Human-factors validation study for a wearable, single-use injector for patients with paroxysmal nocturnal hemoglobinuria

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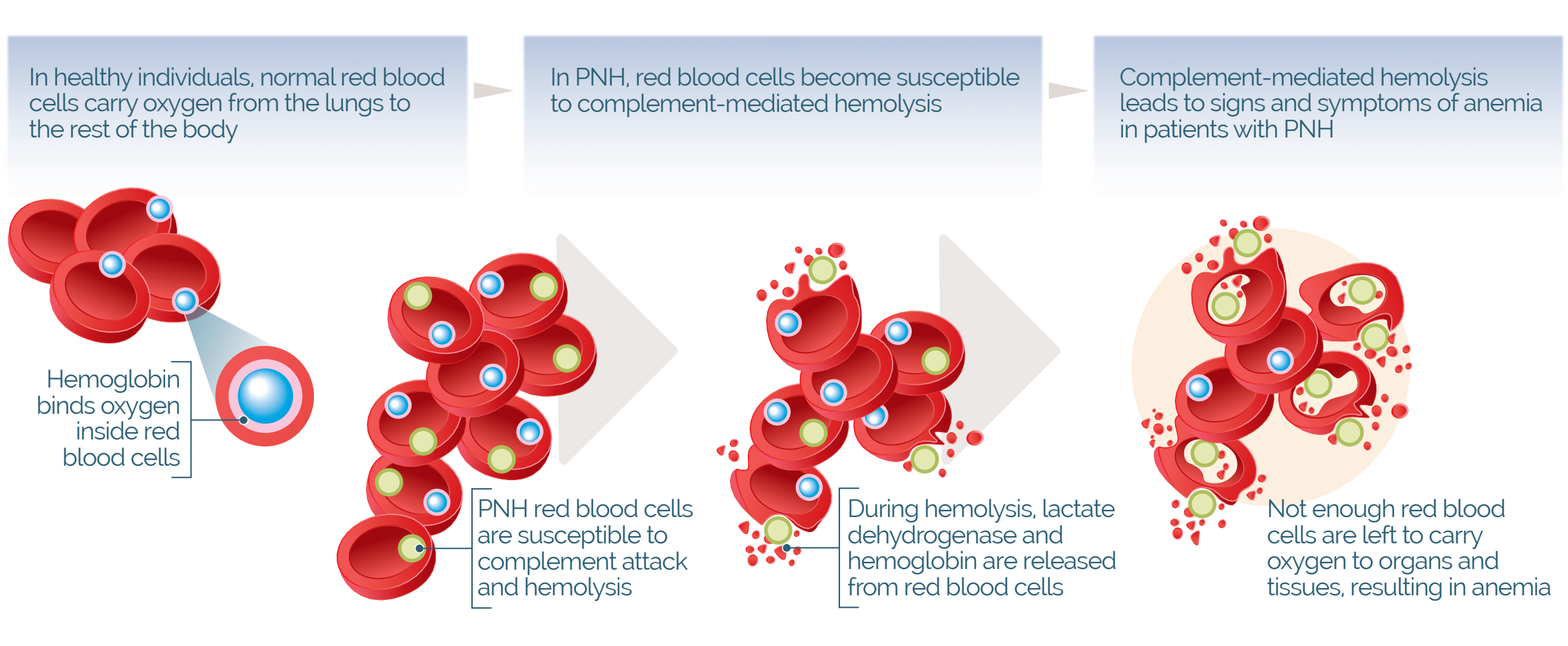
Paroxysmal nocturnal hemoglobinuria (PNH)[1]

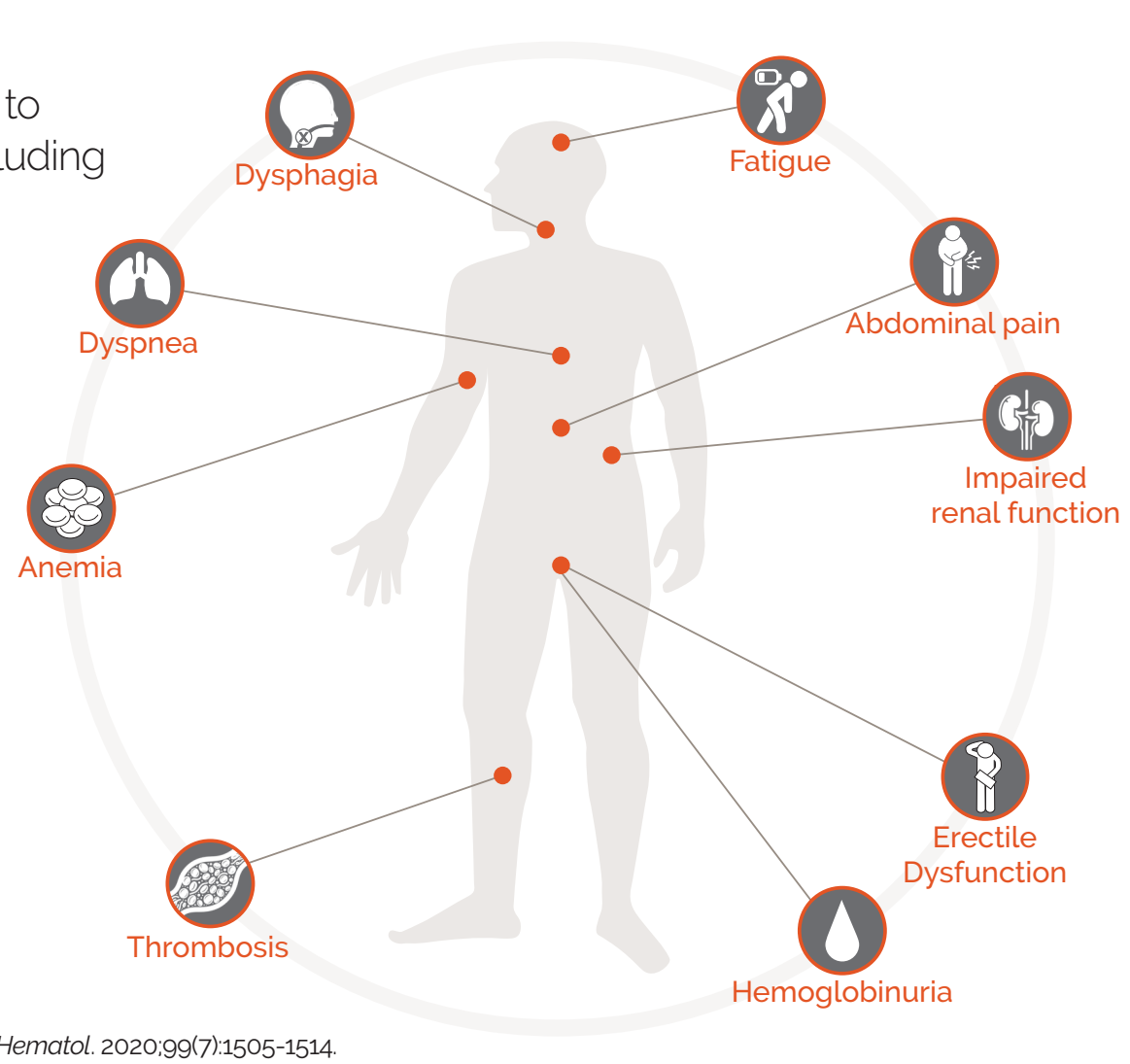
PNH is a rare, acquired, hematologic condition characterized by life-threatening complement system-mediated hemolysis and predisposition for thrombosis


In healthy individuals, normal red blood cells carry oxygen from the lungs to the rest of the body
In PNH, red blood cells become susceptible to complement-mediated hemolysis
Complement-mediated hemolysis leads to signs and symptoms of anemia in patients with PNH
Hemoglobin binds oxygen inside red blood cells
PNH red blood cells are susceptible to complement attack and hemolysis
During hemolysis, lactate dehydrogenase and hemoglobin are released from red blood cells
Not enough red blood cells are left to carry oxygen to organs and tissues, resulting in anemia

1. Brodsky RA. *Blood*. 2021;137(10):1304-1309.

PNH can cause many symptoms that dramatically reduce a person's quality of life[2,3]

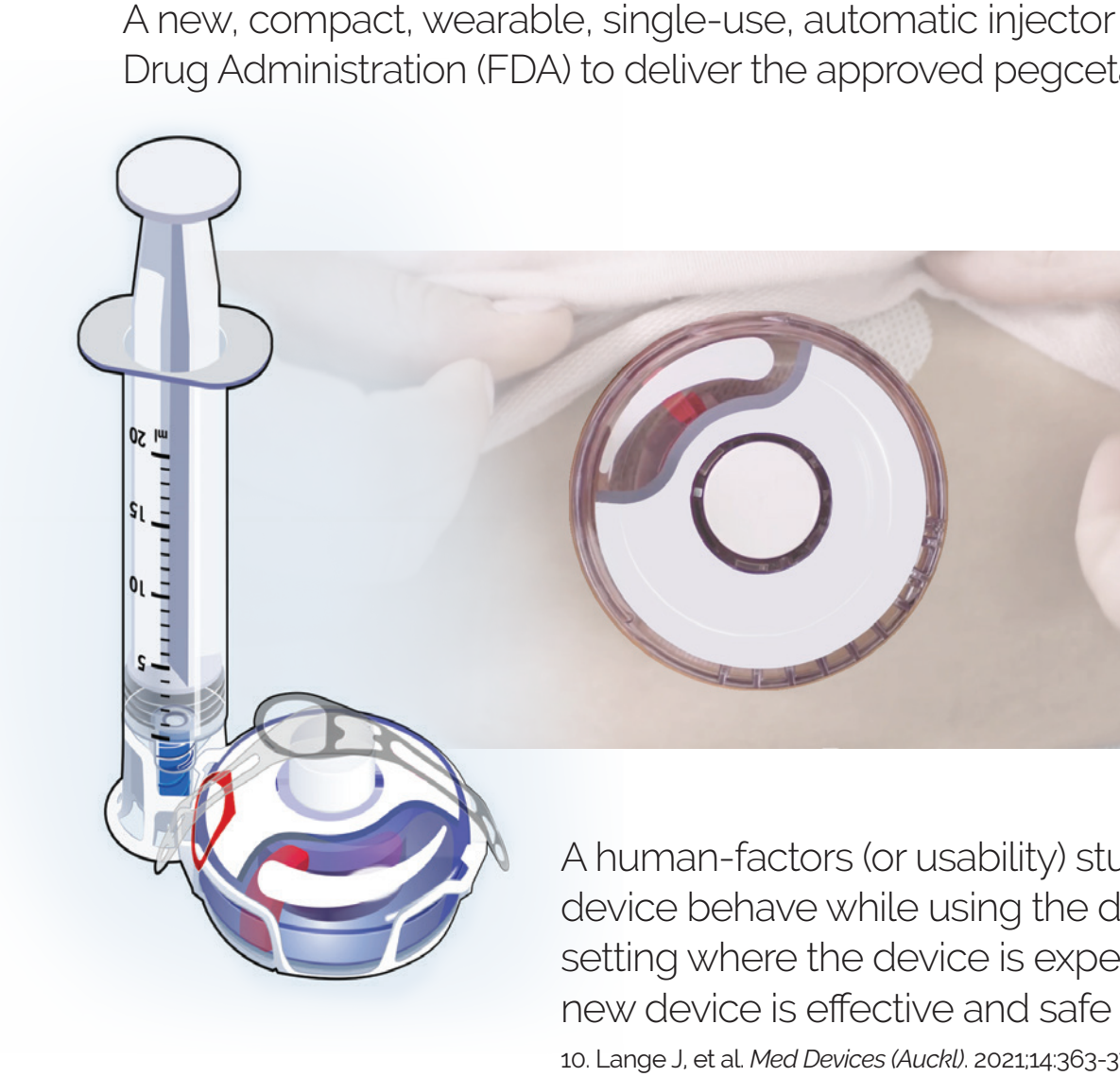
Patients with PNH require continuous treatment to manage chronic and debilitating symptoms, including anemia, fatigue, and hemoglobinuria[2]



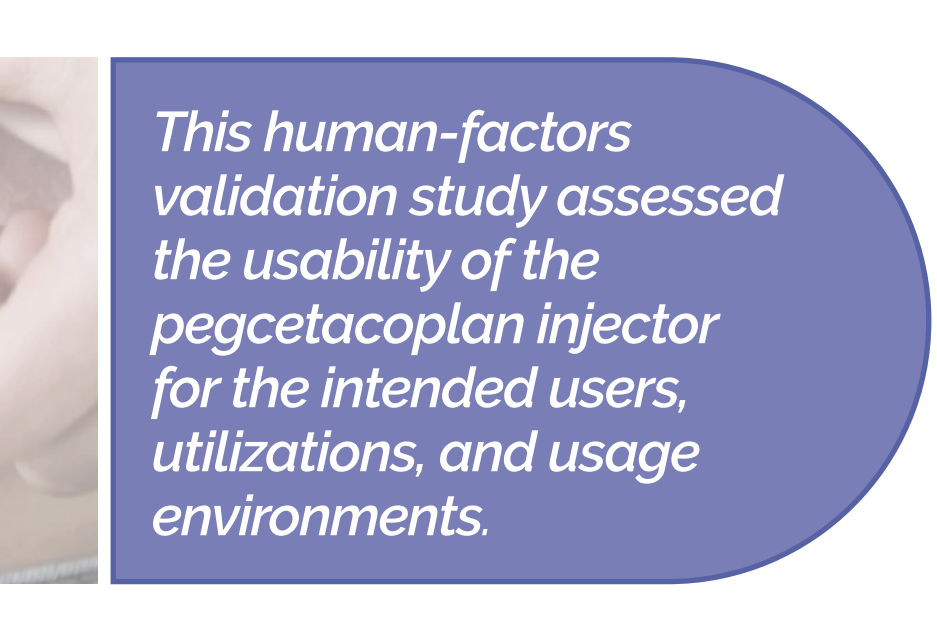
2. Waheed A, et al. *Blood Rev*. 2024;64:101158. 3. Schrezenmeier H, et al. *Ann Hematol*. 2020;99(7):1505-1514.

Pegcetacoplan is the first targeted complement component 3 (C3) therapy approved for PNH[4-9]

By inhibiting complement activation at the C3 and C3b level, pegcetacoplan prevents both C5-mediated intravascular hemolysis and C3b-dependent extravascular hemolysis[4–7]


Complement activation
C3
C3 convertase
Pegcetacoplan: C3 and C3b inhibition prevents both extravascular and intravascular hemolysis
C3a
C3b
Extravascular hemolysis in the liver and spleen
C3b opsonization of red blood cells
C5
C5 inhibitors: only prevent intravascular hemolysis
C5 convertase
C5a
C5b
Intravascular hemolysis in the blood vessels
Formation of complement membrane attack complex C5b-9 on red blood cells

Pegcetacoplan is administered as a 1 or 2 bolus subcutaneous (SC) injection(s) over 30–60 minutes with an ambulatory syringe pump[8,9]



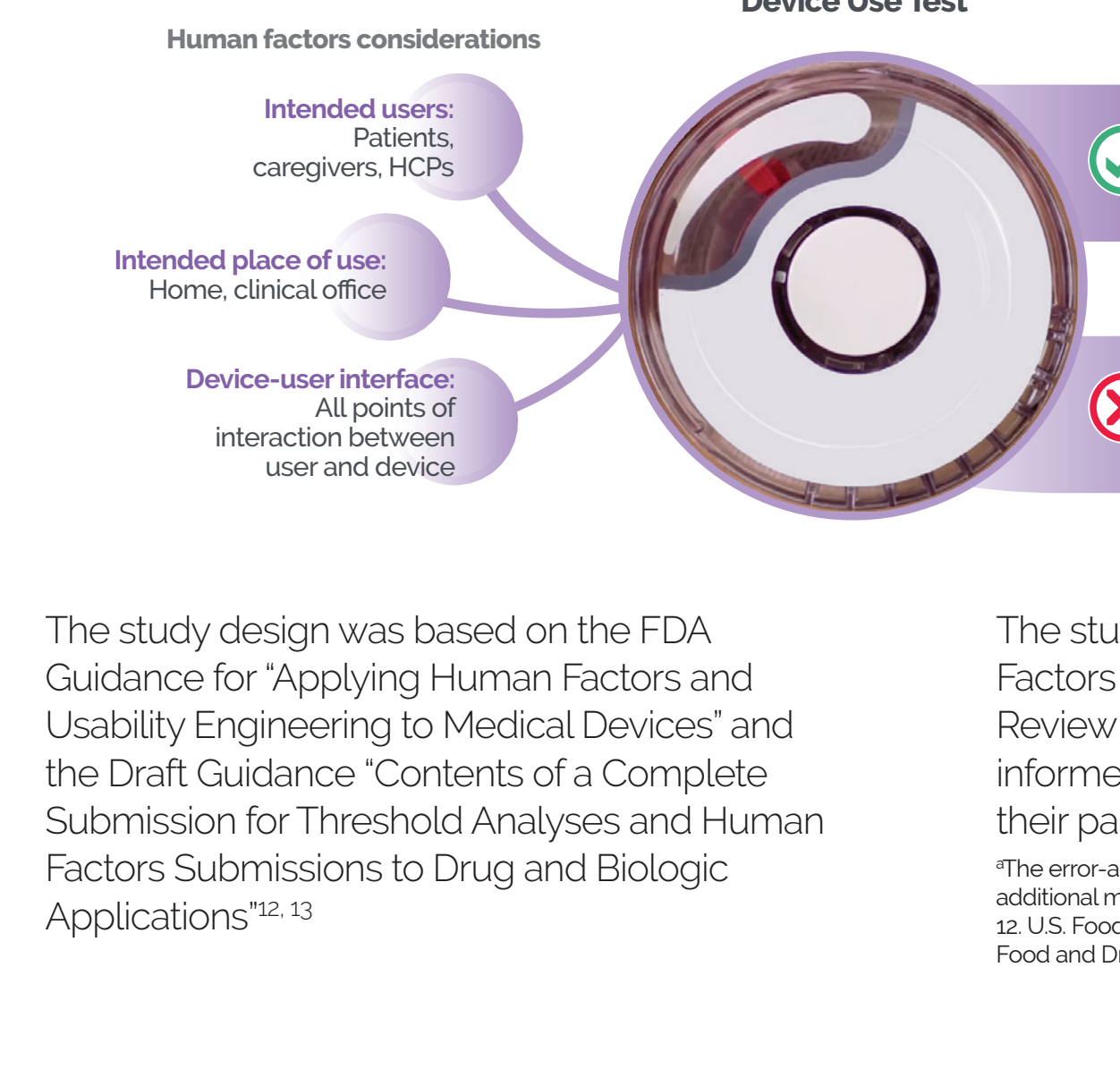
After being trained by a health care provider (HCP), a patient (or their caregiver) may self-administer the SC injection at home[8,9]

4. De Castro C, et al. *Am J Hematol*. 2020;95(11):1334-1343. 5. Hillmen P, et al. *N Engl J Med*. 2021;384(11):1028-1037. 6. de Latour RP, et al. *Lancet Haematol*. 2022;9(9):e648-e659. 7. Wong RSM, et al. *Blood Adv*. 2023;7(11):2468-2478. 8. Empaveli (pegcetacoplan) prescribing information; 2024. 9. Aspaveli (pegcetacoplan) summary of product characteristics; 2024.

Study objective

Wearable autoinjectors have the potential to enable the safe and effective self-administration of single bolus doses, thereby positively impacting quality of life, treatment adherence, and therapy outcomes[10]

A new, compact, wearable, single-use, automatic injector was recently approved by the U.S. Food and Drug Administration (FDA) to deliver the approved pegcetacoplan dose for patients with PNH[11]

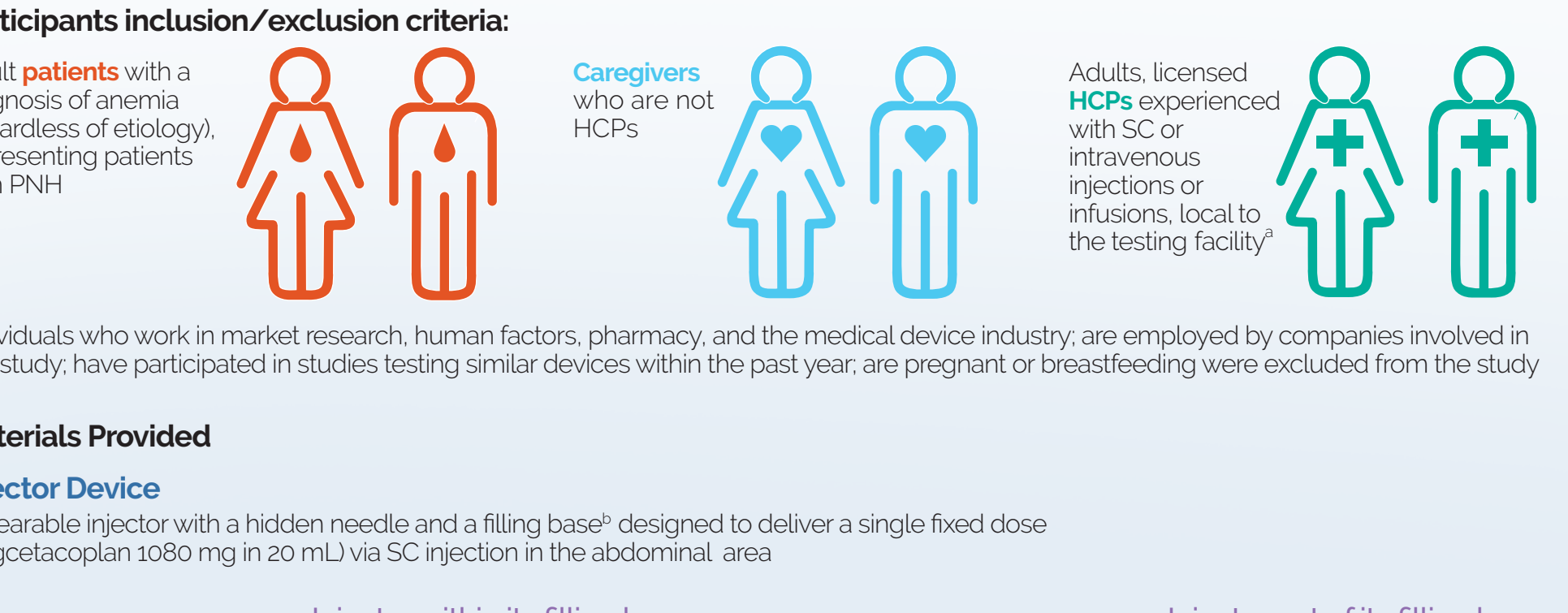


This human-factors validation study assessed the usability of the pegcetacoplan injector for the intended users, utilizations, and usage environments.

A human-factors (or usability) study examines how the planned users of a new device behave while using the device as intended by the manufacturer, in a setting where the device is expected to be used, with the aim to validate the new device is effective and safe for its intended use

10. Lange J, et al. *Med Devices (Auckl)*. 2021;14:363-377. 11. Empaveli (pegcetacoplan) injector instructions for use; 2023.

Human-factors validation study design to evaluate a drug injector device[12,13]


Device Use Test
Human factors considerations
Intended users: Patients, caregivers, HCPs
Intended place of use: Home, clinical office
Device-user interface: All points of interaction between user and device
Outcome
Correct use (no errors/errors with acceptable risk[a]):
Device is safe and effective to use
Use errors (errors leading to unacceptable risk):
Device is unsafe or ineffective to use

The study design was based on the FDA Guidance for "Applying Human Factors and Usability Engineering to Medical Devices" and the Draft Guidance "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications"[12, 13]

The study was approved by the Core Human Factors Inc. (Bala Cynwyd, PA, USA) Institutional Review Board. All participants provided written informed consent and were compensated for their participation.

[a]The error-associated highest severity of harm was below the threshold for additional mitigations and the benefits of the injector outweighed the risks. 12. U.S. Food and Drug Administration (FD) Guidance; February 2016. 13. U.S. Food and Drug Administartion (FDA) Guidance; September 2018.

Study participants and materials provided

Participants inclusion/exclusion criteria:

- Adult **patients** with a diagnosis of anemia (regardless of etiology), representing patients with PNH
- **Caregivers** who are not HCPs
- Adults, licensed **HCPs** experienced with SC or intravenous injections or infusions, local to the testing facility[a]

Individuals who work in market research, human factors, pharmacy, and the medical device industry; are employed by companies involved in this study; have participated in studies testing similar devices within the past year; are pregnant or breastfeeding were excluded from the study

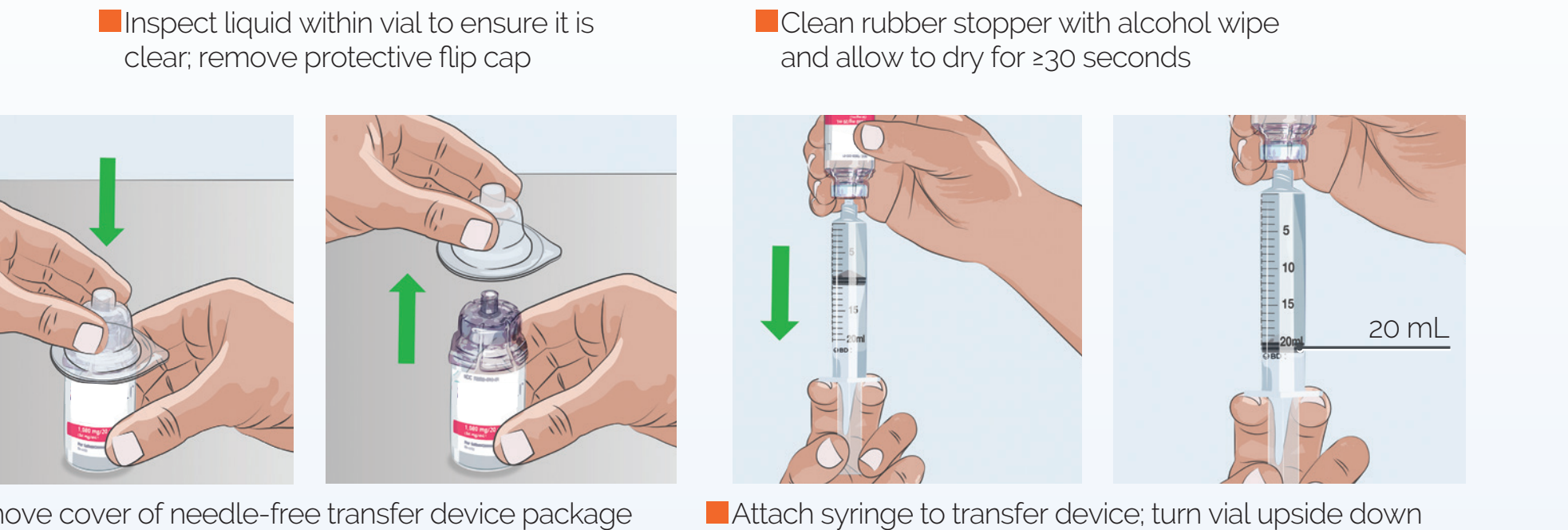
Materials Provided

Injector Device

A wearable injector with a hidden needle and a filling base[b] designed to deliver a single fixed dose (pegcetacoplan 1080 mg in 20 mL) via SC injection in the abdominal area

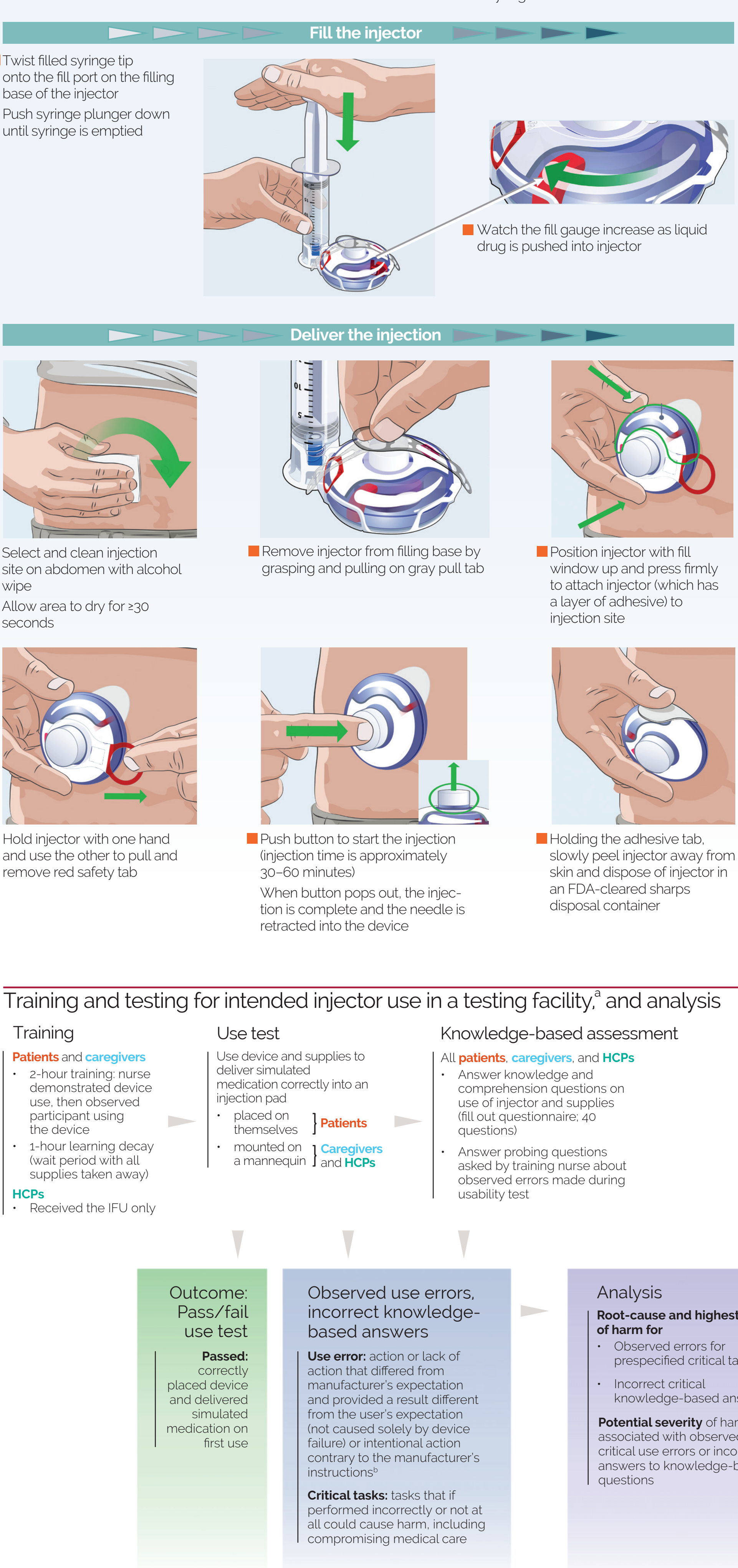
Learning Materials

Ancillary Supplies



[a]Testing facility (Ximedica, Plymouth, MN, USA) simulated a patient's home or HCP's clinical office; [b]Enable Injections, Inc.; Cincinnati, OH, US. [c]IFU overview on next page.

Instruction-for-use (IFU) form overview: 45 identified steps, including 31 critical tasks


Fill the syringe
Flip cap
Gray rubber stopper
Inspect liquid within vial to ensure it is clear; remove protective flip cap
Clean rubber stopper with alcohol wipe and allow to dry for ≥30 seconds
Remove cover of needle-free transfer device package
Secure transfer device onto vial, and remove blister package
20 mL
Attach syringe to transfer device; turn vial upside down and fill syringe with 20 mL of liquid drug by pulling slowly on the plunger
Remove air from syringe by gently pushing plunger
Detach the filled syringe
Fill the injector
Twist filled syringe tip onto the fill port on the filling base of the injector
Push syringe plunger down until syringe is emptied
Watch the fill gauge increase as liquid drug is pushed into injector
Deliver the injection
Select and clean injection site on abdomen with alcohol wipe
Allow area to dry for ≥30 seconds
Remove injector from filling base by grasping and pulling on gray pull tab
Position injector with fill window up and press firmly to attach injector (which has a layer of adhesive) to injection site
Hold injector with one hand and use the other to pull and remove red safety tab
Push button to start the injection (injection time is approximately 30–60 minutes)
When button pops out, the injection is complete and the needle is retracted into the device
Holding the adhesive tab, slowly peel injector away from skin and dispose of injector in an FDA-cleared sharps disposal container

Training and testing for intended injector use in a testing facility,[a] and analysis

Training

Patients and caregivers
- 2-hour training: nurse demonstrated device use, then observed participant using the device
- 1-hour learning decay (wait period with all supplies taken away)

HCPs
- Received the IFU only

Use test

Use device and supplies to deliver simulated medication correctly into an injection pad
- placed on themselves } Patients
- mounted on a mannequin } Caregivers and HCPs

Knowledge-based assessment

All patients, caregivers, and HCPs
- Answer knowledge and comprehension questions on use of injector and supplies (fill out questionnaire; 40 questions)
- Answer probing questions asked by training nurse about observed errors made during usability test

Outcome: Pass/fail use test

Passed: correctly placed and delivered simulated medication on first use

Observed use errors, incorrect knowledge-based answers

Use error: action or lack of action that differed from manufacturer's expectation and provided a result different from the user's expectation (not caused solely by device failure) or intentional action contrary to the manufacturer's instructions[b]

Critical tasks: tasks that if performed incorrectly or not at all could cause harm, including compromising medical care

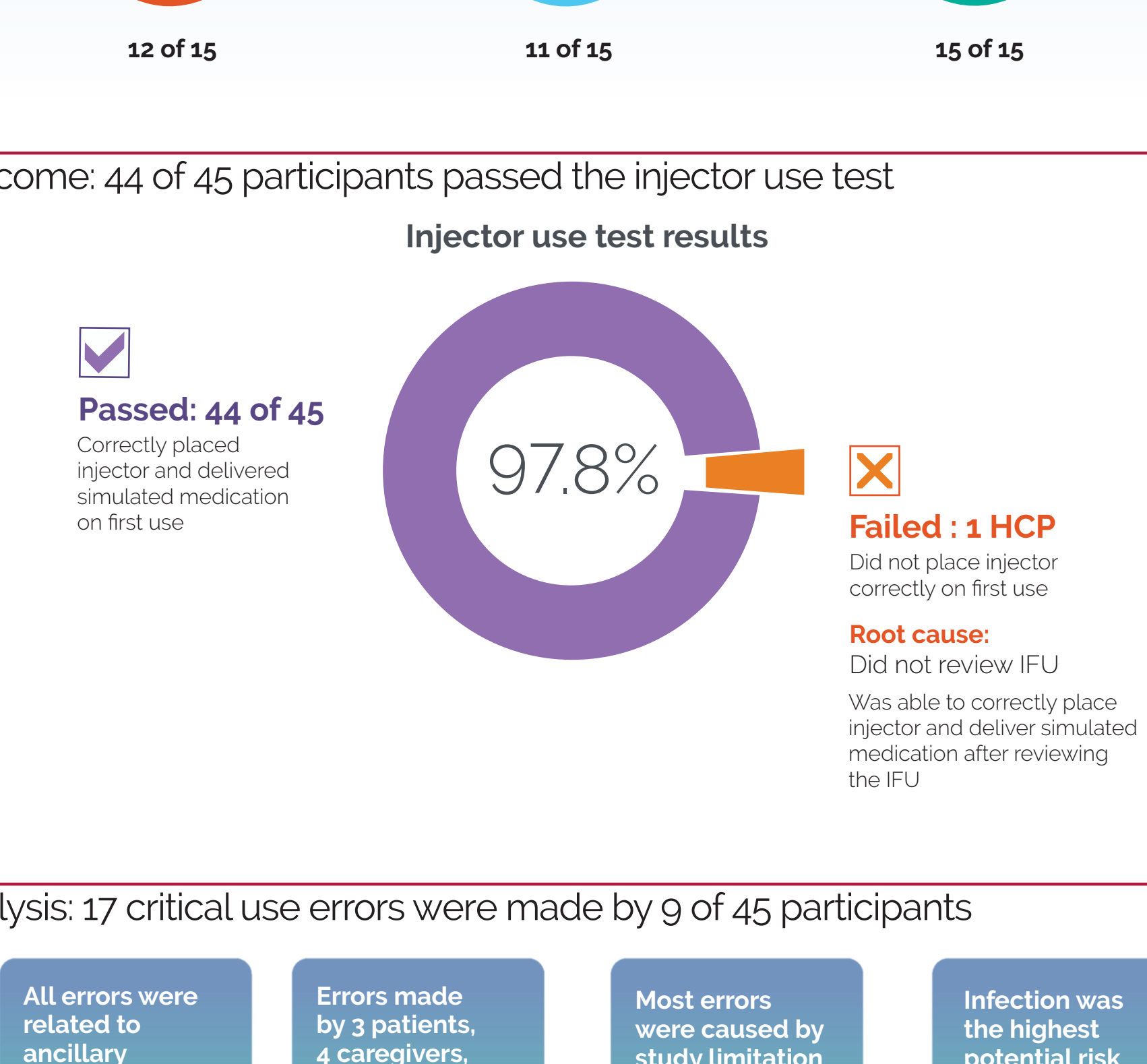
Analysis

Root-cause and highest risk of harm for
- Observed errors for prespecified critical tasks
- Incorrect critical knowledge-based answers

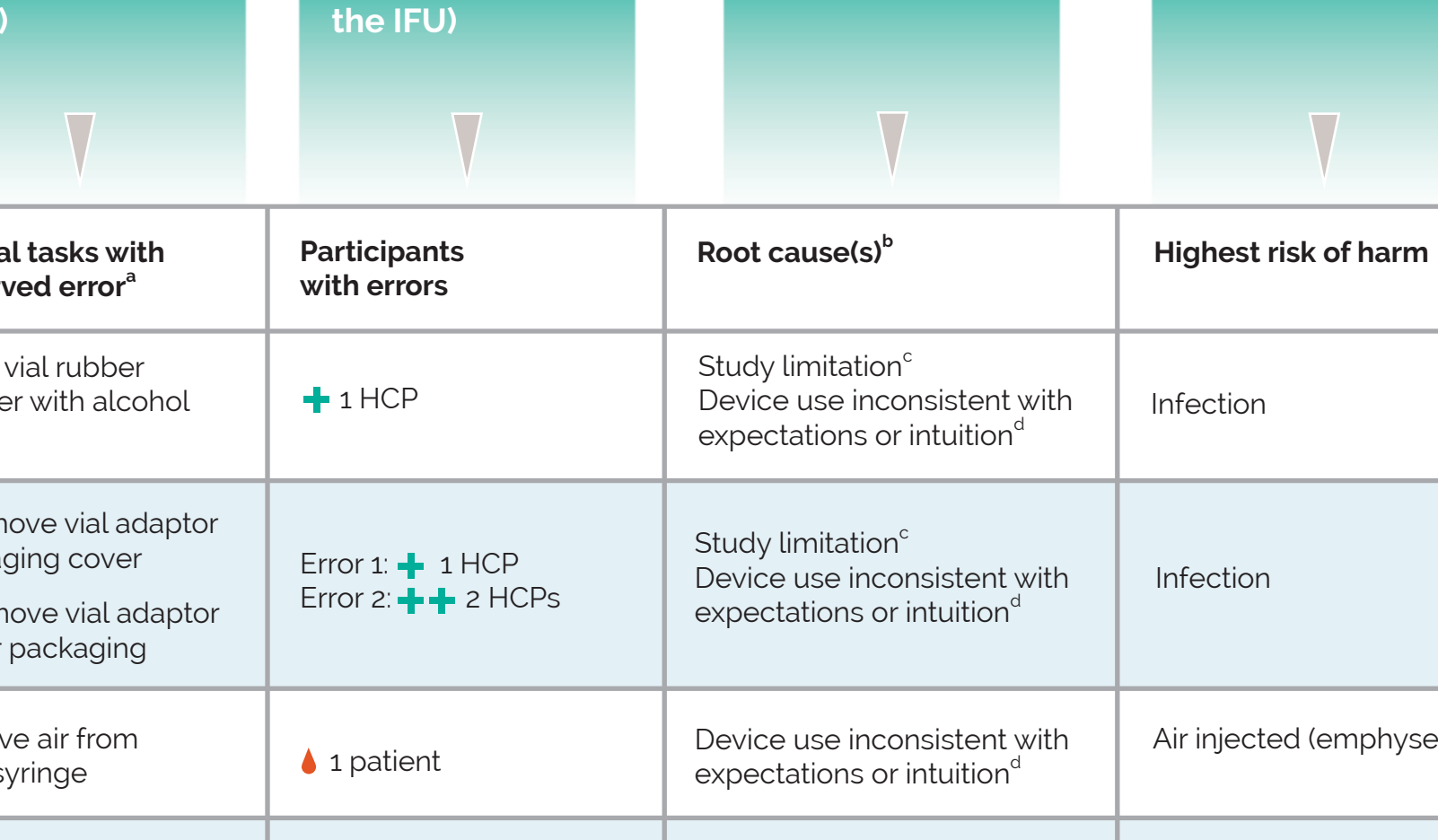
Potential severity of harm associated with observed critical use errors or incorrect answers to knowledge-based questions

[a]Training and testing were conducted in a private room at a facility (Ximedica, Plymouth, MN, USA) that simulated some conditions encountered in a patient's home or HCP's clinical office. [b]Examples of use error include not cleaning the vial rubber stopper with an alcohol wipe, not removing the air bubbles from the syringe, not removing the injector from the filling base, not removing the safely tab, not pushing the injector button, not waiting for the injector button to pop up.

Participants: distribution, age, and experience with injections



Outcome: 44 of 45 participants passed the injector use test


Injector use test results
Passed: 44 of 45
Correctly placed injector and delivered simulated medication on first use
97.8%
Failed : 1 HCP
Did not place injector correctly on first use
Root cause:
Did not review IFU
Was able to correctly place injector and deliver simulated medication after reviewing the IFU

Analysis: 17 critical use errors were made by 9 of 45 participants

- **All errors were related to ancillary supplies use or injection site preparation (not the device use)**
- **Errors made by 3 patients, 4 caregivers, and 2 HCPs (6/10 errors by 1 HCP who had not read the IFU)**
- **Most errors were caused by study limitation (simulated injection) and lapse (omission)**
- **Infection was the highest potential risk of harm**

	Critical tasks with observed error[a]	Participants with errors	Root cause(s)[b]	Highest risk of harm
Filling the syringe	Clean vial rubber stopper with alcohol wipe	1 HCP	Study limitation[c] Device use inconsistent with expectations or intuition[d]	Infection
Filling the syringe	1-Remove vial adaptor packaging cover 2-Remove vial adaptor blister packaging	Error 1: 1 HCP Error 2: 2 HCPs	Study limitation[c] Device use inconsistent with expectations or intuition[d]	Infection
Filling the syringe	Remove air from filled syringe	1 patient	Device use inconsistent with expectations or intuition[d]	Air injected (emphysema)
Filling the syringe	Clean injection area with alcohol wipe	2 caregivers	Lapse (inconsistent alcohol wipes and IFU labelling)[d] Study limitation[c]	Infection
		1 HCP	Study limitation[c] Device use inconsistent with expectations or intuition[d]	
Filling the syringe	Let cleaned injection area dry for ≥30 seconds	2 patients, 1 HCP	Lapse (inconsistent alcohol wipes and IFU labelling)[d]	Infection
		2 caregivers	Study limitation[c] Intentional misuse (thought the site had dried sooner)	
Injection delivery	1-Remove injector from filling base 2-Remove safety tab	Error 1: 1 HCP Error 2: 1 HCP	Study limitation[c] Device use inconsistent with expectations or intuition[d]	Insignificant delay in therapy
Injection delivery	1-Push injector button 2-Wait for button to pop up	Error 1: 1 HCP Error 2: 1 HCP	Study limitation[c] Device use inconsistent with expectations or intuition[d]	Infection

Patient Caregiver HCP

[a]Errors listed in order of tasks within the IFU. [b]More than one cause could be selected. [c]Use of mannequin and simulated medication. [d]Verbiage from FDA Guidance "Applying Human Factors and Usability Engineering to Medical Devices" was applied to modify this root cause category (U.S. Food and Drug Administration [FDA]; February 2016).[12]

Analysis: 6 of 28 critical knowledge-based questions had errors identified

- **For the most common errors (injector exposed to direct sunlight; ok to sweat or sleep while wearing device), participants were able to correctly answer related questions (injector should be stored at room temperature; what to do if device falls off during injection)**
- **Errors were made by 8 patients, 6 caregivers, and 4 HCPs**
- **Most errors were caused by "IFU organization was not intuitive or clear"**
- **Device falling off and exposing the needle was the highest risk of harm**

Knowledge-based questions with observed errors			Participants with errors	Root Cause(s)	Highest risk of harm
Question	Correct answer(s)	Reported incorrect answer(s)			
What to do if injector is exposed to direct sunlight?	Do not use it Call HCP Use a different device	Use it Does not know	5 patients 3 caregivers 1 HCP	IFU organization not intuitive or clear	Injector falls off, needle exposed to others
Is it ok to sweat while wearing the injector?[a]	No	Yes Does not know	2 caregivers 3 HCPs	IFU organization not intuitive or clear	Injector falls off, needle exposed to others
What to do if injector falls off while it is injecting?	Set injector aside and call helpline or HCP	Does not know	2 patients 1 caregivers	IFU organization not intuitive or clear	Injector falls off, needle exposed to others
Is it ok to sleep while wearing the injector?	No	Yes	1 HCP	IFU organization not intuitive or clear	Injector falls off, needle exposed to others
What to do if injector has been dropped?	Do not use it Call HCP	Use it	2 patients	IFU organization not intuitive or clear	Injector falls off, needle exposed to others
Is it ok to store injector after filling?	No	Yes Does not know	1 caregivers	IFU organization not intuitive or clear	Injector falls off, needle exposed to others

Patient Caregiver HCP

[a]Question was flawed and could not be answered.

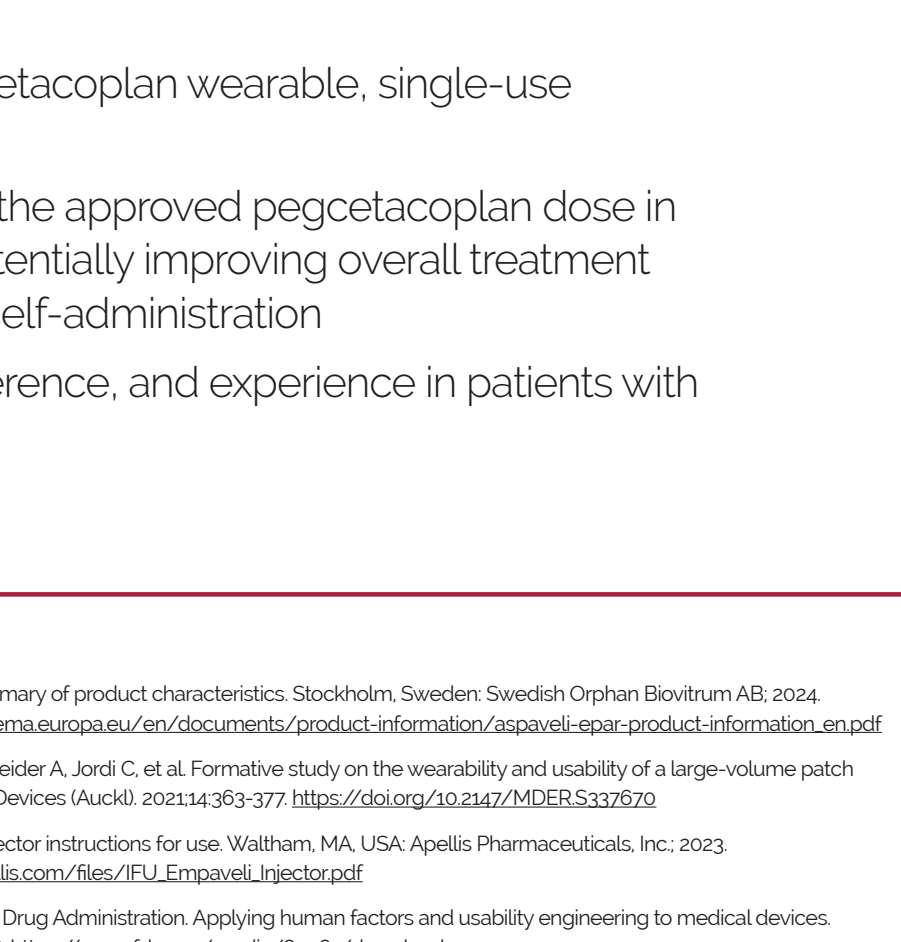
Discussion

This human-factors study validated the usability of the approved pegcetacoplan injector for the prespecified utilization by the intended users in the expected settings

The residual risk of harm from all the errors observed during the study was deemed acceptable and the injector did not need any improvement for its safe use in patients who regularly self-administer SC (patients with PNH)

Individual patient and caregiver education, including education provided by the Apellis Care Educators (ACEs) program, may help further mitigate potential use errors

No adverse event occurred during the study



Limitations:
- Small sample size
- Given the rare nature of PNH,[14] a representative population of patients with anemia was included in this study; however, previous studies demonstrated comparable fatigue levels in patients with PNH or anemia, supporting an overlapping disease burden[5,15]
- An injection pad was used for drug delivery rather than placing it on the patient's skin; however, this simulated protocol is recommended to avoid unnecessary purposeful needle stick[16]

5. Hillmen P, et al. *N Engl J Med*. 2021;384(11):1028-1037. 14. Jalbert JJ, et al. *Blood*. 2019;134(suppl 1):3407. 15. Prochaska MT, et al. *J Hosp Med*. 2017;12(11):898-904. 16. Ballmann J, Ewers M. *Haemophilia*. 2022;28(6):e153-e163.

Conclusion and implications

This study demonstrated the overall usability of the approved pegcetacoplan wearable, single-use automatic injector device

The pegcetacoplan injector may be safe and effective in delivering the approved pegcetacoplan dose in patients with PNH, thereby possibly reducing treatment burden, potentially improving overall treatment compliance, and conceivably enhancing patients' experience with self-administration

Additional studies could further explore the treatment burden, adherence, and experience in patients with PNH who self-administer pegcetacoplan with the new injector

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Disclosures

Hanaa Shahin, Lawton Laurence, and Dana Korkuch are employees of Apellis Pharmaceuticals, Inc. and hold stock or stock options.

The study was conducted by Worrell Design Inc. (Minneapolis, MN, USA) on behalf of Enable Injections, Inc. (Cincinnati, OH, USA). Patients were recruited by Ascendancy Research (Minneapolis, MN, USA), employed by Worrell Design Inc.