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EMapalumaB treatment foR Anticipated Clinical benefit in sepsis driven by the interferon-gamma Endotype (the EMBRACE trial)

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CONCLUSION

The EMBRACE study aims to generate a proof of concept to investigate whether precision treatment with emapalumab improves the outcomes of patients with sepsis driven by the interferon-gamma (IFNγ)-driven sepsis (IDS) endotype.

BACKGROUND

- Identification of endotypes among patients with sepsis may help guide personalised treatment decisions and improve the outcomes of these patients.[1]
  - Currently, two sepsis endotypes have been well-characterised: macrophage activation-like syndrome (MALS) and sepsis-induced (low IFNγ) immunoparalysis.[2]
- Recently, a study in European patients has described a unique endotype existing in sepsis called IFNγ-driven sepsis (IDS), defined as IFNγ >3 pg/mL and CXCL9 >2,200 pg/mL.[2]
  - IDS shows excess production of IFNγ which guides the elevated biosynthesis of the chemokine CXCL9 by tissue macrophages (**Figure 1**).[3,4]
- This previous study, which investigated discovery and validation sets, reported that the IDS endotype had an overall prevalence of ~20% and 28-day mortality ranging from 40 to 43% (**Figure 2**).[2]
- Emapalumab is an anti-IFNγ antibody that binds free and receptor-bound IFNγ, resulting in rapid and targeted control of IFNγ-driven hyperinflammation.[5]

AIM

The EMBRACE trial (NCT06694701) will investigate whether treatment with emapalumab improves outcomes for patients with IDS.[6]

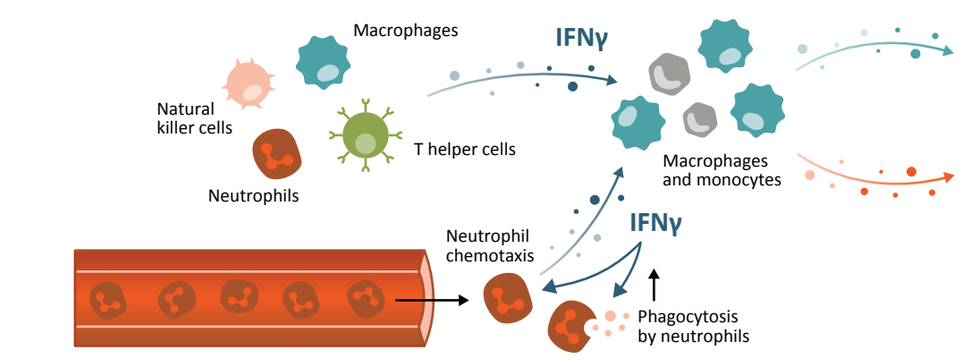
METHODS

- EMBRACE is a three-arm parallel, multicentre, phase 2a, double-blind, randomised controlled trial at 24 study sites in Greece.
- Seventy-five patients will be randomly assigned into three groups (1:1:1) to receive treatment over 28 days (**Figure 3**):
  - Standard-of-care with 6 mg/kg emapalumab at baseline followed by 3 mg/kg emapalumab from day 3 (low dose group);
  - Standard-of-care with 6 mg/kg emapalumab at baseline and on days 3 and 6, followed by 3 mg/kg emapalumab from day 9 (high dose group);
  - Standard-of-care with placebo.
- Eligibility criteria are provided in **Figure 4**.
- Sequential organ failure assessment (SOFA) score, as well as levels of human leukocyte antigen-DR isotype (HLA-DR) and CXCL9, will be monitored and a stopping rule will be applied based on pre-specified threshold levels for safety and efficacy (**Figure 5**).

RESULTS

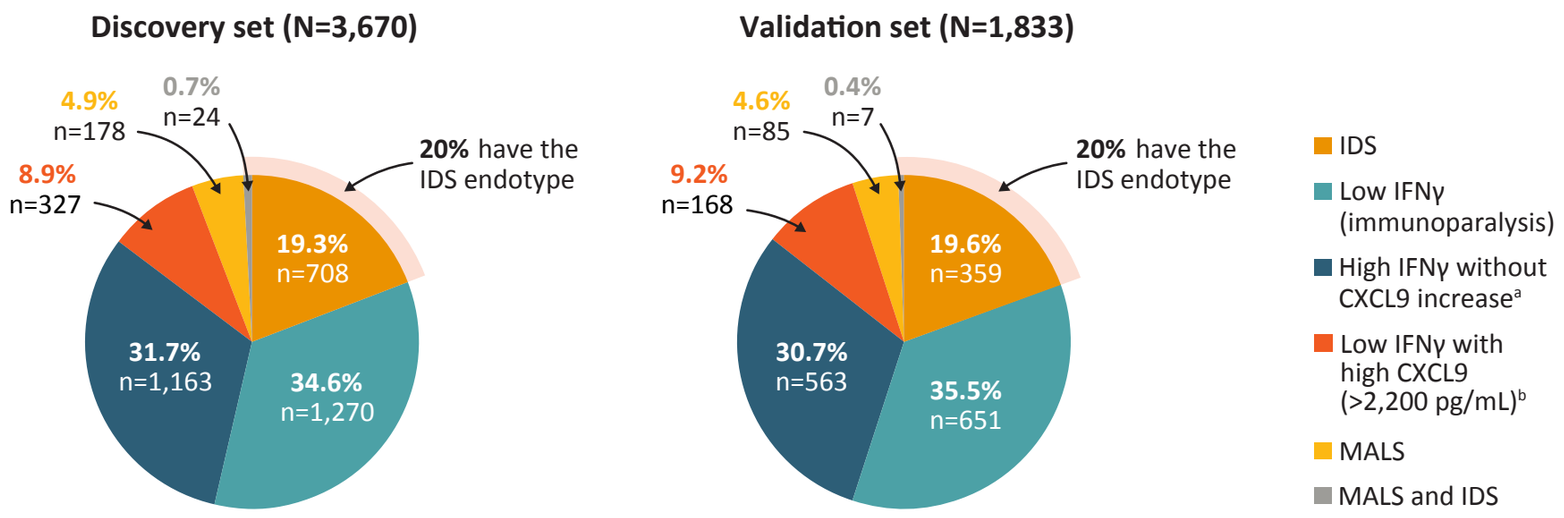
- The primary endpoint is a ≥1.4-point decrease in mean SOFA score from baseline to the end of treatment (EOT) or ≥2.0-point decrease in SOFA score from baseline to the EOT visit (**Figure 6**).
- Secondary endpoints include 28-day mortality, safety, pharmacokinetics and changes in C-reactive protein (CRP), interleukin-6 (IL-6), ferritin, IFNγ and CXCL9 over time.

Figure 1: The IFNγ pathway



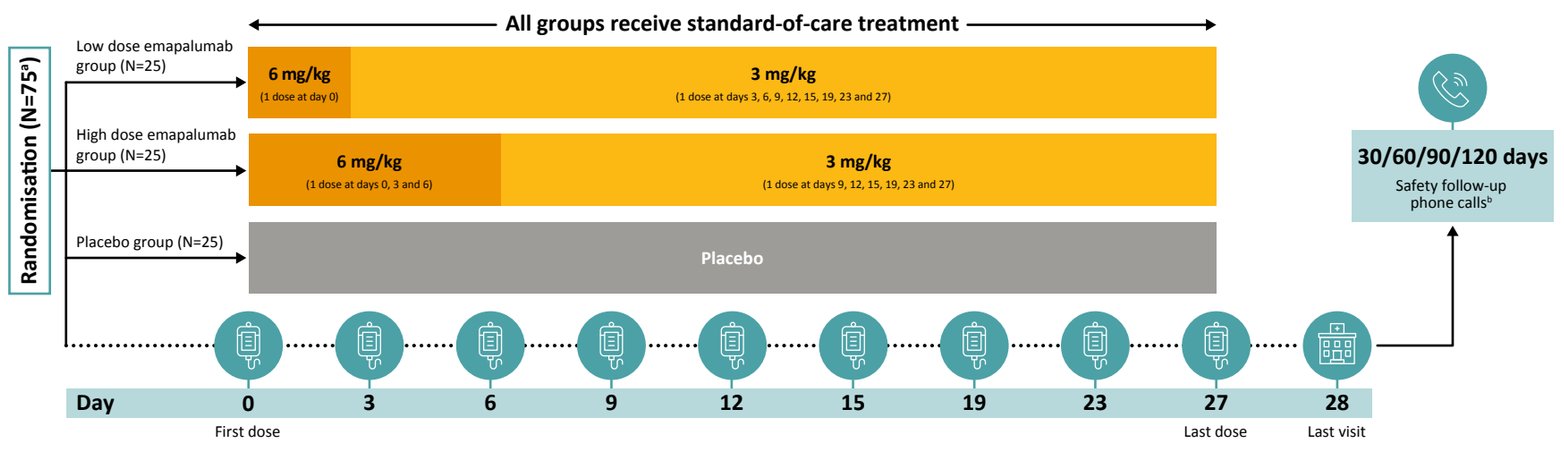
[a] IP-10 is also known as CXCL10.

Figure 2: New sepsis endotype classification: IFNγ-driven sepsis (IDS)



[a] Increases of CXCL9 were defined based on specific cut-offs associated with 28-day mortality. Patients with low IFNγ (i.e. blood IFNγ ≤3 pg/mL) most likely represent patients with sepsis-induced immunoparalysis. [b] The proportion of patients with high CXCL9 (>2,200 pg/mL) is reported in patients with the low IFNγ endotype; these patients cannot be part of the pro-inflammatory IDS endotype since they have laboratory findings compatible with sepsis-induced immunoparalysis. In the discovery set, 126 patients with MALS had IFNγ ≤3 pg/mL, whereas in the validation set, 65 patients with MALS had IFNγ ≤3 pg/mL. Figure adapted from Giamarellos-Bourboulis et al. (2024).[2]

Figure 3: EMBRACE study design



[a] The sample size of 75 patients was chosen since EMBRACE is a phase 2a study and no power calculation applies. It was arbitrarily decided that 25 patients will be enrolled in each group (75 patients in total). [b] Safety follow-up phone call visits will be conducted 30/60/90/120 (±1/±3/±3/±3) days from the infusion of the first dose of the study drug.

Figure 4: Key eligibility criteria

Inclusion criteria

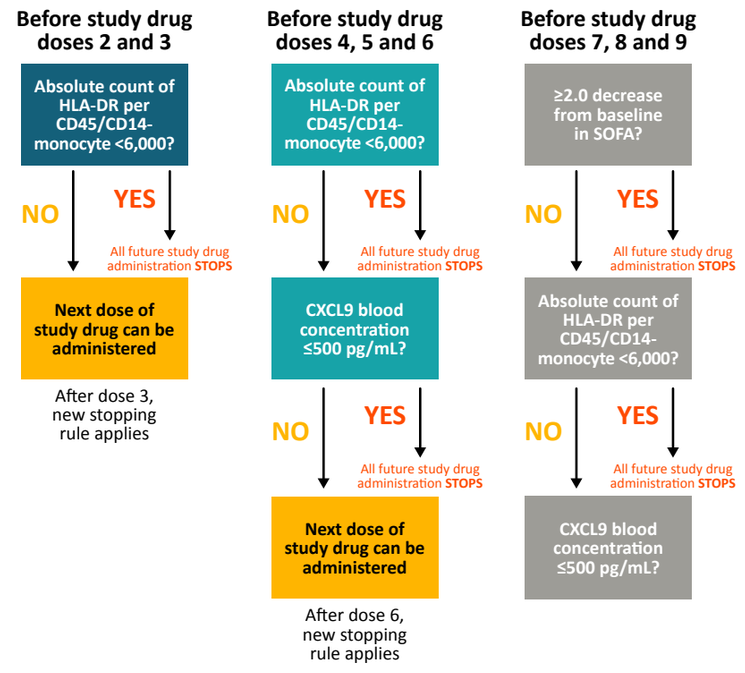
- ≥18 years of age
- Confirmed diagnosis of infection:
  - Lung, intra-abdominal or kidney infections or primary bacteremia
- Sepsis defined by the Sepsis-3 criteria
- Serological diagnosis of IDS

Exclusion criteria

- Body weight >104 kg
- Intake of biologics/JAKi ≤30 days prior to screening
- Active infection by *Mycobacterium tuberculosis*/other mycobacteria/varicella zoster virus/*Histoplasma capsulatum*/*Leishmania*
- Patients living with HIV
- Stage IV solid or haematologic malignancy

Serological diagnosis of IDS is defined as detectable blood IFNγ and CXCL9 >2,200 pg/mL and absence of sepsis-induced immunoparalysis, defined as ≥8,000 of HLA-DR receptors on CD45/CD14-monocytes. Patients must meet all inclusion criteria before participating in the study.

Figure 5: Stopping rule/monitoring criteria



A stopping rule will be applied after the first dose of emapalumab with the aim to deliver the minimum required doses of emapalumab to each patient. This stopping rule will help prevent excess dosing when the pharmacodynamic target of emapalumab is attained, with the aim to minimise the risk of secondary infections through monitoring and maintaining efficient antigen presentation, so that adaptive immune responses are not dysregulated.

Figure 6: Study endpoints

Primary endpoint

1. ≥1.4-point decrease in mean SOFA score from baseline to EOT or any ≥2.0-point decrease in SOFA score from baseline to the EOT visit

Secondary endpoints supporting the primary endpoint

2.
- Number of doses required in each group to achieve the SOFA score response by the EOT
- 28-day mortality

Secondary endpoints

3.
- Rate of serious and non-serious TEAEs
- Change in the SOFA score from days 0–7, 0–28 and 0 to EOT
- Pharmacokinetics of emapalumab
- The need to stop emapalumab due to a drop in numbers of HLA-DR receptors on CD14-monocytes
- Changes in CRP, IL-6, ferritin, IFNγ and CXCL9 over time

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Disclosures

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Abbreviations

CRP: C-reactive protein; **EOT:** end-of-treatment; **HIV:** human immunodeficiency virus; **HLA-DR:** human leukocyte antigen-DR isotype; **IDS:** interferon-gamma-driven sepsis; **IFNα:** interferon-alpha; **IFNγ:** interferon-gamma; **IL:** interleukin; **IP-10:** interferon-gamma-induced protein 10; **JAKi:** Janus kinase inhibitor; **MALS:** macrophage activation-like syndrome; **SOFA:** sequential organ failure assessment; **TEAE:** treatment-emergent adverse event; **TNFα:** tumour necrosis factor-alpha.

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