Piasky (crovalimab-akkz) – New orphan drug approval

- On June 20, 2024, the FDA approved Genentech's Piasky (crovalimab-akkz), for the treatment of adult and pediatric patients 13 years and older with paroxysmal nocturnal hemoglobinuria (PNH) and body weight of at least 40 kg.

- Piasky is a monoclonal antibody that specifically binds with high affinity to the complement protein C5, inhibiting its cleavage into C5a and C5b. Piasky inhibits terminal complement-mediated intravascular hemolysis in patients with PNH.

- The efficacy of Piasky was established in COMMODORE 2, an active-controlled, open-label, non-inferiority study in 204 adult patients (body weight ≥ 40 kg) with PNH not previously treated with a complement inhibitor. Patients were randomized to either Piasky or Soliris® (eculizumab). The study additionally enrolled 6 pediatric patients (aged > 12 years and body weight ≥ 40 kg) to receive Piasky in a separate non-randomized cohort. Efficacy was based on hemolysis control, as measured by the mean proportion of patients with lactate dehydrogenase (LDH) ≤ 1.5x upper limit of normal (ULN) from week 5 to week 25; and the proportion of patients who achieved transfusion avoidance, defined as patients who were packed red blood cells transfusion-free, from baseline through week 25.

    - In the adult population, hemolysis control was achieved in 79.3% of patients with Piasky vs. 79.0% with Soliris (odds ratio 1.02, 95% CI: 0.57, 1.82; non-inferiority met).
    - Transfusion avoidance was achieved in 65.7% of patients with Piasky vs. 68.1% with Soliris (difference -2.8, 95% CI: -15.7, 11.1; non-inferiority met).

- Additionally, the efficacy of Piasky was evaluated in 12 pediatric patients in COMMODORE 2, COMMODORE 1, and in a single arm study in patients who were complement-inhibitor naïve, COMMODORE 3.

    - Hemolysis control from baseline to week 25 was achieved in 7 of the 9 patients who were treatment-naïve, and the 3 patients switching from Soliris or Ultomiris® (ravulizumab) to Piasky maintained hemolysis control through 24 weeks of Piasky treatment.
    - Nine (six patients who were treatment-naïve and three patients who switched from Soliris or Ultomiris) out of the 12 pediatric patients achieved transfusion avoidance and hemoglobin stabilization, and no patients had a breakthrough hemolysis event during the 24-week treatment period.
    - Overall, the treatment effect of Piasky in pediatric patients with PNH was consistent with that observed in adults with PNH.

- Piasky carries a boxed warning for serious meningococcal infections.

    - Piasky is available only through a restricted program called the Piasky REMS.

- Piasky is contraindicated:

    - For initiation in patients with an unresolved serious *Neisseria meningitidis* infection
    - In patients with a known serious hypersensitivity reaction to crovalimab or any of the excipients.

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- Additional warnings and precautions for Piasky include Type III hypersensitivity reaction related to drug-target-drug complexes; other infections; infusion- and injection-related reactions; and monitoring PNH manifestations after discontinuation of Piasky.

- The most common adverse reactions (≥ 10%) with Piasky use were infusion-related reaction, respiratory tract infection, viral infection, and Type III hypersensitivity reactions.

- The recommended dosage of Piasky consists of one loading dose administered by intravenous (IV) infusion (on day 1), followed by four additional weekly loading doses administered by subcutaneous (SC) injection (on days 2, 8, 15, and 22). The maintenance dose starts on day 29 and is then administered every 4 weeks by SC injection. The dosing is based on the patient's actual body weight, as shown in the table below.

    — Only healthcare providers should administer Piasky.
    — Healthcare providers should consider the benefits of the timing of switching C5 inhibitors vs. the risks of Type III hypersensitivity reactions. For patients switching from another C5 inhibitor (eg, Soliris or Ultomiris), the first IV loading dose of Piasky should be administered no sooner than the time of the next scheduled complement inhibitor administration. The administration of the additional SC loading doses and maintenance doses of Piasky should follow as per the schedule shown in the table below.

Body weight	≥ 40 kg to < 100 kg	≥ 100 kg
Loading dose		
Day 1	1,000 mg IV	1,500 IV
Day 2, 8, 15, 22	340 mg SC	340 mg SC
Maintenance dose		
Day 29 and every 4 weeks thereafter	680 mg (SC)	1,020 (SC)

- Genentech's launch plans for Piasky are pending. Piasky will be available as a 340 mg/2 mL (170 mg/mL) single-dose vial.

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