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Calquence approved in the US for adult patients with chronic lymphocytic leukaemia

Two Phase III Calquence trials demonstrated superior progression-free survival across multiple settings while maintaining favourable tolerability

Calquence combined with obinutuzumab and as monotherapy reduced the risk of disease progression or death by 90% and 80%, respectively in ELEVATE-TN

AstraZeneca today announced that the US Food and Drug Administration (FDA) has approved *Calquence* (acalabrutinib) for adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).[1] The US approval was granted under the FDA's Real-Time Oncology Review and newly established Project Orbis programmes.

The approval is based on positive results from the interim analyses of two Phase III clinical trials, ELEVATE-TN in patients with previously untreated CLL and ASCEND in patients with relapsed or refractory CLL. Together, the trials showed that *Calquence* in combination with obinutuzumab or as a monotherapy significantly reduced the relative risk of disease progression or death versus the comparator arms in both 1st-line and relapsed or refractory CLL. Across both trials, the safety and tolerability of *Calquence* were consistent with its established profile.[1]

Dave Fredrickson, Executive Vice President, Oncology Business Unit said: "With over 20,000 new cases anticipated this year in the US alone, today's approval of *Calquence* provides new hope for patients with one of the most common types of adult leukaemia, offering outstanding efficacy and a favourable tolerability profile. The chronic lymphocytic leukaemia patient population is known to face multiple comorbidities, and tolerability is a critical factor in their treatment."

Dr Jeff Sharman, Director of Research at Willamette Valley Cancer Institute, Medical Director of Hematology Research for The US Oncology Network, and a lead author of the ELEVATE-TN trial, said: "Tolerability remains an issue in the current treatment landscape of chronic lymphocytic leukaemia, which may require ongoing therapy for many years. In the ELEVATE-TN and ASCEND trials comparing *Calquence* to commonly used treatment regimens, *Calquence* demonstrated a clinically meaningful improvement in progression-free survival in patients across multiple settings, while maintaining its favourable tolerability and safety profile."

The results of the interim analysis of the ELEVATE-TN trial will be presented at the upcoming American Society of Hematology congress.[2]

The trial showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) for patients treated with either *Calquence* in combination with obinutuzumab or *Calquence* monotherapy versus chlorambucil chemotherapy plus obinutuzumab, a current standard-of-care combination used in the control arm.[1]

In the *Calquence* combination arm, risk of disease progression or death was reduced by 90% (HR 0.10; 95% CI, 0.06-0.17, p<0.0001) and in the monotherapy arm it was reduced by 80% (HR 0.20; 95% CI, 0.13-0.30, p<0.0001).[1]

The median time to disease progression for patients treated with *Calquence* in combination with obinutuzumab or as a monotherapy has not yet been reached versus 22.6 months (95% CI, 20-28) for chlorambucil plus obinutuzumab.[1]

ELEVATE-TN safety overview (most common ARs, ≥15%):[1]

	***Calquence* plus obinutuzumab (n=178)**		***Calquence* monotherapy (n=179)**		**Chlorambucil plus obinutuzumab (n=169)**	
Adverse reaction	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Infection†	69%	22%	65%	14%	46%	13%
Neutropenia†	53%	37%	23%	13%	78%	50%
Anemia†	52%	12%	53%	10%	54%	14%
Thrombocytopenia†	51%	12%	32%	3.4%	61%	16%
Headache	40%	1.1%	39%	1.1%	12%	0
Diarrhoea	39%	4.5%	35%	0.6%	21%	1.8%
Musculoskeletal pain†	37%	2.2%	32%	1.1%	16%	2.4%
Fatigue	34%	2.2%	23%	1.1%	24%	1.2%
Bruising†	31%	0	21%	0	5%	0
Rash†	26%	2.2%	25%	0.6%	9%	0.6%
Arthralgia	22%	1%	16%	0.6%	4.7%	1.2%
Dizziness	20%	0	12%	0	7%	0
Hemorrhage†	20%	1.7%	20%	1.7%	6%	0
Nausea	20%	0	22%	0	31%	0
Lymphocytosis†	12%	11%	16%	15%	0.6%	0.6%

†Includes multiple ADR terms.

In patients treated with the combination of *Calquence* plus obinutuzumab, adverse reactions (ARs) led to treatment discontinuation in 11% of patients and a dose reduction of *Calquence* in 7% of patients. In the monotherapy arm, ARs led to discontinuation in 10% and dose reduction in 4% of patients.[1] In the control arm, ARs led to regimen discontinuation in 14% of patients with a dose reduction of chlorambucil in 28% of patients.[3] There were no dose reductions for obinutuzumab.[1,3]

In 1,029 patients with haematologic malignancies who were treated with *Calquence* 100mg approximately every 12 hours across multiple clinical trials, where 88% received treatment for at least six months and 79% received treatment for at least one year, serious or Grade ≥3 infections occurred in 19%, and Grade 3 atrial fibrillation and flutter occurred in 1.1% of patients. In the same patient population, major haemorrhage occurred in 3.0% (serious or Grade ≥3 bleeding or any central nervous system bleeding), with fatal haemorrhage occurring in 0.1% of patients. Second primary malignancies (all grades) including skin cancers occurred in 12% of patients.[1]

The US approval is among the first to be granted under Project Orbis, an initiative of the US FDA Oncology Center of Excellence, which provides a framework for concurrent submission and review of oncology medicines among international partners. The FDA, the Australian Therapeutic Goods Administration, and Health Canada collaborated on this review. [4]

About *Calquence*

In the US, *Calquence* (acalabrutinib) is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL). In the US, Canada, Australia, Brazil, Qatar, the United Arab Emirates, Mexico, Argentina, Singapore, Chile, and

recently India, *Calquence* is indicated for adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Approved under accelerated review in the US, continued approval for previously treated MCL is contingent upon verification and confirmation of clinical benefit in confirmatory trials.

Calquence is a next-generation selective inhibitor of Bruton's tyrosine kinase (BTK). *Calquence* binds covalently to BTK, thereby inhibiting its activity.[1,5,6,7] In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion.[1]

As part of an extensive clinical development programme, AstraZeneca and Acerta Pharma are currently evaluating *Calquence* in 23 company-sponsored clinical trials. *Calquence* is being developed for the treatment of multiple B-cell blood cancers including CLL, MCL, diffuse large B-cell lymphoma, Waldenström macroglobulinaemia and follicular lymphoma and other haematologic malignancies. Several Phase III clinical trials in CLL are ongoing, including ASCEND, ELEVATE-TN, ELEVATE-RR (ACE-CL-006) evaluating *Calquence* versus ibrutinib in patients with previously treated high-risk CLL, and ACE-CL-311 evaluating *Calquence* in combination with venetoclax and with/without obinutuzumab versus chemoimmunotherapy in patients with previously untreated CLL without 17p deletion or *TP53* mutation.

About ELEVATE-TN

ELEVATE-TN (ACE-CL-007) is a randomised, multicentre, open-label Phase III trial evaluating the safety and efficacy of *Calquence* in combination with obinutuzumab, a CD20 monoclonal antibody, or *Calquence* alone versus chlorambucil, a chemotherapy, in combination with obinutuzumab in previously untreated patients with CLL. In the trial, 535 patients were randomised (1:1:1) into three arms. Patients in the first arm received chlorambucil in combination with obinutuzumab. Patients in the second arm received *Calquence* (100mg twice daily until disease progression or unacceptable toxicity) in combination with obinutuzumab. Patients in the third arm received *Calquence* monotherapy (100mg twice daily until disease progression or unacceptable toxicity).[1,8]

The primary endpoint is PFS in the *Calquence* and obinutuzumab arm compared to the chlorambucil and obinutuzumab arm, assessed by an independent review committee (IRC), and a key secondary endpoint is IRC-assessed PFS in the *Calquence* monotherapy arm compared to the chlorambucil and obinutuzumab arm. Other secondary endpoints include objective response rate, time to next treatment and overall survival.[1,8]

About ASCEND

ASCEND (ACE-CL-309) is a global, randomised, multicentre, open-label Phase III trial evaluating the efficacy of *Calquence* in previously treated patients with CLL. In the trial, 310 patients were randomised (1:1) into two arms. Patients in the first arm received *Calquence* monotherapy (100mg twice daily until disease progression or unacceptable toxicity). Patients in the second arm received investigator's choice of either rituximab, a CD20 monoclonal antibody, in combination with idelalisib, a PI3K inhibitor, or rituximab in combination with bendamustine, a chemotherapy.[1,9]

The primary endpoint is PFS assessed by an IRC, and key secondary endpoints include physician-assessed PFS, IRC- and physician-assessed overall response rate and duration of response, as well as overall survival, patient-reported outcomes and time to next treatment.[1,9]

About CLL

Chronic lymphocytic leukaemia (CLL) is one of the most common types of leukaemia in adults, with an estimated 105,000 new cases globally each year and 20,720 new cases in the US in 2019, and the number of people living with CLL is expected to grow with improved treatment as patients live longer with the disease.[10,11,12,13] In CLL, too many blood stem cells in

the bone marrow become abnormal lymphocytes and these abnormal cells have difficulty fighting infections.[10] As the number of abnormal cells grows there is less room for healthy white blood cells, red blood cells and platelets.[10] This could result in anaemia, infection and bleeding.[10] B-cell receptor signalling through BTK is one of the essential growth pathways for CLL.

About AstraZeneca in haematology
Leveraging its strength in oncology, AstraZeneca has established haematology as one of four key oncology disease areas of focus. The Company's haematology franchise includes two US FDA-approved medicines and a robust global development programme for a broad portfolio of potential blood cancer treatments. Acerta Pharma serves as AstraZeneca's haematology research and development arm. AstraZeneca partners with like-minded science-led companies to advance the discovery and development of therapies to address unmet need.

About AstraZeneca in oncology
AstraZeneca has a deep-rooted heritage in oncology and offers a quickly-growing portfolio of new medicines that has the potential to transform patients' lives and the Company's future. With at least six new medicines to be launched between 2014 and 2020, and a broad pipeline of small molecules and biologics in development, the Company is committed to advance oncology as a key growth driver for AstraZeneca focused on lung, ovarian, breast and blood cancers. In addition to AstraZeneca's main capabilities, the Company is actively pursuing innovative partnerships and investments that accelerate the delivery of our strategy, as illustrated by the investment in Acerta Pharma in haematology.

By harnessing the power of four scientific platforms - Immuno-Oncology, Tumour Drivers and Resistance, DNA Damage Response and Antibody Drug Conjugates - and by championing the development of personalised combinations, AstraZeneca has the vision to redefine cancer treatment and, one day, eliminate cancer as a cause of death.

About AstraZeneca
AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas - Oncology, Cardiovascular, Renal and Metabolism, and Respiratory. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

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