. PMID: 32743813.
8. Konstantinos Anagnostakos, Philip Hitzler, Dietrich Pape, Dieter Kohn & Jens Kelm (2008) Persistence of bacterial growth on antibiotic-loaded beads: Is it actually a problem?, *Acta Orthopaedica*, 79:2, 302-307, DOI: [10.1080/17453670710015120](https://doi.org/10.1080/17453670710015120)
9. N. Emanuel, D. Segal, Y. Rosenfeld, O. Cohen, Y.H. Applbaum and Y. Barenholz, BonyPid™: A lipid-and-polymer-based novel local drug delivery system Physicochemical aspects and therapy, *European Cells and Materials* Vol. 24. Suppl. 1, 2012 (page 42)
10. N. Emanuel, D. Segal, Y. Rosenfeld, O. Cohen and Y. Barenholz, The PolyPid - A novel local delivery system: from the physicochemical aspects to innovative and superior therapeutic potential, *European Cells and Materials* Vol. 21. Suppl. 2, 2011 (page 17)
11. Vibramycin, Doryx (doxycycline) dosing, indications, interactions, adverse effects, and more. (2020, May 28). Retrieved December 4, 2021, from <https://reference.medscape.com/drug/vibramycin-doryx-doxycycline-342548>
12. Holmes NE, Charles PGP. Safety and Efficacy Review of Doxycycline. *Clinical Medicine Therapeutics*. January 2009. doi:10.4137/CMT.S2035
13. Senagore, A., Emanuel, N. (2020, May 16-17). *Prolonged Drug Delivery* [Conference presentation]. ASCRS 2020 Convention, Virtual.
14. [For Internal Use Only] Emanuel, N. et al., Clinical Study Report: D-PLEX 310. April 2020.
15. [For Internal Use Only] Emanuel, N. et al., Clinical Study Report: D-PLEX 310. April 2020. Section 7.3
16. [For Internal Use Only] Emanuel, N. et al., Clinical Study Report: D-PLEX 310. April 2020. Table 11.4.1.4-1
17. [For Internal Use Only] Emanuel, N. et al., Prevention of surgical site infection in elective colon surgery with localized post-operative antibiotic releasing product, D-PLEX100: A Randomized double-blind trial [Manuscript]. Table 2
18. [For Internal Use Only] Emanuel, N. et al., Clinical Study Report: D-PLEX 310. April 2020. Table 36