2 EXECUTIVE SUMMARY

Acute lymphoblastic leukemia (ALL) affects between 1 and 4.75 per 100 000 people (Redaelli, A. et al. 2005), and accounts for 80% of all leukemia cases in children. The aim of this systematic literature review (SLR) was to understand the existing evidence regarding the clinical effectiveness and safety of treatments administered for pediatric populations (aged from > 28 days to < 18 years) with high-risk first-relapse Philadelphia chromosome-negative (Ph-) BCP-ALL.

This SLR follows Cochrane review methodology for SLRs and was registered with the international prospective register of systematic reviews (PROSPERO). MEDLINE®, Embase, and the Cochrane Library were interrogated. Additional congress searches were performed from 2018 to 2020, as well as hand-searches of clinicaltrials.gov and European Clinical Trials Register databases. A total of 1774 papers were initially identified. Of these, 316 studies were included for full-text review, during which 289 were excluded. Seven SLR or meta-analysis studies were excluded but tagged for future reference, as were 35 studies that met all inclusion criteria except for clear reporting of the Ph status of their participants.

Hand searching identified five more studies that also met all inclusion criteria except clear reporting of Ph chromosome status. These were again tagged for future reference if needed. It should be noted, however, that the majority of pediatric patients with BCP-ALL are Ph- (around 95%) (Koo, H. H. 2011), and therefore these studies were tagged separately from other excluded studies, for future reference if needed.

Finally, four studies were identified that met the inclusion criteria fully, and the data were extracted from these into an Amgen-approved data extraction table. Of the four identified studies, two evaluated blinatumomab (BLINCYTO®), a bispecific T-cell engager (BiTE®), as an intervention Locatelli, F et al. 2020; the Amgen 20120215 study (clinicaltrials.gov listing NCT02393859), one studied idarubicin and mitoxantrone (Irving, J. et al. 2016), and a small case series of five patients used allogeneic engineered T-cells expressing an anti-CD19 chimeric antigen receptor (Qasim, W et al. 2018)

The blinatumomab studies reported that, compared with the third block of standard of care consolidation chemotherapy in first-line relapse treatment, blinatumomab provided better

event-free survival and overall survival (OS), with fewer Grade ≥3 and serious treatment-emergent adverse events, and a minimal residual disease response of 73−91%.

One identified observational, post-hoc study (Irving, J. et al. 2016) compared high- and standard-risk patients in the ALL R3 trial (Parker, C. et al. 2010), reporting significantly worse 5-year OS (hazard ratio [HR] 4.15; 95% CI 3.07, 5.61; $p < 0.001$]) and progression-free survival (HR 3.45; 95% CI 2.60, 4.60; $p < 0.001$) in high-risk patients than in those classified as standard risk.

A small Phase I study of five patients was also identified (Qasim, W et al. 2018). Patients were treated with UCART19 (anti-CD19 scFv- 41BB- CD3ζ), a genetically modified chimeric antigen receptor T-cell product manufactured from healthy donor cells, in which the *TRAC* and *CD52* genes have been disrupted to allow administration in non-human leukocyte antigen (HLA)-matched patients. All patients achieved a complete remission with incomplete hematologic recovery (CRi) and underwent a subsequent allogeneic stem cell transplant (alloSCT). Two patients relapsed and died, another patient died from transplant-related complications, and two patients remained in remission at the time of writing.

Safety results were sparsely reported in the identified studies; however, the 20120215 results indicated that blinatumomab, when compared with HC3 chemotherapy, was associated with fewer Grade ≥ 3 treatment-related adverse events overall and, specifically, fewer incidences of febrile neutropenia, leukopenia, neutropenia, thrombocytopenia, acute pancreatitis, and stomatitis. Using a cut-off of 3% of affected patients, neurological adverse events such as seizures were reported as serious adverse events more frequently with blinatumomab than with the third block of high-risk consolidation chemotherapy.

The available evidence suggests that high-risk patients will likely experience significantly worse outcomes than patients with lower risk profiles. According to findings in this SLR, blinatumomab, the bispecific T-cell engager (BiTE®), has a good safety profile and is an effective treatment for pediatric patients with high-risk, first-relapse Ph- BCP-ALL, when used as consolidation therapy. Chimeric antigen receptor T-cell products may be a possible avenue of treatment, but more research is needed. Overall, this is a very limited patient population and, as such, further research is warranted in pediatric patients with high-risk, first-relapse Ph- BCP-ALL.