Cost Minimization Analysis of Bruton Tyrosine Kinase Inhibitors in Adults With Relapsed/Refractory Chronic Lymphocytic Leukemia

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INTRODUCTION

- Chronic lymphocytic leukemia (CLL) is associated with high disease morbidity and detriments to quality of life; it accounts for 1% of all cancers in the UK (2016-2018)[1,2]
  - Following an initial response to treatment, most patients with CLL experience relapse and need additional therapy, while a proportion of patients have disease that becomes refractory to initial treatment[3]
  - The 2022 British Society for Haematology guidelines suggest that the optimal treatment following progression varies depending on the front-line therapy.[4] For patients experiencing progression following front-line treatment with a Bruton tyrosine kinase inhibitor (BTKi), a B-cell lymphoma 2 inhibitor (BCL2i) regimen (eg, venetoclax ± rituximab) is recommended; for patients experiencing progression following front-line treatment with a BCL2i, BTKis such as ibrutinib and acalabrutinib are recommended
- Zanubrutinib, a next-generation BTKi, demonstrated clinical superiority vs ibrutinib, a first-generation BTKi, for the treatment of adults with relapsed/refractory (R/R) CLL in the ALPINE trial (NCT03734016; hazard ratio [HR] for progression-free survival [PFS], 0.65; 95% CI, 0.49-0.86; *P*=.002)[5]
- The objective of this study was to conduct a cost minimization analysis (CMA) to assess the costs associated with BTKi monotherapies (zanubrutinib, acalabrutinib, and ibrutinib) for the treatment of R/R CLL in adults who have received ≥1 previous therapy

METHODS

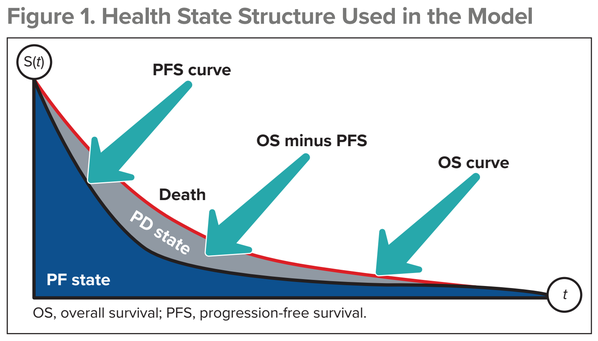
Model Overview

- The CMA approach (which assumes equal efficacy of zanubrutinib to ibrutinib and acalabrutinib) was selected for the following reasons:
  - Statistically significant improvement in primary and key secondary endpoints was demonstrated with zanubrutinib vs ibrutinib in the ALPINE trial.[5] To be conservative, the analysis was conducted assuming zanubrutinib to be noninferior to ibrutinib
  - Given the same mechanism of action of zanubrutinib and acalabrutinib, which are next-generation BTKis, an assumption of noninferiority was made and validated by expert clinical advice

Model Structure

- A partition survival model with 3 mutually exclusive health states–progression free, progressive disease, and death–was developed (**Figure 1**). The model accrued and compared patients' survival outcomes and associated costs over the time horizon for each BTKi monotherapy
  - A 4-week (28-day) cycle length was used to accommodate the administration schedule of treatment regimens, while allowing sufficient granularity to accurately capture differences in cost and health effects between cycles

Figure 1. Health State Structure Used in the Model



OS, overall survival; PFS, progression-free survival.

Model Inputs

- The model was developed using clinical trial data and published costs and resource use data to estimate the costs over the 30-year time horizon from a UK National Health Service (NHS) and Personal Social Services perspective; the annual discount rate for cost outcomes was 3.5%.[6] An overview of key model inputs and sources is provided in **Table 1**

Table 1. Summary of Key Model Inputs and Sources

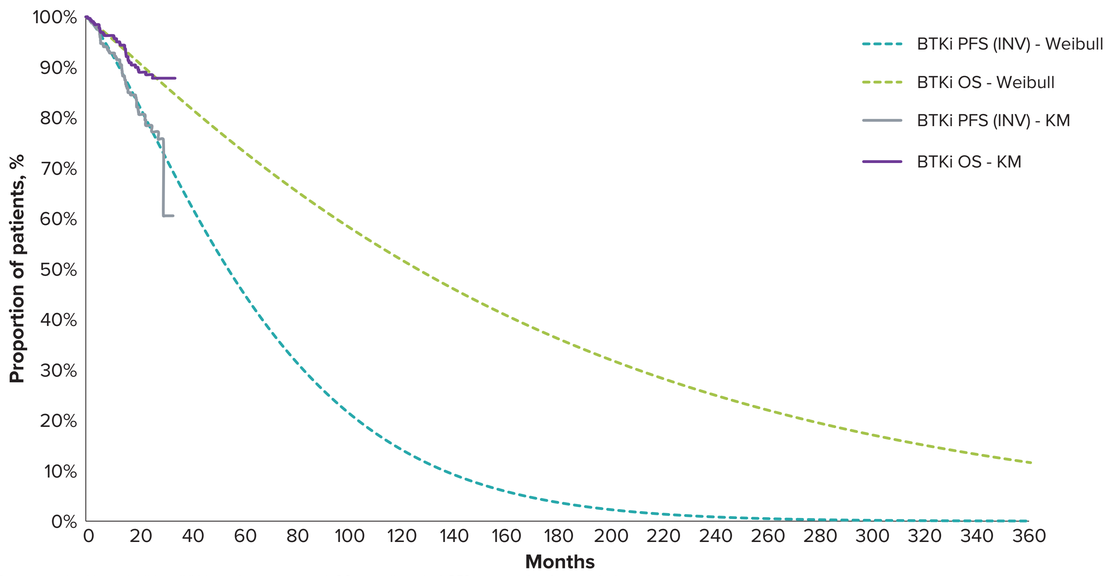
Input	Values	Sources
Baseline characteristics		
Starting age, years	66.90	ALPINE study[5]
Women, %	31.7	
Weight, kg	78.53	
Clinical parameters		
PFS INV	Weibull distribution selected for zanubrutinib; HR of 1 applied for acalabrutinib and ibrutinib	ALPINE study[5]
OS		
TTD	Treated until progression	
Cost parameters (2022), £		
Zanubrutinib[a]	4600.07 (per cycle)	BNF 2022,[7] 160 mg BID[8]
Acalabrutinib[a]	4721.73 (per cycle)	BNF 2022,[7] 100 mg BID[9]
Ibrutinib[a]	4292.40 (per cycle)	BNF 2022,[7] 420 mg QD[10]

[a] BTKis are administered orally; therefore, the model assumed no administration costs. Relative dosing intensity of 100%. Acquisition costs are based on BNF list prices excluding any patient access scheme discounts.
BNF; British National Formulary; BTKi, Bruton tyrosine kinase inhibitor; HR, hazard ratio; INV, investigator assessed; OS, overall survival; PFS, progression-free survival; QD, once daily; TTD, time to treatment discontinuation.

Clinical Parameters

- The key clinical parameters used in the model were PFS, overall survival (OS), and time to treatment discontinuation (TTD; for cost calculations only). For each parameter, parametric survival analysis was conducted by fitting survival functions to patient-level data of the ALPINE trial (zanubrutinib arm) to estimate long-term extrapolation according to the guidance from the National Institute for Health and Care Excellence (**Figure 2**)[11]
- To model noninferiority within the CMA framework, the following assumptions were made:
  - An HR of 1 (vs zanubrutinib) was assumed for both acalabrutinib and ibrutinib for PFS and OS
  - Time on treatment was assumed to be equal across zanubrutinib, acalabrutinib, and ibrutinib, with all BTKis modeled to be given until progression (ie, TTD was capped by PFS)

Figure 2. Model Inputs: Survival Projections for BTKis



BTKi, Bruton tyrosine kinase inhibitor; INV, investigator assessed; OS, overall survival; PFS, progression-free survival.
A cost minimization analysis is used, assuming noninferiority between zanubrutinib, acalabrutinib, and ibrutinib.
PFS and OS curves are therefore assumed to be equivalent across all BTKis.

CONCLUSIONS

- Zanubrutinib provides an alternative, next-generation BTKi option for adult patients with R/R CLL in the UK, with lower lifetime costs compared with acalabrutinib
- Managing AEs for zanubrutinib is, on average, less costly than for both acalabrutinib and ibrutinib
- Further exploration into the comparative efficacy and cost-effectiveness of BTKis is warranted to reflect the improved efficacy and safety of zanubrutinib

Safety Parameters

- The model accounts for the impact of all grade ≥3 treatment-related adverse events (AEs) occurring in ≥2% of study participants receiving treatment (across any BTKi treatment option)
- All AEs were assumed to occur and be resolved in the first 4 weeks of treatment. Therefore, all AE-related costs were applied to the proportion of patients experiencing the event in the first cycle of the model

Cost Parameters

- The cost categories included in the model were drug acquisition, drug administration, and costs associated with the management of treatment-related AEs. All cost inputs are shown in Great British Pound for 2022 UK cost year
  - The sources used to derive AE costs included AE incidence from Brown et al 2023[5], Ghia et al 2020[12], Shadman et al 2023[13], and Shanafelt et al 2019[14]; and unit costs from the National Schedule of NHS Costs 2020/2021[15]
  - Costs associated with disease management and monitoring and subsequent treatments, as well as terminal care costs, were assumed to be equal across BTKis given the equal efficacy assumption; these costs were omitted from the analysis

RESULTS

- Over a lifetime horizon, treatment with zanubrutinib in adults with R/R CLL was associated with cost savings of £7802 per person vs acalabrutinib and an incremental cost of £19,677 per person vs ibrutinib (**Table 2**)
  - Difference in drug acquisition costs was the key reason for the cost differential between treatments. Zanubrutinib was associated with fewer AE management costs compared with acalabrutinib and ibrutinib, due to an improved safety profile (**Table 2**)
  - A deterministic sensitivity analysis indicated that the model was most sensitive to changes in the intercept parameter of the Weibull model used for PFS. Variation in intercept resulted in a total increment cost range of £14,191 to £26,636 vs ibrutinib and −£10,554 to −£5,633 vs acalabrutinib. Variation in all other parameters had minimal impact on the overall incremental costs
- A probabilistic sensitivity analysis assessed joint parameter uncertainty (based on a 95% CI or published ranges) over 1000 model iterations and indicated that the model is robust considering all parameter uncertainties (**Table 2**)

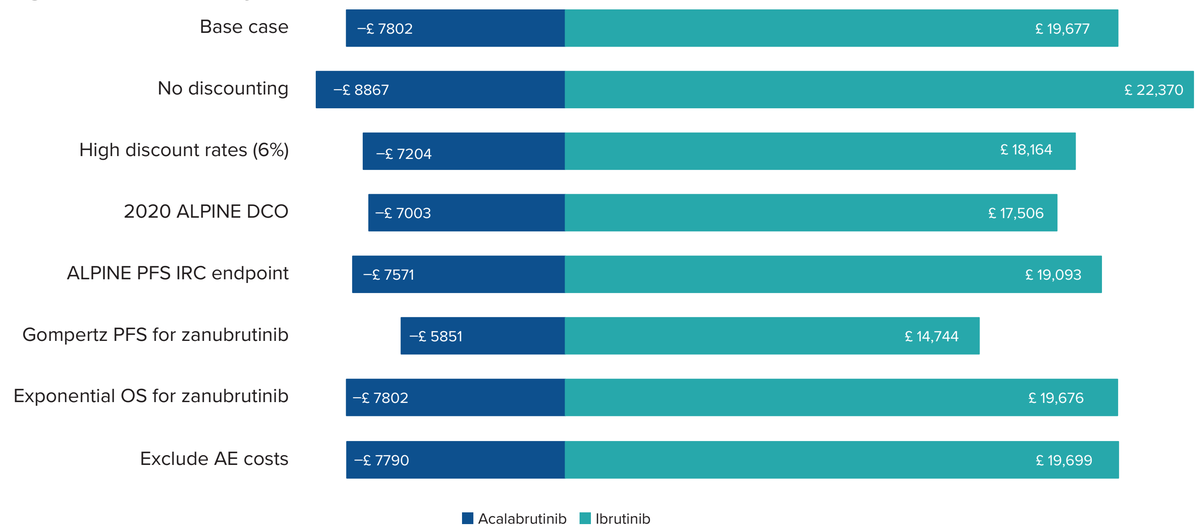
Table 2. Model Results

Input, £	Zanubrutinib	Ibrutinib	Acalabrutinib
Deterministic results			
Drug acquisition	294,529	274,830	302,319
AE management	286	309	298
Total costs	294,815	275,139	302,617
Incremental costs	–	19,677	−7802
Probabilistic results			
Incremental costs, mean (95% CI)	–	19,868 (14,162 to 26,661)	−7876 (−10,603 to −5630)

AE, adverse event.

- Scenario analysis was conducted to test the impact of alternative input values and sources (**Figure 3**)
  - Zanubrutinib use resulted in cost savings vs acalabrutinib in all scenarios considered
  - Using a Gompertz distribution to extrapolate PFS for BTKis reduced the incremental cost in favor of zanubrutinib (£14,744) vs ibrutinib

Figure 3. Scenario Analysis: Incremental Costs for Zanubrutinib vs Acalabrutinib and Ibrutinib



AE, adverse event; DCO, data cutoff; IRC, institutional review committee; OS, overall survival; PFS, progression-free survival.

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DISCLOSURES

AC-K: Consultancy for and honoraria from BeiGene; Holder of equity or stock options and member of Board of Directors or advisory committees for Ascentage, Cellectar, Starton, and Alpha2; Patents and royalties from Alpha2. **LM, KY**: Employment: BeiGene. **LW**, **SU**: Employment: FIECON, which received consultancy fees from BeiGene. **RG, AS**: Employment: Evidera, a part of PPD, which received funding from BeiGene.

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