Pfizer Limited
Walton Oaks, Dorking Road, Walton on the Hill,
Tadworth, Surrey KT20 7NS, UK
Telephone: +44 (0)1304 616161

Worldwide Biopharmaceutical Businesses

Dr. Rosie Bennyworth
Appeals Committee Vice Chair
National Institute for Health & Care Excellence
10 Spring Gardens
LONDON
SW1A 2BU

4 September 2017

Dear Dr. Bennyworth,

APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION FOR INOTUZUMAB OZOGAMICIN FOR TREATING RELAPSED OR REFRACTORY B-CELL ACUTE LYPHOBLASTIC LEUKAEMIA

Pfizer Ltd hereby gives notice that it would like to appeal against the final appraisal determination for inotuzumab ozogamicin for the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL), ID893.

EXECUTIVE SUMMARY

Pfizer's appeal against the Final Appraisal Determination for inotuzumab ozogamicin ("inotuzumab") for treating relapsed or refractory B-cell acute lymphoblastic leukaemia is based on the following grounds:

Ground 1

- The Appraisal Committee has seemingly failed to consider the cost-effectiveness of inotuzumab applicable to UK practice, when used in accordance with its marketing authorisation.
- The fact that a number of important clinical issues were raised during the consultation on the ACD, clinical experts were not invited to the second meeting of the Appraisal Committee, meaning that important clinical advice was not available to guide the preparation of the FAD.
- The Committee has provided no explanation for its decision to reject the utilities proposed in the revised Pfizer base case for the post HSCT period and submitted in response to consultation.

Ground 2

- The Appraisal Committee's reasons for disregarding key assumptions used for the purposes of NICE's appraisal of blinatumomab do not explain the choices that were made in relation to inotuzumab.
- The Committee has seemingly misunderstood the utilities submitted by Pfizer in response to consultation on the ACD.
- The Committee has misinterpreted Pfizer's revised submission on administration costs.

When these points, indicative of lack of procedural fairness and conclusions which are unreasonable, are corrected, they result in an ICER which is well within the range viewed as an acceptable use of NHS resources for treatments for patients at the end of life.

INTRODUCTION

Inotuzumab is an antibody-drug conjugate (ADC) comprising a derivative of calicheamicin (a cytotoxic antibody agent) attached to an engineered humanised monoclonal immunoglobulin G4 (IgG4) antibody, which targets CD22, a protein expressed in B-cell ALL. Inotuzumab received orphan designation from the European Commission for the treatment of B-cell acute lymphoblastic leukaemia on 7 June 2013, and a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) on 21 April 2017. It was granted a marketing authorisation under the centralised procedure on 29 June 2017. The authorisation states:

> "[Inotuzumab] is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI)".

Inotuzumab is administered by intravenous infusion in 3-4 week cycles. The approved Summary of Product Characteristics (SmPC) states that, for patients proceeding to haematopoietic stem cell transplant (HSCT), 2 cycles of treatment are recommended. A third cycle may be considered for those patients who do not achieve a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) and minimal residual disease (MRD) negativity after 2 cycles. For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered. The SmPC states that patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment.

PROCEDURAL HISTORY OF THE APPRAISAL

Inotuzumab was referred to NICE for consideration for appraisal on 8 June 2016. Pfizer provided a submission to NICE on 8 February 2017 and the Evidence Review Group, the CRD and CHE Technology Assessment Group, University of York, completed its Report on 12 April 2017.

The first meeting of the Appraisal Committee to consider inotuzumab took place on 16 May 2017 and an Appraisal Consultation Document (ACD) was issued for consultation on 6 June 2017. The preliminary recommendation at paragraph 1.1 of the ACD stated:

> "Inotuzumab ozogamicin is not recommended for treating relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia".

Responses to consultation were provided by stakeholders (including Pfizer) by 4 July 2017 and inotuzumab was considered by the Appraisal Committee for a second time on 12 July 2017. A Final Appraisal Determination (FAD) was issued on 18 August 2017. The FAD included the following recommendation at paragraph 1.1:

> "Inotuzumab ozogamicin is not recommended, within its marketing authorisation, for treating relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia in adults".

B-CELL ACUTE LYPHOBLASTIC LEUKAEMIA: BACKGROUND INFORMATION

Pfizer refers to its original submission in this appraisal. While a summary is provided below, this is not intended to replace the details originally supplied to NICE.

Acute lymphoblastic leukaemia (ALL) is a blood cancer that develops from lymphocytes (white blood cells) in the bone marrow. The disease results in immature and poorly differentiated cells, known as blasts, being disseminated in blood and affecting other tissues. The most common type of ALL is derived from B-lymphocytes (so-called B-cell ALL).

ALL may also be classified by the status of the Philadelphia chromosome, an abnormal version of chromosome 22, which incorporates a section of chromosome 9; Philadelphia chromosome positive ALL is associated with a worse prognosis than forms of the disease which are Philadelphia chromosome negative.

ALL is a rare cancer with around 760 patients diagnosed each year in England; some 40% of these patients are adults. Approximately 75% of ALL patients have the B-cell form of the disease. While adults account for only 40% of ALL patients, they account for 80% of ALL deaths, suggesting a more aggressive course of the disease when diagnosed in adults, as adults are more likely to present with unfavourable cytogenetic abnormalities or be unable to tolerate available treatment options.

The aim of treatment in patients with ALL is to achieve complete remission (CR) or complete remission with incomplete haematologic recovery (CRi) with minimal residual disease negativity (defined as having less than 1 x 10^{-4} (<0.01%) detectable leukaemic cells in bone marrow samples) so that patients can, if possible, proceed to haematopoietic stem cell transplantation (HSCT). However following initial treatment, approximately 48% of ALL patients are either shown to be treatment refractory or experience relapse. In general, adult patients with B-cell ALL experience very poor outcomes with average life expectancy well below a year.

There is currently no standard treatment pathway for patients with relapsed or refractory ALL in England. Current treatment options include fludarabine, cytarabine, and granulocyte colony-stimulating factor (G-CSF) (FLAG)-based chemotherapy, which is associated with prolonged hospitalisation and substantial toxicity. [redacted], one of the clinical experts for this appraisal, described such treatment as consisting of "relatively ineffective and highly toxic regimens of combination chemotherapy composed largely of agents used during the initial

therapy of ALL", emphasising the need for new treatment options for patients with relapsed or refractory ALL.

Around 117 patients per year are expected to be eligible for inotuzumab in England and Wales.

GROUNDS OF APPEAL

1. **GROUND 1: IN MAKING THE ASSESSMENT THAT PRECEDED THE RECOMMENDATION, NICE HAS a) FAILED TO ACT FAIRLY OR b) EXCEEDED ITS POWERS**

   1.1. The Appraisal Committee has seemingly failed to consider the cost-effectiveness of inotuzumab, applicable to UK clinical practice, when used in accordance with its marketing authorisation.

   The original submission by Pfizer proposed a key scenario analysis (section 5.8.3) whereby a maximum of three cycles of inotuzumab treatment was included in the economic model. This scenario was identified as being particularly relevant to decision making as it reflected the intended use of inotuzumab in the UK, as a treatment to bridge patients to HSCT (as supported and advised by clinical experts) rather than use as palliative care, and reflected the recommended administration in the draft SmPC. However, this scenario was not considered by the Appraisal Committee who, for the purposes of the ACD, accepted the base case scenario which included patients treating beyond three cycles, not reflective of UK clinical practice.

   The marketing authorisation for inotuzumab was granted after the initial meeting of the Appraisal Committee and confirmed that:

   > "For patients proceeding to haematopoietic stem cell transplant (HSCT), the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) and minimal residual disease (MRD) negativity after 2 cycles (see section 4.4). For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered. Patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment"

   Pfizer had indicated in its original submission, dated 8 February 2017, that inotuzumab is expected to be used as a bridge to potentially curative therapy, such as HSCT. Therefore, following grant of the marketing authorisation for inotuzumab on 29 June 2017, in Pfizer described the scenario involving three cycles of inotuzumab as the "key" scenario, noting that this was consistent with the SmPC (which precludes treatment involving more than three cycles) in patients intending to proceed to HSCT. Pfizer re-confirmed this was in line with expected practice through clinical expert consultation, as stated in the response to the ACD.

   For the avoidance of doubt, while the INO-VATE trial allowed up to six cycles of inotuzumab, all patients who achieved CR/CRi did so within three cycles. As stated in the response to ACD, as CR/CRi is the typical pre-requisite for HSCT, it would be expected that, if treatment is administered for a maximum of three cycles, this would result in the

same proportion of patients reaching HSCT as was observed in the INO-VATE trial (as the rate of CR/CRi is not impacted reported in the trial is not affected, i.e. no impact on efficacy).

In these circumstances, the cost-effectiveness of inotuzumab for patients proceeding to HSCT (the use considered by the Appraisal Committee) should have been based on a maximum of three cycles of therapy, consistent with the approved dosage, applicable to UK patients (bridging to HSCT) set out in the SmPC.

- NICE's Guide to the Technology Appraisal Processes states that guidance will generally be issued only in respect of a licenced medicine and a licenced treatment regime:

  > "Unless the Department of Health specifically indicates otherwise, NICE will not publish guidance on the use of a technology for indications that have not been given regulatory approval in the UK (that is, for unlicensed or 'off-label' use outside the terms of the technology's marketing authorisation).

- The Scope for this appraisal states that the remit is:

  > "To appraise the clinical and cost effectiveness of inotuzumab ozogamicin within its marketing authorisation for treating relapsed or refractory B-cell acute lymphoblastic leukaemia".

- The preliminary recommendation at paragraph 1.1 of the FAD refers to usage of inotuzumab "within its marketing authorisation".

However, while six cycles of treatment is not consistent with the marketing authorisation for inotuzumab when the product is used as a bridge for patients proceeding to HSCT (the intended use in the UK) and thus does not form a valid basis for considering the cost-effectiveness of inotuzumab used in accordance with its marketing authorisation for this indication, the Appraisal Committee either failed to consider economic modelling using only three cycles for the purposes of the FAD or, if it did consider three cycles, has failed to explain why it has not based its guidance on this scenario. This omission and/or lack of transparency is unfair.

For completeness, the use of six cycles of treatment for patients prescribed inotuzumab as a bridge to HSCT, as currently reflected in the modelling accepted by the Committee in the FAD, artificially and significantly inflates the ICER as compared with a calculation based on the dosage regimen for this patient population specified in the marketing authorisation.

1.2. The fact that the clinical experts were not invited to the second meeting of the Appraisal Committee meant that important clinical advice was not available to guide the preparation of the FAD

While clinical experts are always invited to the first meeting of the Appraisal Committee in order to provide advice and clarification to the Committee on matters that are not reflected in the published literature, whether they are invited to the second meeting is determined at the discretion of the Committee Chairman "if clarification of issues raised during the consultation period is needed" (paragraph 3.7.35 of NICE's Guide to the

Processes of Technology Appraisal). The discretion of the Chairman must be exercised fairly.

A number of important clinical issues were raised during consultation on the ACD, including:

- Mortality in patients with ALL who have undergone HSCT and have reached the cure point, including changes in survival over the past 37 years, in circumstances where the Appraisal Committee's conclusions are currently based on historic data from a published paper covering the period 1980-2002. As was stated by the company to the Committee at the second Appraisal Committee meeting, new innovative agents changing the treatment paradigm, combined with significant improvements in clinical practice over time, render it invalid to use historic data to estimate long term mortality risk following HSCT; in these circumstances clinical expert opinion in relation to survival following transplant in the UK was necessary for any determination of estimates of survival after the cure point post-HSCT in 2017. How long term survival has changed over time, and in the face of new treatment options, was not discussed with the clinical expert at the first Appraisal Committee meeting and the Committee therefore had no expert clinical advice to assist them on this point.
- Health related quality of life in patients with ALL who have undergone HSCT and have reached the cure point, in circumstances where the Committee concluded, contrary to the decision of the committee who considered blinatumomab, that quality of life continues to be impaired post cure point in those patients who remain disease-free;
- Clinical similarity between the population of patients considered in the appraisal of blinatumomab and those considered in the appraisal of inotuzumab, in particular similarities in patients who had undergone a successful HSCT, were no longer receiving treatment, and then had passed the cure point;
- Arrangements for administration of treatment of patients receiving inotuzumab and those receiving FLAG-based chemotherapy (i.e. number of days of inpatient hospitalisation required for administration, as distinct from other aspects of care) in circumstances where the conclusions of the Committee conflict with the submissions provided by Pfizer in response to the ACD and were reached without further expert clinical input
- The number of cycles of inotuzumab treatment which would be used in clinical practice in England, in circumstances where the Committee seemingly disregarded the submissions provided by Pfizer which included clinical expert advice, without providing any explanation and without receiving any advice on this issue from clinical experts.

In particular, the clinical experts themselves raised relevant concerns about clinical assumptions and decision-making during the consultation on the ACD for inotuzumab. By way of example, [redacted] stated:

> "My specific concern regarding this decision relates to:
>
> 1) Fairness. I have also participated in a consultation of another novel agent for the therapy of ALL - blinatumomab. This was considered by a different committee. The agent was approved. As an academic who specialises in the treatment of ALL, if asked to comment on the relative merits of blinatumomab and inotuzumab, I absolutely would not be able to recommend one agent over the other except in very specific clinical

circumstances. So I find it hard that two separate committees of NICE - without apparently having consulted each other and having used different input organisations for ERG have nonetheless gone ahead and made this decision for the community and for our patients.

2) Modelling. I am not an expert in the modelling of ICER but I am concerned that different assumptions were used for inotuzumab versus blinatumomab. I respectfully would request the committees review the modelling and assumptions on which this decision was based to ensure that they are completely congruous for both agents and that the identical baseline considerations and future projections have been taken into account."

Despite these very serious concerns being raised by a clinical expert, the Chairman did not exercise his discretion to invite any of the experts to attend the second meeting of the Appraisal Committee, but instead relied upon evidence from the ERG, including on clinical matters, to explain why it had not used the same assumptions as those used in the appraisal of blinatumomab. The issues raised by the clinical expert were not addressed during the public section of the meeting or referenced in the FAD. The failure to invite the clinical experts to the second meeting of the Appraisal Committee is particularly troubling in circumstances where [redacted], one of the invited clinical experts, was unable to attend for the entirety of the first meeting (indeed NICE were made aware in advance that attendance of leading UK clinical experts to the meeting was difficult this day due to a national transplant conference taking place in London) and was therefore unavailable when assumptions used for economic modelling were considered during the second half of the meeting, and the second clinical expert, [redacted], was unable to attend any of the first meeting.

On any view this has been a controversial appraisal and it is inevitably troubling where different approaches to non-treatment related assumptions are used by different committees to reach different outcomes in relation to two very similar technologies that will be both used to bridge relapsed and refractory ALL patients to HSCT. In these circumstances we believe it was incumbent upon the Chairman to ensure that the issues and concerns raised by the clinical specialists were fully discussed at the second meeting of the Committee so that these could be considered when the FAD was formulated, rather than simply relying on the non-clinical views of the ERG.

1.3. The Committee has provided no explanation for its decision to reject the utilities proposed in the revised Pfizer base case for the post HSCT period and submitted in response to consultation.

The economic model originally submitted by Pfizer proposed use of utility values for the post HSCT post cure point period taken from Kurosawa et al (2016), but with a key scenario analysis (Table 82 in the company's original submission) whereby patients returned to normal population utility past this point, reflecting the utilities from the SMC submission for blinatumomab. At the time the submission for inotuzumab was provided to NICE, a separate NICE committee were also considering this same approach in the base case of the blinatumomab appraisal, as discussed further at point 2.1 below. Following consideration, NICE published Guidance on blinatumomab for the same disease indication (relapsed or refractory B-cell ALL), in which that appraisal committee accepted a model in which a patient's health related quality of life returns to that of the general population after the cure point. This Guidance was published prior to the first Appraisal Committee meeting for

inotuzumab, An approach of consistency in assumptions across both appraisals would be assumed and was subsequently supported in the clinical expert advice NICE received during the consultation on the ACD.

While there was no discussion or citation of the Guidance for blinatumomab in the ACD for inotuzumab, in its response to consultation on the ACD Pfizer suggested that the same approach should be followed. Accordingly we proposed that utility values equivalent to the normal population should be applied to patients after the cure point, in circumstances where there is no reason why quality of life should be any different post cure point whether pre-transplant treatment has been blinatumomab or inotuzumab or chemotherapy. It should be noted that normal population utility was only assumed to apply post cure point to those patients who remained progression-free (i.e. did not relapse), and that any disutility from transplant was accounted for pre-cure point. While the Appraisal Committee notes Pfizer's submission at paragraph 3.20 of the FAD and the ERG's view that the Kurosawa are "preferable to the new assumption, which is not supported by evidence", there is no indication that the Appraisal Committee gave any consideration to Pfizer's revised base case submitted in response to ACD, or to the conclusions of the committee in the blinatumomab appraisal. Instead the FAD states simply "utilities from Kuroswa et al 2016 for disease-free patients are its preferred assumptions". The Committee has therefore either failed to give any proper consideration to Pfizer's proposals or alternatively, if it has considered them, has failed to explain its reasons for rejecting them.

Such an approach is generally inconsistent with a fair procedure. In this case, the requirement to provide credible reasons is enhanced by the fact that a different committee considering a technology for the same set of patients (i.e. patients with relapsed or refractory ALL who have undergone HSCT and have passed the cure-point post-HSCT) reached a different conclusion and, in the absence of properly considered reasons, the decision of the Committee appears arbitrary.

2. GROUND 2: THE RECOMMENDATION IS UNREASONABLE IN THE LIGHT OF THE EVIDENCE SUBMITTED TO NICE

2.1. The Appraisal Committee's reasons for disregarding key assumptions used for the purposes of NICE's appraisal of blinatumomab do not explain the choices that were made in relation to inotuzumab

The appraisal of inotuzumab commenced while the appraisal of blinatumomab, also indicated for the treatment of relapsed or refractory ALL, was in progress. A FAD was issued for blinatumomab, in April 2017, before the first meeting of the Appraisal Committee to consider inotuzumab. (The data presented in the blinatumomab appraisal were considered to be so favourable that no ACD was issued and the appraisal proceeded directly to FAD stage.) Blinatumomab was considered by a different appraisal committee than inotuzumab, Committee A and relied upon an ERG Report prepared by a different ERG, Warwick Evidence, University of Warwick. Pfizer raised awareness of the blinatumomab FAD and the need for consistency in decision making due to the similarities in the appraisals to NICE in writing, ahead of the first inotuzumab Committee meeting.

Following consideration of the preliminary guidance set out in the ACD for inotuzumab, a general theme of stakeholder responses was to express concern and disagreement that a

different and inconsistent approach had been followed as compared with that used in the appraisal of blinatumomab. While the Appraisal Committee declined to revise its conclusions following consultation, it included a new paragraph 3.17 in the FAD, which provides its reasons for diverging from the appraisal of blinatumomab in relation to assumptions, including (a) longer term survival post-cure point; and (b) health related quality of life post-cure point.

The Committee stated at paragraph 3.17 that it "was not bound by the modelling and interpretation of a separate appraisal". Its reasons for adopting a different approach in the context of its consideration of inotuzumab are as follows:

- "The Committee noted that the marketing authorisations for the two drugs are different: blinatumomab has a marketing authorisation for Philadelphia-chromosome-negative acute lymphoblastic leukaemia, whereas inotuzumab ozogamicin has a marketing authorisation for Philadelphia-chromosome-positive and -negative acute lymphoblastic leukaemia".

- "The ERG stated that there are differences in the mechanism of action between the two drugs".

- "The ERG also highlighted that although the survival benefit with inotuzumab ozogamicin was uncertain (see Section 3.4), blinatumomab showed a statistically significant benefit in survival compared with standard of care in the TOWER trial".

- "The ERG further noted that the company did not include blinatumomab in any of its analyses for inotuzumab".

- "The Committee understood that the populations considered in both appraisals were similar, but it concluded that because the evidence available for each appraisal is different, differences in modelling are unavoidable".

These reasons are either incorrect or misleading or they relate solely to assumptions which may be linked to the treatment effect of the two products and have no relevance to modelling post-cure point. Treatment-related effectiveness will impact a patient prior to HSCT, and potentially through minimal residual disease (MRD)-negativity in the initial years after HSCT (noting the Committee's preference at paragraphs 3.8 and 3.19 of the FAD). Both Committee A which considered the blinatumomab appraisal and Committee C in the current appraisal of inotuzumab preferred models in which a single set of assumptions are applied to patients post-cure point with respect to mortality risk and utility, irrespective of pre-HSCT treatment (i.e. the pre-HSCT treatment has no differentiating effects on patients once they have passed the cure point post-HSCT; patients at this point can be considered the same). In these circumstances, Committee C's approach to inotuzumab, which is different in material respects from that followed by Committee A in considering blinatumomab, appears arbitrary and therefore unreasonable.

We address each of the reasons provided by the Appraisal Committee and would ask the Appeal Panel to consider each of them independently:

2.1.1. <u>Differences in the marketing authorisations for inotuzumab and blinatumomab</u>

The SmPC for blinatumomab states that the product is indicated "for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)".

The indication for the use of inotuzumab, as quoted above (see Indication section) is also for the treatment of adults with B-precursor ALL although it incorporates patients who are both Philadelphia chromosome-positive and negative.

No explanation is provided by the Committee to explain which differences in the marketing authorisation are thought to require a different approach to modelling and why, or different choices in assumptions that relate to the patient populations. The inclusion of Philadelphia chromosome-positive patients within the marketing authorisation for inotuzumab does not alter modelling of the presentation of the disease or health related quality of life or prognosis past the cure point (once a patient has recovered from HSCT) and, during the appraisal of inotuzumab, the cost-effectiveness of Philadelphia chromosome-positive and negative patients are considered together with no suggestion by the ERG or the Committee that use of inotuzumab in these groups should be appraised separately.

Furthermore, a blinatumomab patient was invited to the first meeting of the Appraisal Committee to consider inotuzumab and, while the patient was not able to comment on inotuzumab, the description of the disease and their experience post-HSCT (as they were approaching the cure point) was considered directly relevant to the Committee's consideration of the current appraisal. The invitation to the patient to provide such testimony inherently implies that the experience of patients with relapsed or refractory ALL post-HSCT and, in particular, post cure-point, is similar irrespective of the induction regimen received pre-HSCT.

Pfizer accepts that there are differences in the marketing authorisations for inotuzumab and blinatumomab in relation to matters such as posology and toxicity and that these may be relevant to the treatment effects of the two products; however, the inconsistencies in modelling which the Committee sought to explain at paragraph 3.17 of the FAD relate to matters post treatment effect (specifically post-HSCT cure point) which the marketing authorisations of the two products do not explain.

2.1.2. Differences in the mechanism of action

Blinatumomab is a T-cell engager antibody targeting CD19 and the CD3/T-cell receptor. Inotuzumab is an antibody drug conjugate which acts by targeting CD22, expressed on immature B-cells in ALL.

Differences in mechanism of action may explain differences in treatment effects, but not differences in the assumptions relied upon after the cure point post-HSCT, namely the approach to longer term survival post-cure point and the calculation of health related quality of life post-cure point. Again, the Appraisal Committee has provided no explanation to justify its conclusion that a different mechanism of action requires different assumptions to be applied in the modelling once treatment effects cease to be relevant post cure point.

2.1.3. The ERG's assertion that although the survival benefit with inotuzumab was uncertain, blinatumomab showed a statistically significant benefit in survival compared with standard of care.

One reason given by the Appraisal Committee to justify use of different assumptions post cure point is that the ERG stated that while the survival benefit with inotuzumab is uncertain, blinatumomab had shown a statistically significant benefit in survival compared with standard of care in the TOWER trial. This conclusion, however, is not a reasonable basis for decision-making.

While neither Pfizer nor any other stakeholder has suggested that the Appraisal Committee should conduct a comparison between blinatumomab and inotuzumab (and this was not envisaged by the Scope for this appraisal), it is in any event scientifically invalid to carry out such a comparison between data from TOWER and INO-VATE. A comparison of median estimates of OS is not a fair reflection of survival in a disease area where HSCT is the key driver of survival and less than half (i.e. beyond the median point) of patients receive HSCT. In particular, the characterisation of the TOWER data simply as showing a statistically significant benefit is misleading. Paragraph 4.6 of the guidance for blinatumomab refers to the statistically significant result and states

> "The committee noted that although blinatumomab was associated with improved survival up to 15 months, the Kaplan-Meier curves of the 2 treatment arms came together at this point. However it also noted that the data were immature and that there were very small numbers of patients alive at 15 months. The committee concluded that blinatumomab is clinically effective in improving overall survival compared with standard of care in the short term, but there is uncertainty about the long-term survival benefit".

Furthermore, the conclusions by the ERG (accepted by the Appraisal Committee at Paragraph 3.4 of the FAD) that median OS data from the INO-VATE trial were not statistically significant, fails to take into account the regulatory analysis of the data as set out in the European Public Assessment Report (EPAR) (referred to in section 4.7 of the original company submission), which stated

> "For the second primary endpoint, OS, there was not a statistically significant improvement in median OS for inotuzumab ozogamicin compared to the chosen chemotherapy regimen (7.7 vs. 6.7 months) according to the pre-specified cut-off level of one-sided $P < 0.0104$ (adjusted for the interim analysis) [stratified HR 0.770 (97.5% CI 0.578,1.026), $P = 0.0203$]. However, the planned testing strategy is over conservative. If both primary endpoints are tested at one-sided $P < 0.025$, the OS result could be considered to be positive while still controlling a type I error at conventional levels (required one-sided $P < 0.0229$ after adjusting for the interim analysis)."

No reasons were provided by the Committee for disregarding this important conclusion of the regulatory authorities, which formed the basis for the marketing authorisation for inotuzumab and in the absence of reasons, the conclusion must be assumed to be arbitrary and therefore unreasonable.

The regulatory authorities also accepted the restricted mean survival time (RMST) results, with those analyses published in the EPAR for inotuzumab. These results follow a valid, well-established methodology, as set out in Section 4.4 of the company's submission (alongside appraisals in which NICE had previously accepted these analyses). The Committee fail to cite these results here, nor the highly significant OS benefit measured by 2- and 3-year landmark survival. It should be noted that while it is correct that "the results of the restricted mean survival time analysis depended on when it was cut short", the "cut

short" time point was determined by the last available follow-up time of the two comparator arms; the company results were not "inflated" as mischaracterised by the ERG.

Lastly, it is important to consider that alongside the committee's citation of the ERG's assertion that the survival benefit of inotuzumab is "uncertain", the model which "includes all the committee's preferred assumptions" (FAD 3.16), which is the ERG's base case model, shows that there is an increase to the average patient's life expectancy by over 2 years with inotuzumab versus the standard of care (mean LYs = 2.35 years in the model that pertains to the ICER of £114,078 which is cited in section 3.16). The statement of "uncertain" benefit also contrasts to the awarding of end of life criteria (FAD section 3.24), whereby the Committee conclude that it is likely that by increasing "inotuzumab ozogamicin would increase mean survival … by more than 3 months."

In summary therefore, as would be expected in the context of an oncology treatment for an ultra-orphan indication at the time of launch, there is some uncertainty over the long term benefits associated with both blinatumomab and inotuzumab. It is scientifically invalid and incorrect to compare the data from different analyses from these trials (particular when the available blinatumomab data is less mature with shorter follow-up than that available for inotuzumab), and in particular to focus on median estimates when OS is assumedly driven by HSCT rate (noting the high rate of HSCT associated with inotuzumab), and to draw any conclusions over relative effectiveness through such naïve comparisons. This should be considered alongside the opinion of [redacted] who stated in her response to the ACD for inotuzumab:

> "As an academic who specialises in the treatment of ALL, if asked to comment on the relative merits of blinatumomab and inotuzumab, I absolutely would not be able to recommend one agent over the other except in very specific clinical circumstances."

2.1.4. <u>The Committee's assertion that, where the evidence available for each appraisal is different, differences in modelling are unavoidable</u>

Pfizer does not suggest that Appraisal Committee C was required to follow the modelling approach adopted by Appraisal Committee A for blinatumomab in all respects. However, where treatment effects are not relevant (as they are not where post cure point modelling is concerned), the use of different assumptions is unsatisfactory and requires proper justification.

Therefore, while differences in modelling based on evidence of treatment effects prior to HSCT and the cure point may be appropriate, there appears no reasonable basis for a difference in approach between the two products after the cure point. To the extent that Committee C wishes to diverge from the assumptions selected and relied upon by Appraisal Committee A in situations which are in material respects indistinguishable, such divergence must be adequately explained by reasons. In this case the explanations given by the Committee do not justify the decisions that were made, which must therefore be viewed as arbitrary and unreasonable.

In particular, it is not in the interests of the NHS, of patients or any stakeholder in any appraisal that the difference between a positive recommendation and a negative one depends on which Appraisal Committee and which ERG consider a technology rather than issues of clinical and cost-effectiveness.

In summary, as described in the points above, the Appraisal Committee does not appear to have recognised the similarity of patient population and the disease area, the patient pathway, and the patient populations considered in each of the two appraisals. Both appraisals are for same disease indication (relapsed or refractory ALL), and the primary clinical goal with both inotuzumab and blinatumomab is the same: to achieve CR/CRi so that a patient has the ability to proceed to potentially curative HSCT. As previously discussed, both Committees accepted models which assumed no differences in the assumptions applied in the patient populations after the cure point post-HSCT, clinical expert advice explicitly draws on similarities between the medicines, and the NICE Committee for inotuzumab drew upon the testimony provided for the experience post-HSCT provided by a patient who had been on blinatumomab. As such, NICE's treatment-specific rationale for dismissal of similarities between the appraisals has no validity post-cure point and lack of consistency is arbitrary and unreasonable.

2.2. The Committee has seemingly misunderstood the utilities submitted by Pfizer in response to consultation on the ACD

In its response to consultation on the ACD, Pfizer submitted utilities for the purposes of the post cure point period, reflecting health related quality of life in the general population. These are referenced by the Appraisal Committee at paragraph 3.20 of the FAD

> "In addition, the company applied a general population utility (0.88) for disease-free patients post-cure".

However this is incorrect. In fact, as stated in section 1 of Pfizer's response to the ACD, Pfizer accepted the need to adjust utilities for age and therefore a range of utilities applicable to the general population - from 0.55 for the oldest patient to 0.88 for the youngest in the model. In these circumstances, the description given at paragraph 3.20 of the FAD suggests erroneously that Pfizer's submission was unrealistic. Further, the value taken from the literature as cited in the FAD (0.74/0.76) reflects all patients in the longer term, whereas the use of normal population utilities in the revised Pfizer base case (0.55 to 0.88) was *only* for disease-free patients. Pfizer continues to include, for a cohort of patients who may relapse in the longer term, a much lower utility of 0.30. So it is wrong to consider that the Pfizer model assumes all patients return to normal population utility, as is suggested in the FAD, with the Pfizer model using a utility, on average, which is lower than the normal population because of allowing for disease progression post-cure point. It should further be noted that the disutility from post-HSCT adverse events is also counted into the model. This misunderstanding of Pfizer's submission is likely to have misled the Committee in its consideration of this issue and is therefore unreasonable.

2.3. The Committee has misinterpreted Pfizer's revised submission on administration costs

The economic model originally submitted by Pfizer assumed that administration costs of inotuzumab would comprise those associated with three outpatient visits and no inpatient days per cycle, compared with no outpatient visits and 6.2 inpatient days for standard of care. The ERG conducted an exploratory analysis which assumed an average inpatient stay of 9.5 days for both inotuzumab and standard of care, derived from all-cause hospital admission data in the INO-VATE trial. The ERG's analysis, that applied the same number of inpatients administration days to both arms, was accepted by the Appraisal Committee

in the ACD, indicating the Committee's view that inotuzumab would be administered in an inpatient setting.

Following ACD consultation and taking into account the views of experts, Pfizer submitted a revised base case which included one day of inpatient stay for inotuzumab and 14 days of inpatient stay for standard of care related to the administration of these medicines. This response is addressed in the FAD at Paragraph 3.22. The Committee initially observed that "it would have preferred" Pfizer to have based the calculation of inpatient days on the INO-VATE trial (even though a multicentre clinical trial conducted in a range of countries is unlikely to reflect the organisation of NHS care provided in England in this respect) and then proceeded to consider "the need for hospitalisation for patients having inotuzumab ozogamicin and standard of care" stating:

> "The Committee agreed that one inpatient day for inotuzumab ozogamicin is too low, and that it is likely there is a difference in the number of inpatient days for inotuzumab ozogamicin and standard of care, but that the ratio is likely to be larger than the ratio used in the company's analysis (1/14). The Committee therefore concluded that the number of inpatient days in the company's revised model leads to the ICER being underestimated".

However, the Committee has misunderstood Pfizer's submission and has construed this as reflecting the total number of inpatient days associated with inotuzumab, rather than the number of inpatient days attributed solely to administration of the product. This was despite Pfizer making the position clear in its response to consultation on the ACD. In its response, Pfizer initially explained why hospitalisation data from the INO-VATE trial would not be appropriate for this purpose:

> "It is important to note that in the INO-VATE trial, hospitalisation is for a variety of reasons including underlying disease, comorbid conditions, and adverse events. Further, this cost differs between countries in the international trial due to differences in clinical practice. Using data which encompasses all such reasons and applying this as specifically an administration cost is inaccurate. Further, it risks double-counting elsewhere in the model: for example, where inpatient stays related to adverse events are already costed".

Pfizer proceeded to explain why it had revised its submission on administration costs to include some inpatient costs (i.e. guidance from the clinical experts) and to explain that a key advantage of inotuzumab over standard of care is that it can be administered in an outpatient setting. The Committee were of course already aware of this as a result of evidence provided by both clinical specialists, [redacted] and [redacted], in their evidence to the Committee.

[redacted] stated

> "The drug IO is easily delivered, by weekly injection, including the possibility to treat on an out-patient basis, whereas the combination chemotherapy drugs used often necessitate inpatient stays lasting several weeks".

In addition:

> "The agent is easy to administer requiring less time and skill to prescribe, administer and monitor than complex standard of care regimens Patients can receive the agent as out patients if they have no other reason for inpatient hospitalisation".

[redacted] stated in his submission:

> "The other advantage of inotuzumab is that it can be given in an outpatient setting and most patients do not require hospital admission".

Following the evidence of the clinical specialists, Pfizer also provided an explanation for its submission of 14 days inpatient stay for standard of care stating

> "The clinical experts' estimate of three weeks was tested with the consulted experts recently consulted, who agreed it was reasonable to assume FLAG-based chemotherapy would frequently require around three weeks of inpatient admission. However, in the revised base case Pfizer uses a more conservative estimate of two weeks of inpatient stay as administration, noting that adverse events are costed separately for the use for an estimate of three weeks costs may risk double counting".

In summary therefore, the submission by Pfizer of one day of hospital costs for administration of inotuzumab with 14 days of standard of care, were limited to administration costs only. (The data from INO-VATE on hospitalisation did not separate the number of inpatient stays attributed specifically to administration and those attributed to other matters, such as comorbid conditions or adverse events.) Costs associated with adverse events were included in the model separately. All the evidence before the Committee points to the fact that inotuzumab would be administered in the outpatient setting. Pfizer continued to include outpatient visit costs for all administrations of inotuzumab which, by including double counting of both an outpatients and an inpatients cost on this first administration of inotuzumab, represents a conservative approach.

In contrast however, paragraphs 3.22 of the FAD (which is headed simply "inpatient days" rather than simply the "administration costs" described in Pfizer's submission) appears to misunderstand Pfizer's submission as covering simply any inpatient hospitalisation and to disregard the explanations provided and the fact that hospitalisations for reasons other than administration are dealt with elsewhere. To this extent therefore the Committee's rejection of Pfizer's submitted administration costs and its finding that "The Committee therefore concluded that the number of inpatient days in the company's revised model leads to the ICER being underestimated" is unreasonable.

THE DETERMINATION OF THIS APPEAL

Pfizer requests that this appeal should be determined at an oral hearing.

REQUESTED OUTCOME FOLLOWING APPEAL

The points raised by Pfizer in its appeal are important, both because they are indicative of lack of procedural fairness and conclusions which are unreasonable, but because, if corrected, they

result in a plausible ICER which is below the estimate generally viewed as an acceptable use of NHS resources for treatments of this nature indicated for patients at the end of life (i.e. below £50,000 per QALY).

Pfizer therefore respectfully requests the Appeal Panel to:

- Return this appraisal to the Appraisal Committee for further consideration
- To direct that the clinical experts are invited to a third meeting of the Committee
- To require that the Committee considers inotuzumab for patients proceeding to HSCT within the scope of its marketing authorisation in relation to its intended use in UK practice (a maximum of three cycles of treatment)
- To direct the Committee to adopt a similar approach in modelling non-treatment related assumptions (particularly, after the cure point post-HSCT) to those accepted for the purpose of the Guidance issued for blinatumomab
- To require the Committee to consider the utility values proposed by Pfizer for the post cure point period
- To correct the Committee's understanding of administration costs for inotuzumab with hospitalisation costs reflecting advice from experts.

To the extent that you have any further questions or require additional clarification, we will be pleased to assist.

Yours sincerely,

[redacted], Pfizer UK