Health Technology Briefing
October 2022

CAEL-101 for treating amyloid light chain amyloidosis

Company/Developer	Alexion Pharmaceuticals

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29774	NICE ID: 10666	UKPS ID: 660232

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

CAEL-101 is in clinical development for the treatment of amyloid light chain (AL) amyloidosis. AL amyloidosis belongs to a group of diseases called systemic amyloidosis in which deposits of proteins (called amyloids) accumulate and cause damage in tissues and organs, such as the kidneys, liver, gut, heart and nerves. In AL amyloidosis, the deposits are made up of proteins (called immunoglobulin light chains) produced in excess by malfunctioning white blood cells in the bone marrow. AL amyloidosis is a life-threatening and long-term debilitating condition because of the damage to organs, particularly the heart and kidneys. There are limited treatment options for AL amyloidosis that treats the amyloid deposits that have accumulated in tissues and organs.

CAEL-101 is a monoclonal antibody (a type of protein), which recognises and attaches to light chain fibrils (the structures that build up in amyloidosis). CAEL-101 is administered by intravenous infusion over the course of 2 hours. It acts by helping the removal of amyloid fibrils in the tissues and has been shown to improve heart and kidney function in people with AL amyloidosis. If licenced, CAEL-101 would offer a treatment option for people with AL amyloidosis that improves organ function by reducing the amyloid deposits in the tissues/organs.

Proposed Indication

Mayo stage IIIa/b Amyloid Light chain (AL) amyloidosis.[1-3]

Technology

Description

CAEL-101 (chimeric fibril-reactive IgG1k monoclonal antibody 11-1F4) is a chimeric immunoglobulin G1 kappa (κ) isotype that reacts specifically with light chain fibrils, irrespective of their κ or lambda (λ) isotype, but not with the native forms. CAEL-101 was shown to bind to a cryptic epitope at the N-terminal of light chain proteins that adopt a non-native b-sheet structure, which is conserved in κ and λ mis-folded light chains. It is hypothesized that CAEL-101 will modify the disease course of AL amyloidosis by facilitating the removal of amyloid fibrils deposited in tissues.[4]

CAEL-101 is in clinical development for the treatment of Mayo stage IIIa/b PCD treatment-naïve AL amyloidosis patients. In the phase III clinical trials (NCT04512235; NCT04504825), CAEL-101 is administered by intravenous (IV) infusion at a dose of 300mg over approximately 2 hours. The minimum planned treatment time for each patient will be at least 50 weeks or until the patient's death.[2,3]

Key Innovation

CAEL-101 is a first-in-class monoclonal antibody (mAb) designed to improve organ function by reducing or eliminating amyloid deposits in the tissues and organs of patients with AL amyloidosis. In an ongoing phase II clinical trial (CAEL101-203, NCT04304144), 49-week results have shown it is generally well-tolerated, and exploratory clinical biomarker data suggests possible cardiac disease improvements and renal response.[5]

If licensed, CAEL-101 in combination with SoC would be an additional treatment option for patients with Mayo stage IIIa/b AL amyloidosis.

Regulatory & Development Status

CAEL-101 does not currently have Marketing Authorisation in the EU/UK for any indication.

CAEL-101 has orphan drug designation in the EU in 2019 for the treatment of AL amyloidosis.[6,7] It was also granted US FDA Fast Track Designation in June 2021.[7]

Patient Group

Disease Area and Clinical Need

Amyloidosis is the name for a group of rare, serious conditions caused by a build-up of an abnormal protein, called amyloid, in organs and tissues throughout the body. This build-up of amyloid proteins can make it difficult for organs and tissues to function properly and, without treatment, can lead to organ failure. AL amyloidosis is the most common type of amyloidosis and is caused by an abnormality in plasma cells in the bone marrow. In healthy individuals, plasma cells produce light chain proteins as part of natural antibody proteins, which help protect the body from infection. In AL amyloidosis, abnormal light chains clump together in amyloid fibrils that the body cannot easily clear away, resulting in a build-up and leading to the malfunction of tissues and organs. Symptoms of AL amyloidosis depend on which tissues and organs are affected but can include kidney and heart failure which can cause fluid retention, tiredness, weakness, loss

of appetite, shortness of breath, and abnormal heartbeat. Other symptoms include light-headedness or fainting, numbness or tingling in the hand and feet, nausea, diarrhoea or constipation, and easy bruising.[8]

In the UK about 500-600 new cases are diagnosed each year and it is the cause of death in between 0.5 to 1 out of every 1000 people.[9] In England, 2021-22, there were 4,798 finished consultant episodes (FCE) for patients with a primary diagnosis with amyloidosis (ICD-10 code E85), resulting in 8,874 FCE bed days and 3,231 day cases.[10]

Recommended Treatment Options
Daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone is the only approved pharmacological treatment option for AL amyloidosis.[11]

Clinical Trial Information

Trial	NCT04512235; EudraCT 2020-000713-32; A Phase 3, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of CAEL-101 and Plasma Cell Dyscrasia Treatment Versus Placebo and Plasma Cell Dyscrasia Treatment in Plasma Cell Dyscrasia Treatment Naïve Patients With Mayo Stage IIIa AL Amyloidosis **Phase III –** Recruiting **Location(s):** 8 EU countries, UK, USA, Canada and other countries **Primary completion date:** March 2025
Trial Design	Randomised, double-blind, parallel assignment
Population	N=267 (estimated); aged 18 years and older; Patients with Mayo stage IIIa PCD treatment-naïve AL amyloidosis
Intervention(s)	300mg of CAEL-101 (IV) (concentration of 30mg/ml) over approximately 2 hours + Standard of Care (SoC). The minimum planned treatment time for each patient will be at least 50 weeks or until the patient's death
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measures: 1) Time from the date of randomization to date of death or end of study [Time Frame: 50 weeks] 2) Number of patients with treatment emergent adverse events as assessed by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [Time Frame: 50 weeks] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT04504825; EudraCT 2019-004254-28; A Phase 3, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of CAEL-101 and Plasma Cell Dyscrasia Treatment Versus Placebo and Plasma Cell Dyscrasia Treatment in

	Plasma Cell Dyscrasia Treatment Naïve Patients With Mayo Stage IIIb AL Amyloidosis **Phase III –** Recruiting **Location(s):** 9 EU countries, UK, USA, Canada and other countries **Primary completion date:** December 2024
Trial Design	Randomised, double-blind, parallel assignment
Population	N=124 (estimated); aged 18 years and older; Patients with Mayo stage IIIb PCD treatment-naïve AL amyloidosis
Intervention(s)	300mg of CAEL-101 (IV) (concentration of 30mg/ml) over approximately 2 hours + Standard of Care (SoC). The minimum planned treatment time for each patient will be at least 50 weeks or until the patient's death
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measures: 1) Time from the date of randomization to date of death or end of study. [Time Frame: 50 weeks] 2) Number of patients with treatment emergent adverse events as assessed by CTCAE v5.0 [Time Frame: 50 weeks] See trial record for full list of other outcomes,
Results (efficacy)	-
Results (safety)	-

Trial	**CAEL101-203; NCT04304144;** A Phase 2, Open-label, Multicenter Dose Selection Study to Evaluate the Safety and Tolerability of CAEL-101 in Patients With AL Amyloidosis **Phase II –** Active, not recruiting **Location(s):** USA **Primary completion date:** January 2023
Trial Design	Open label, non-randomised, sequential assignment
Population	N=25 (actual); aged 18 years or older; Patients with AL amyloidosis Mayo stage I, II, or IIIa
Intervention(s)	• **Part A: CAEL-101 + SoC (cyclophosphamide, bortezomib, and Dexamethasone (CyBorD)** CAEL-101 (IV) over approximately 2 hours. The initial cohort dose assignments of CAEL-101 will be Cohort 1 - 500 mg/m^2; Cohort 2 - 750 mg/m^2; Cohort 3 - 1000 mg/m^2. CAEL-101 will be administered weekly for the first 4 weeks, and then every other week until end of study, in combination with the SoC CyBorD chemotherapy. • **Part B: CAEL-101 + SoC CyBorD and daratumumab** CAEL-101 (IV) at the recommended Phase 3 dose (RP3D) dose level. CAEL-101 will be administered weekly for the first 4 weeks, and then

	every other week until end of study, in combination with the SoC CyBorD chemotherapy and daratumumab.
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: Dose Toxicity [Time Frame: 4 weeks]
Results (efficacy)	Organ responses (most notably renal response) have occurred early in the course of therapy and appears to be durable. Organ responses in some patients have also improved over time with some significant improvement in patient global peak longitudinal strain (GLS) evaluations by echocardiogram.[12]
Results (safety)	All patients were treated successfully through their fourth dose, the highest (1000 mg/m^2) cohort enrolling six patients. No dose-limiting toxicities (DLT) were observed, and CAEL-101 was well-tolerated by all patients. The most common treatment emergent adverse events (TEAEs) were diarrhoea and nausea (each 30.8%).[4] CAEL-101 with anti-plasma cell therapy remains reasonably well-tolerated with no unanticipated adverse effects.[12]

Estimated Cost

The cost of CAEL-101 is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Daratumumab in combination for untreated systemic amyloid light-chain amyloidosis (ID3748). Expected date of issue to be confirmed.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Amyloidosis (All Ages). E13/S(HSS)/c.

Other Guidance

- British Society for Haematology. Guidelines on the diagnosis and investigation of AL amyloidosis. October 2014.[13]
- British Society for Haematology. Guidelines on the management of AL amyloidosis. October 2014.[14]

Additional Information

References

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