1. CLINICAL TRIAL SUMMARY REPORT

Acronym	BaP
Title	Single Arm Phase II trial assessing the safety, compliance with and activity of Bezafibrate and medroxyProgesterone acetate (BaP) therapy against myeloid and lymphoid cancers
Sponsor	University of Birmingham
Sponsor Ref Number	RG_11-054
EudraCT Number	2011-001955-35
REC Reference Number	11/EM/0426
Countries of Study	United Kingdom only
Investigational Medicinal Product(s)	Modified Release Bezafibrate (MR BEZ) Standard Release Bezafibrate (SR BEZ) Medroxyprogesterone acetate (MPA)
Arms	**All patients:** 5 x 200 mg Medroxyprogesterone acetate tablets daily. **Patients with an estimated Glomerular Filtration Rate (eGFR) ≥60 ml/min:** Starting dose of Bezafibrate (modified release) 2 x 400 mg twice daily rising to a maximum of 6 x 400 mg twice daily, increasing at a maximum rate of 800 mg a day. **Patients with an eGFR <60 ml/min:** Starting dose of Bezafibrate (standard release) 2 x 200 mg twice daily rising to a maximum of 6 x 200 mg twice daily, increasing at a maximum rate of 400 mg a day.
Date of Initial MHRA Approval	03-Jan-2012
End of Trial	10-Sep-2014

This report was prepared by the Chief Investigator and the Cancer Research UK Clinical Trials Unit (CRCTU) on behalf of the Sponsor.

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2. SIGNATURE PAGE

BaP Clinical Trial Summary Report v1.0, 08-Sep-2015

This report has been approved by:

Name: Professor Mark Drayson Trial Role: Chief Investigator

Signature: [redacted] Date: 08/09/2015 DD/MM/YYYY

3. GENERAL INFORMATION

3.1. Background

More than half of all patients with Acute Myeloid Leukaemia (AML) and substantial proportions of Chronic Lymphocytic Leukaemia (CLL) and B-cell Non-Hodgkins Lymphoma (BNHL) patients either present, or arrive, at a point in their disease, where anti-cancer therapy is inappropriate because it is no longer effective or its toxicity cannot be tolerated usually due to age and infirmity. At this stage of their disease the loss of normal haemopoiesis creates life-threatening deficits of erythrocytes, platelets, and neutrophils that are managed by supportive care, involving blood and platelet transfusion and aggressive treatment of infection arising in association with neutropenia. Other than palliative treatment with prednisolone in B cell malignancy and hydroxyurea to control rising myeloid blast counts, there is no available treatment and survival is poor. In a typical haemato-oncology unit the incidence of patients in this circumstance is about one per month for each of the three diseases.

Acute Myeloid Leukaemia

A review of 36 AML studies involving a total of 12,370 patients (median age 70 years) found that for AML patients receiving supportive care alone, or supportive care plus non-intensive chemotherapy, median overall survival was only 7.5 and 12 weeks respectively [1]. Consequently these patients represent a group with very poor prognosis and in none of whom would improved haemopoiesis or reduction in disease activity be expected without effective anti-AML therapy [2].

Chronic Lymphocytic Leukaemia

CLL is the most common adult leukaemia and remains incurable although many patients have indolent asymptomatic disease. The majority of patients are elderly; often tolerate intensive chemotherapy poorly and the outlook for patients unsuitable for further therapy is poor [3, 4]. There is a need for effective, easily deliverable and well tolerated novel therapies for these patients; such non-toxic therapies would also have potential as adjunctive treatment in fitter patients receiving conventional treatments.

B-cell Non-Hodgkins Lymphoma

Non-Hodgkins lymphoma (NHL) is the most common haematological cancer in adults [5]. Approximately 85% of NHL are of B cell origin (BHNL) and are responsible for >4,000 UK deaths per annum. Many BNHLs are indolent but they are incurable and often the cause of death. In contrast other BNHL are aggressive and may be rapidly fatal. Whilst some patients are curable, a high proportion become resistant to or are unable to tolerate current therapies [6, 7].

Thus, AML, CLL and BNHL are united by the need for new therapies that have anti-cancer activity in association with minimal systemic and haematological toxicities.

In a Leukaemia and Lymphoma Research (LLR) funded Specialist Programme we identified the combination of the lipid-regulating drug bezafibrate (BEZ) and the sex hormone medroxyprogesterone acetate (MPA) as having in vitro activity against AML, BNHL and CLL [8-10]. We call this drug combination ‘BaP’.

We have reported the safety and efficacy of low dose BaP in 20 AML patients for whom chemotherapy was not an option (ISRCTN50635541) [11]. No patient exhibited haematological toxicity from BaP and significant responses were observed. Subsequent in vitro studies indicate that full dose BaP (BEZ dose 12x and MPA dose 2.5x that used in the above study), would have substantially greater efficacy against AML [10]. We have reported the safety and efficacy of BaP in primary resistant and relapsed Burkitt lymphoma in Malawi (ISRCTN34303497). 30 patients received

low dose Bap, 10 intermediate dose and 20 full dose without evidence of toxicity and with evidence of anti-lymphoma activity most effective at the full dose [12].

If full dose BaP is shown to induce haematological responses this could greatly benefit a group of patients for whom no active treatment is currently available. If full dose BaP is shown to induce disease responses then it could be considered as adjunctive therapy to conventional cytotoxic therapy.

3.1.1. Justification for design

The safety of BaP in elderly patients with AML has already been demonstrated in a small Phase I study. We reported the safety and efficacy of low dose BaP in 20 AML patients for whom chemotherapy was not an option (ISRCTN50635541). The study also provided evidence of both anti-AML activity and improved haemopoiesis [11].

Subsequent in vitro studies indicate that full dose BaP (BEZ dose 12x and MPA dose 2.5x , would have substantially greater efficacy against AML [10]. In an ongoing trial of BaP in primary resistant and relapsed Burkitt lymphoma in Malawi (ISRCTN34303497) 30 children received low dose Bap, 10 intermediate dose and 20 full dose without evidence of toxicity and with evidence of anti-Burkitt activity most effective at the full dose [12].

The study being proposed here has been designed to further evaluate the safety, compliance (feasibility of delivery) and activity of full dose BaP in adults with AML (and high risk MDS), CLL or BNHL. We anticipate that continuous day to day BaP activity against these blood cancers will reduce tumour burden and thus produce a level of haematological response which will reduce patient requirement for red cell and platelet transfusions and increase blood neutrophil numbers with consequent reduced inpatient hospitalisations due to infection.

Please see the attached protocol v7.0 30-Apr-2013 for further background information for the BaP Trial.

3.2. Objectives

To evaluate in patients with AML (and high risk MDS), CLL and BNHL the following outcomes of BAP administration over 18 weeks:

- Safety
- Compliance (feasibility of delivery)
- Anti-cancer activity
- Change in quality of Life

The trial registered overall survival.

3.3. Outcomes Measures

- **Safety:** The number and type of grade 3 and 4 Adverse Reactions and Serious Adverse Reactions (SARs) attributable to the trial drugs
- **Patient compliance [1]:** Percentage of allocated treatment taken
- **Activity [2, 3]:**
  - Haematological Response in the first 18 weeks of treatment
  - Clinical Response in the first 18 weeks of treatment
- **Overall survival**: The time from registration to death from any cause (surviving patients will be censored at the date last seen)
- **Quality of life:** EORTC QLQ-C30 questionnaire

[1]* **Compliance** will be monitored via the use of patient diary cards (up to Week 18), drug returns and accountability records.

[2]***Haematological response or improvement 0 - 18 weeks:** The haematological response criteria as published by the International Working Group criteria for myelodysplasia will be used. Improvements must last at least 8 weeks in the absence of ongoing cytotoxic therapy [13].

[3]* **Clinical response:**

- For AML and MDS clinical response will be defined according to the Revised Recommendations of the International Working Group for the Diagnosis, Standardisation of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukaemia [14].
- For CLL patients clinical response will be defined according to guidelines from the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) [15].
- For BNHL clinical response will be defined according to the Revised Response Criteria for malignant Lymphoma [16].

The International AML response criteria [14] state that Complete Remission (CR) is the most important initial response reported in phase III trials, precisely because it is the sole outcome currently associated with improved survival. However, in patients deemed unfit for intensive chemotherapy, non-myeloablative therapies, because of their specificity for the leukaemia cells, can have clinical benefit without achieving CR. Such anti-AML therapies can be administered continuously without haematological toxicity, allowing clinically significant recovery of haemopoiesis by sustained suppression rather than transient ablation of AML activity as can be seen with imatinib therapy for CML. The same applies to active CLL and BNHL.

It is anticipated that it will take 4 weeks for BaP to induce a significant haematological response and thus reduce the risk of death. As deaths in this first 4 weeks are common (10 – 20%), patients who do not achieve 4 weeks of treatment will be replaced but still included in the analysis.

From the time of achieving maximal haematological response it takes a further 8 weeks of maintained response to fulfil the IWG criteria of haematological response. Accordingly both haematological and clinical response should be measurable within a study time of 18 weeks.

3.4. Statistical Considerations

3.4.1. Analysis of Outcome Measures

Analyses will be descriptive. Each of the three diseases will be presented separately. Baseline features of the patient population will be tabulated. Adverse events, including SAEs, will be summarised by type and grade. Compliance will be reported as a percentage of protocol specified doses taken, with reasons for reducing or stopping therapy. The haematological and disease response rates will be presented with overall survival with a 95% confidence interval (CI).
Historically, no improvement has been seen in QoL in this group of patients. Change in QoL will be measured for patients who complete the baseline and midpoint (between weeks 7-11) and/or week 18 questionnaires.

3.4.2. Sample Size

This pilot study will not involve any formal statistical hypothesis testing. With 20 patients recruited in each of the three diseases, there will be sufficient data on safety, feasibility and activity to enable a clinical decision to be reached as to whether further evaluation of BaP in further trials is warranted.
Since this decision will be multi-factorial, balancing safety, feasibility and activity, it is not possible to specify precise stop/go criteria for further trials. However, as guidance it is likely that if >10% of patients suffer drug related toxicity that required treatment to be permanently stopped or if the haematological response rate is <20% then further investigation may not be warranted. If haematological response rates are >20% with acceptable toxicity then the trial treatment could be of benefit to patients receiving conventional anti blood cancer therapies. Randomised studies of the trial therapy as adjunctive therapy to standard anti-cancer therapies would be undertaken with survival as the primary endpoint. For patients of the type eligible for the current trial (that is for whom conventional anti-blood cancer therapy is not an option) then further studies may be required to further establish the types and proportions of patients

3.5. Patient Safety

3.5.1. Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 3 for definition) should be reported. Please note that this includes abnormal laboratory findings which meet CTCAE criteria.

3.5.2. Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 3 for definition) and are not excluded from the reporting process as described below.

3.5.3. Events that do not require reporting on a Serious Adverse Event Form

The following events should not be reported on an SAE Form:

- Hospitalisations for:
  - Protocol defined treatment
  - Pre-planned elective procedures, including blood transfusions, unless the condition worsens
  - Treatment for progression of the patient's cancer including:
    - Admissions to control anaemia, neutropenia, neutropenic sepsis or infection, unless the condition is life threatening or proves fatal

- Progression or death as a result of the patient's cancer, as this information is captured on the Death Form. Deaths will be included in the Development Safety Update Report.

3.5.4. Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the Trials Office as soon as possible. If it is the patient who is pregnant, provide outcome data on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant consent must first be obtained and the patient should be given a Release of Medical Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the Release of Medical Information Form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

3.5.5. Reporting period

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

3.6. Trial Population

The BaP Study was stratified on disease type with a recruitment target of 20 patients in each arm. The three disease types were acute myeloid leukaemia (AML) or high risk myelodysplasia (MDS-RAEB2), chronic lymphocytic leukaemia (CLL) and B-cell Non-Hodgkin's Lymphoma (BNHL). The planned analysis was to take place on each of the disease types independently.

Number of patients expected: 60
Number of patients recruited: 18

4. SUBJECT DISPOSITION

4.1. Eligibility Criteria

4.1.1. Inclusion Criteria

- Patients must:
  - have one of the following diagnoses:
    - AML or high risk myelodysplasia (RAEB2 WHO criteria, Appendix 5)
    - CLL
    - BNHL
  - be 18 years or older
  - have given written informed consent

For AML and RAEB-2

- Haemopoiesis must be impaired by the disease as judged by an abnormal FBC (International Working Group response criteria in myelodysplasia [13]) and, where there is doubt as to the cause of impaired haemopoiesis, there must be bone marrow aspirate evidence that impaired haemopoiesis is due to cancer involvement of the bone marrow.
- Abnormal values are haemoglobin level less than 11 g/dL or RBC transfusion dependence, platelet count less than 100 x 10^9/L or platelet-transfusion dependence, absolute neutrophil count less than 1.0x 10^9/L. Pretreatment baseline measures of cytopenias are averages of at least 2 measurements (not influenced by transfusions, i.e., no RBC transfusions for at least 1 week and no platelet transfusions for at least 3 days) over at least 1 week prior to therapy.

For CLL and BNHL

- Patients must have either measurable disease (tumour cells in blood at >5 x 10^9/L, or lymphadenopathy >1 cm) or bone marrow failure due to disease as stated above for AML.

4.1.2. Exclusion Criteria

- Patient considered suitable for other forms of anti-cancer therapy (either accepted standard therapy or therapy in the context of a clinical trial) other than palliative corticosteroids or hydroxyurea
- Patient has an estimated Glomerular Filtration Rate (eGFR) <40 ml/min
- Patient known to be allergic to trial drugs
- Patient has received treatment with any investigational medicinal product within the previous 28 days
- Patient requires treatment with statins that cannot be stopped for the duration of treatment with Bezafibrate
- Patient unable to swallow orally administered medications
- Patient has uncontrolled seizures
- Patient has active infection requiring systemic antibiotics, antifungal or antiviral drugs
- Patient has concurrent severe and/or uncontrolled medical condition (e.g. severe COPD, severe Parkinson's disease) or psychiatric condition
- Patient has significant hepatic disease as defined as ALT or AST >2.5 x ULN, Bilirubin > 2 x ULN
- Patient has gall bladder disease with or without choleithiasis
- Patient has thrombophlebitis, thrombo-embolic disorders, or a high risk of developing such manifestations (presence or history of atrial fibrillation, valvular disorders, endocarditis, heart

failure, pulmonary embolism; thrombo-embolic ischaemic attack (TIA), cerebral infarction; atherosclerosis; immediate post surgery period)

- Patient has hypercalcaemia in patients with osseous metastases
- Patient has missed abortion, metrorrhagia or undiagnosed vaginal bleeding
- Patient has previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- Patient has active or recent (within 1 year) arterial thromboembolic disease (e.g., angina, myocardial infarction)
- Patient has suspected or early breast carcinoma
- Women of child-bearing potential and men who have partners of child-bearing potential who are not willing to practice effective contraception for the duration of the study and for three months after the last study drug administration

Pregnant or lactating women. Pre-menopausal women of child bearing potential must have a negative urine or serum pregnancy test within 7 days prior to registration.

4.2. Recruitment

4.2.1. Recruitment by site

The BNHL and CLL patients both registered at The Queen Elizabeth Hospital.

Table 1: Recruitment of all 18 patients by site

Site	Principal Investigator	Date Activated	Number of Patients Recruited
Queen Elizabeth Hospital	[redacted]	20-Jun-2012	7
Heartlands Hospital	[redacted]	02-Nov-2012	4
Good Hope Hospital	[redacted]	02-Nov-2012	2
Worcester Royal Infirmary	[redacted]	08-Jul-2013	1
New Cross Hospital	[redacted]	30-Aug-2013	4

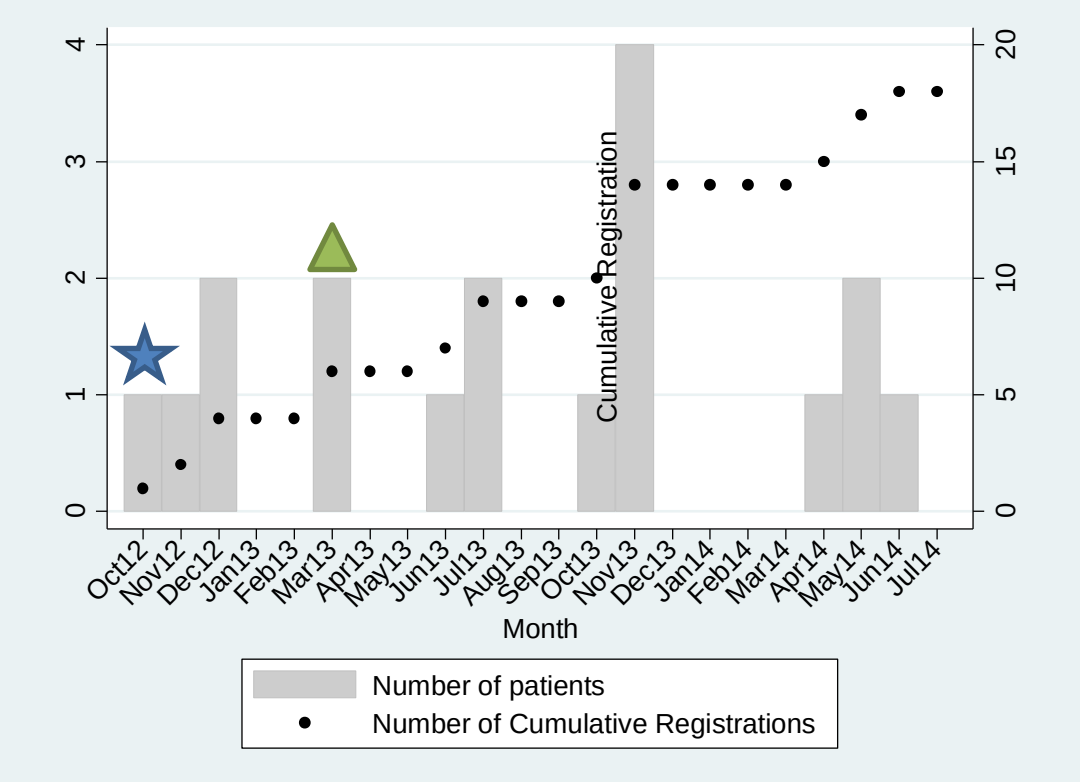
4.2.2. Recruitment by disease

Table 2: Recruitment per disease

Disease type	Number of Patients Recruited
AML/MDS (RAEB2)	16
CLL	1
BNHL	1

4.2.3. Monthly accrual

Figure 1: Recruitment plot (monthly accrual) – the CLL patient is indicated with a blue star and the BNHL patient is indicated with a green triangle



4.2.4. Ineligible patients

Two patients registered onto the BaP Trial were ineligible according to the eligibility criteria in the Protocol. The eligibility criteria stated that patients were required to have high risk myelodysplasia RAEB-2 in accordance with the WHO criteria which was supplied in Appendix 5. In 2012, the WHO guidelines were replaced with the Revised International Prognostic Scoring System for Myelodysplastic Syndromes, however, the Protocol was not updated to reflect this change. Patient [redacted] and patient [redacted] were eligible according to the updated criteria but not the WHO criteria specified in the Protocol and were therefore ineligible. The BaP Trials Office mistakenly allowed patient [redacted] to be recruited but were only made aware of patient [redacted]'s ineligibility following a monitoring visit at the site.

4.2.5. Issues with recruitment

The BaP study was funded by the Queen Elizabeth Hospital Birmingham Charity and it was not adopted to the National Cancer Institutes of Health Research's (NIHR) portfolio. Since the trial was not eligible for receiving service support costs from hospitals, it was very difficult to generate interest at sites and to recruit additional centres. The funding also restricted the study to open at sites to the West Midlands only, meaning that we could not expand the number of centres contributing to recruitment. Subsequently, despite a 12 month extension to the study and revisions of the eligibility criteria, we were unable to recruit the study to planned target.

CLL patients were difficult to recruit to the study due to the abundance of other treatments that became available to patients after the study opened. Eligible BNHL patients proved difficult to identify and one of the centres was unable to enter BNHL lymphoma patients due to budget restrictions not allowing them to perform the necessary baseline CT scans.

4.3. Treatment discontinuation and patient withdrawal

4.3.1. Treatment discontinuation

Table 3: Number of treatment discontinuations prior to completing 18 weeks of treatment – unless otherwise stated patients have AML/MDS (RAEB2)

Number of patients that received less than 18 weeks of treatment:	16 [1 CLL & 15 AML/MDS (RAEB2)]
Reason for discontinuing treatment:	
(a) Death:	4 (25.0%)
(b) Disease progression:	1 (6.3%)
(c) Disease progression and other:	2 (12.5%)
(d) Toxicity and disease progression:	1 (6.3%)
(e) Withdrawal and disease progression:	1 (6.3%)
(f) Withdrawal and toxicity:	3 [1 CLL] (18.5%)
(g) Withdrawal, toxicity and disease progression:	1 (6.3%)
(h) Withdrawal, toxicity and other:	1 (6.3%)
(i) Other:	2 (12.5%)

Table 4: Reasons for treatment discontinuation after completing the protocol mandated trial treatment – unless otherwise stated patients have AML/MDS (RAEB2)

Number of patients that received at least 18 weeks of treatment:	2 [1 AML & 1 BNHL]
Reason for discontinuing treatment:	
(a) Disease progression:	1 [BNHL] (50.0%)
(b) Other: decided to stop treatment	1 (50.0%)

4.3.2. Treatment withdrawals

Table 5: Number of patient withdrawals – unless otherwise stated patients have AML/MDS (RAEB2)

Number of withdrawals from trial:	6 [1 CLL & 5 AML/MDS (RAEB2)]
Type of withdrawal:	
(a) Withdraw from trial treatment, but seen in accordance with trial follow up schedule:	0
(b) Withdraw from trial, willing for data to be collected at routine visits:	1 [CLL] (16.7%)
(c) Withdraw from trial, not willing for further data to be supplied:	5 (83.3%)
Reason for withdrawal:	
(a) Perceived side effects:	4 [1 CLL] (66.6%)
(b) Disease progression and perceived side effects:	1 (16.7%)
(c) Struggling with tablets and perceived side effects:	1 (16.7%)

4.3.3. Issues with withdrawals

The number of patient withdrawals in this study was higher than we would have expected. Patients cited on the number of toxicities that they had experienced whilst on trial and difficulty taking the number of tablets required (up to 17 tablets a day on full dose BaP) as reasons for withdrawal. These issues are explored further in section 7.3.

5. BASELINE CHARACTERISTICS

5.1. Baseline characteristics of AML/MDS (RAEB2) patients

The youngest patient in the AML/MDS (RAEB2) disease group was 47.3 years of age, whereas the oldest was 86.2 years old.

Table 6: Baseline patient characteristics of AML/MDS (RAEB2) patients - n=16 unless stated otherwise. N.B. Patient 12 became unwell immediately after registration and so did not start treatment or provide baseline information, which accounts for the missing data in the table.

Baseline characteristics	
Median (IQR) age (years)	75.3 (67.9 – 77.8)
Sex	
Male	11 (68.7%)
Female	5 (31.3%)
ECOG performance status	
0	4 (25.0%)
1	7 (43.7%)
2	2 (12.5%)
3	2 (12.5%)
Missing	1
Median (IQR) time from original diagnosis to trial entry (weeks)	13.3 (3.6 – 75.0)
Missing	1
Disease status	
Previously untreated	8 (50.0%)
Relapsed	5 (31.3%)
Refractory	2 (12.5%)
Missing	1
Previous therapies of relapsed/refractory patients	
AC220, Azacitidine, Fludarabine Melphalan Campath, MIDAC & Ponatinib	1 (14.3%)
Allograft BMT Fludarabine Melphalan Alemtuzumab, AML 16 Trial 3x DA Chemo, Azacitidine DLI & Top-up BMT Fludarabine Campath	1 (14.3%)
Ara-C, DA & MIDAC	1 (14.3%)
Azacitidine	1 (14.3%)
DA - AML-17 Trial	1 (14.3%)
Daunorubicin (3+10) chemotherapy	1 (14.3%)
Daunorubicin and Ara-C - 3 courses (AML 16 Trial) & High Dose Cytarabine x 2 courses	1 (14.3%)

Table 6 (continued): Baseline patient characteristics of AML/MDS (RAEB2) patients - n=16 unless stated otherwise.

Baseline characteristics (continued)	
Transfusion dependent (TD) patients	
Red blood cell	9 (56.3%)
Platelet	4 (25.0%)
Missing	1
Haemoglobin in patients that are not red blood cell TD	(n=6)
Median (IQR) Haemoglobin (g/dL)	10.4 (9.4 – 12.0)
Platelets in patients that are not platelet TD	(n=11)
>100 x 10^9/L	4 (36.4%)
20-100 x 10^9/L	5 (45.4%)
<20 x 10^9/L	2 (18.2%)
Median counts (IQR)	
White cell count (x10^9/L)	2.2 (1.4 – 7.0)
Missing	1
Neutrophils (x10^9/L)	
≥1 x 10^9/L	4 (25.0%)
<1 x 10^9/L	10 (62.5%)
Not known	1 (6.3%)
Missing	1

Bone marrow blast counts were available for seven out of 16 AML/MDS (RAEB2) patients at baseline with a median of 47.0% blasts in the marrow (37.5 – 64.5). In the absence of a bone marrow count, one patient had circulating blasts in the blood at 90.0% of total blood nucleated cells.

5.2. Baseline characteristics of BHNL patient

One patient was recruited in the BNHL disease group. This patient was male, 71.9 years of age and had ECOG performance status of 0.This patient had relapsed from their original diagnosis which was detected 788.6 weeks prior to trial entry. Previous therapies included Beam Auto, C.H.O.P., Decabeam, RCeVP and Radiotherapy. The patient was not transfusion dependent and had a haemoglobin count of 12.2 g/dL and platelet count greater than 100 x 10^9/L. The neutrophil count was greater than 1 x 10^9/L and the white cell count was 6.1 x 10^9/L. The clinical examination of the spleen and liver was normal at baseline; however the lymph nodes were abnormal with small nodes detectable in the left posterior triangle.

5.3. Baseline characteristics of CLL patient

One patient was recruited in the CLL disease group.

This patient was male, 81.4 years of age and had ECOG performance status of 1. This patient had relapsed from their original diagnosis which was detected 355.9 weeks prior to trial entry. Previous therapies included Fludarabine and Cyclophosphamide. The patient was not transfusion dependent and had a haemoglobin count of 9.6 g/dL and platelet count between 20 and 100 x 10^9/L. The neutrophil count and lymphocyte count was not known however the white cell count was 177.9 x 10^9/L. The clinical examination of the spleen and liver was normal at baseline; however the lymph nodes were abnormal. The size of the largest nodes in the cervical, supraclavicular and inguinal were less than 2 cm, but the size of the largest node in the axillary was between 2 and 5 cm.

6. ENDPOINTS

6.1. Patient Outcome Summary

6.1.1. AML/MDS (RAEB2) patients

The median (IQR) duration on trial of AML/MDS (RAEB2) patients was 6.4 (2.8 – 10.0) weeks.

Table 7: Response to BaP therapy of AML/MDS (RAEB2) patients that received less than 4 weeks of treatment.

TNO	Duration on trial (weeks)	Mode (range) dose of bezafibrate treatment (mg)	Reason for stopping BaP therapy	Time from registration to death (weeks)	Number of weeks during trial duration that treatment was prescribed from treatment form (%)		
					MPA	MR BEZ	SR BEZ
[redacted]	1.4	4800 (-)	PD	1.9	1.4 (100.0)	1.4 (100.0)	0
[redacted]	0.9	4800 (-)	W, T	46.6	0.9 (100.0)	0.9 (100.0)	0
[redacted]	0.7	4800 (-)	W, T	55.7	0.7 (100.0)	0.7 (100.0)	0
[redacted]	2.9	1600 (0 – 1600)	T, PD	6.4	2.6 (90.0)	2.6 (90.0)	0
[redacted]	Discontinued prior to starting treatment	N/A	O – Unstable to start treatment	N/A	N/A	N/A	N/A
[redacted]	2.6	800 (0 – 1200)	W, T, O – issues with tablets	7.3	2.1 (83.3)	0	2.1 (83.3)

Reasons for stopping treatment: D –Death, NR - No response, PD - Disease Progression, T – Toxicity, W – Withdrawn, O – Other, see tables 14 and 15

Table 8: Response to BaP therapy of AML/MDS (RAEB2) patients that received more than 4 weeks of treatment

TNO	Duration on trial (weeks)	Mode (range) dose of bezafibrate treatment (mg)	Reason for stopping BaP therapy	Time from registration to death (weeks)	Number of weeks treatment that was prescribed according to treatment form (%)			Haematological Response (N/A for patients with <4 weeks of treatment)			
					MPA	MR BEZ	SR BEZ	Erythroid	Platelet	Neutrophil	Progression / relapse
Patients that received >4 but less than 18 weeks of treatment											
■	5.7	1600 (0 – 2400)	W, T, PD	24.7	5.7 (100.0)	4.1 (72.5)	0	No	No	No	No
■	8.6	3200 (1600 – 4000)	PD, O – deterioration in health	10.6	8.6 (100.0)	8.6 (100.0)	0	No	No	No	No
■	13.6	800 (SR) (0 – 1000) (SR) (0 – 1600) (MR)	O – issues with tablets	17.7	13.6 (100.0)	1.7 (12.7)	9.7 (71.5)	No	No	No	No
■	6.4	0 (0 – 800)	D – disease related, sepsis	6.6	6.4 (100.0)	0	1.3 (20.1)	No	No	No	No
■	9.7	0 (0 – 400) (SR) (0 – 1600) (MR)	W, PD	20.6	5.3 (54.4)	0.9 (8.8)	0.9 (8.8)	No	No	No	No
■	5.4	1600 (1600 – 2000)	PD O – issues with tablets	7.0	5.4 (100.0)	5.4 (100.0)	0	No	No	No	No
■	15.4	0 (0 – 400) (SR) (0 – 1600) (MR)	D – sepsis	15.4	12.4 (80.5)	4.9 (31.5)	5.1 (33.3)	No	No	No	No
■	10.3	1600 (MR) (0 – 1600) (MR) (0 – 800) (SR)	D – disease related	10.4	10.3 (100.0)	7.0 (68.0)	2.3 (22.3)	No	No	No	No
■	8.7	1600 (0 – 2400)	D – disease related	9.0	7.7 (88.5)	6.6 (75.4)	0	No	No	No	No
Patients that received ≥ 18 weeks of treatment											
■	41.9	0 (0 – 2400)	O – decided to stop BaP therapy	45.9	41.4 (99.0)	0	5.9 (14.0)	Yes 14 wk	Yes 20wk	No	Yes

Reasons for stopping treatment: D – Death, NR – No response, PD – Disease Progression, T – Toxicity, W – Withdrawn, O – Other, see tables 14 and 15

6.1.2. BNHL patient

The patient in the BNHL disease group stayed on the trial for 18.0 weeks and discontinued BaP therapy due to disease progression. Out of 18 weeks on trial, the patient was prescribed 18.0 (100.0%) weeks of medroxyprogesterone acetate, 5.0 (27.8%) weeks of standard release bezafibrate and 4.9 (27.0%) weeks of modified release bezafibrate. The modal dose of bezafibrate treatment is 0mg (MR range: 0 – 4800 and SR range: 0 – 2400). The haematological response was not assessed as the criterion was only applicable to myelodysplasia. The patient had stable disease for 9.9 weeks after which bilateral axillary lymphadenopathy developed and the patient died 28.0 weeks after registration.

6.1.3. CLL patient

The CLL patient stayed on the trial for 0.7 weeks and withdrew BaP therapy due to toxicities experienced. Out of 0.7 weeks on trial, the patient was prescribed 0.7 (100.0%) weeks of medroxyprogesterone acetate and 0.7 (100.0 %) weeks of 2400mg standard release bezafibrate. The haematological response was not assessed as the criterion was only applicable to myelodysplasia. The patient died 27.7 weeks after registration.

6.2. Safety

6.2.1. Adverse Events experienced at baseline

Adverse Events (AEs) that patients experienced at baseline were not uniformly reported with baseline AEs being reported for only 12 patients. Seven out of 12 patients were reported as experiencing at least one grade 3 or above AEs at baseline.

Table 9: Table of adverse event episodes at baseline by grade of all patients

Episode	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
Anaemia	1	4	2			7
Anxiety		2				2
Constipation	1					1
Cough		1				1
Diarrhoea	1					1
Dizziness	1					1
Elevated urea	1					1
Fatigue	1	1				2
Hyperkalemia			1			1
Infection		1				1
Insomnia	1					1
Laryngeal inflammation	1					1
Low red cell count	3				1	4
Loss of appetite		1				1
Lymphocyte count decreased	1	1		1		3
Nausea		1				1
Neck Pain		1				1
Neutrophil count decreased				5		5
Oral haemorrhage	1					1
Pain	1					1
Platelet count decreased	2			3		5
Sore throat		1				1
Thrombocytopenia (refractory)				1		1
White blood cell decreased			2	2		4
Overall	16	14	5	12	1	48

6.2.2. Adverse events experienced whilst on treatment

15 out of 18 patients experienced at least one grade 3 or above AEs whilst on treatment.

6.2.2.1. Unrelated Adverse Events

Table 11: Table of AEs experienced recorded as unrelated or unlikely to be related whilst on treatment by grade, grouped by category - all patients

Category	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
Blood and lymphatic system disorders	8	13	10	2		33
Cardiac disorders		1				1
Eye disorders	2	1				3
Gastrointestinal disorders	5	2	2	1	1	11
General disorders and administration site conditions	4	3	1		1	9
Infection	1	2	2			5
Injury, poisoning and procedural complications		1				1
Investigations	35	7	10	21		73
Metabolism and nutrition disorders	2	2	2			6
Musculoskeletal and connective tissue disorders	3	3				6
Nervous system disorders		1				1
Psychiatric disorders	1					1
Respiratory, thoracic and mediastinal disorders	4	6	2		1	13
Skin and subcutaneous tissue disorders	4	1	1			6
Overall	**69**	**43**	**30**	**24**	**3**	**169**

Table 12: Table of AEs experienced recorded as unrelated or unlikely to be related whilst on treatment by grade, grouped by episode - all patients

Episode	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
Abdominal pain			1			1
Alkaline phosphatase increased	1					1
Altered taste	1					1
Anal hemorrhage		1				1
Anemia	5	13	9	2		29
Arthralgia	1					1
Aspartate aminotransferase increased	1					1
Back pain		1				1
Bilateral subconjunctival haemorrhages		1				1
Bullous dermatitis	1					1

Table 12 (cont): Table of AEs experienced recorded as unrelated or unlikely to be related whilst on treatment by grade, grouped by episode - all patients

Episode	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
Cellulitis			1			1
Constipation	1					1
Cough		1				1
Creatinine increased	2	1				3
Decreased eGFR	1	1				2
Dry mouth	1	1				2
Dyspnea	4	2	1		1	8
Edema limbs	2					2
Elevated CRP	6					6
Fall		1				1
Fatigue		2				2
Febrile neutropenia			1			1
Flashing lights	1					1
Flu like symptoms			1			1
Haematocrit decreased	1					1
Hiccups			1			1
Hypermagnesemia	1					1
Hypokalemia		1	1			2
Hyponatremia	1					1
Hypophosphatemia		1	1			2
Hypoxia		1				1
Infusion related reaction					1	1
Insomnia	1					1
Intra- Retinal Haemorrhage	1					1
Lactate dehydrogenase elevated	1					1
Laryngopharyngeal dysesthesia		1				1
LDH elevated	2					2
Left axillary Lymphadenopathy	1					1
Lethargy		1				1
Leukocytosis	3					3
Localised oedema	1					1
Lymphocyte count decreased	2	1	2			5
Monocyte Count decreased	1					1
Monocytes elevated	2					2
Mucosal infection	1					1
Mucositis oral	1					1
Myalgia	2	1				3
Nausea	2					2
Neutrophil count decreased	2	3	2	6		13

Table 12 (cont): Table of AEs experienced recorded as unrelated or unlikely to be related whilst on treatment by grade, grouped by episode - all patients

Episode	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
Neutrophils Elevated	3					3
Pain		1				1
Pain in extremity		1				1
Petechiae	1					1
Platelet count decreased	1		3	9		13
Platelets increased	1					1
Red Blood cell decreased	1					1
Sepsis			1			1
Skin infection		1	1			2
Skin ulceration	2	1				3
Sore throat		1				1
Tachycardia		1				1
Total Protein increased	1					1
Upper gastrointestinal hemorrhage				1		1
Upper respiratory infection		1				1
Urea decreased	1					1
Urea Increased	1					1
Vomiting			1		1	2
WCC elevated	2					2
White blood cell decreased	1	1	3	6		11

6.2.2.2. Possibly Related Adverse Events

Table 13: Table of AEs experienced recorded as possibly related, probably related or definitely related whilst on treatment by grade, grouped by category - all patients

Category	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
Blood and lymphatic system disorders		7	3			10
Ear and labyrinth disorders		1				1
Eye disorders	1					1
Gastrointestinal disorders	10	8			1	19
General disorders and administration site conditions	1	8	1			10
Hepatobiliary disorders					1	1
Infections		2				2
Investigations	52	11	6	5		74
Metabolism and nutrition disorders	37	8		1		46
Musculoskeletal and connective tissue disorders	2	5	2			9
Nervous system disorders	4	1				5
Respiratory, thoracic and mediastinal disorders	2	3				5
Skin and subcutaneous tissue disorders	2					2
Overall	**111**	**54**	**12**	**6**	**2**	**185**

Table 14: Table of AEs experienced recorded as possibly related or probably related whilst on treatment by grade, grouped by episode - all patients

Episode	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
Abdominal pain					1	1
Alanine aminotransferase increased	7		1			8
Alkaline phosphatase increased	1	1				2
ALP Decreased	4					4
Anemia		7	3			10
Anorexia	2	1				3
Aspartate aminotransferase increased	1					1
Bloating	3	1				4
Blood bilirubin increased	1			1		2
Blurred vision	1					1
C reactive protein increased	2					2
Constipation	1					1
Cough		1				1
CPK increased	1	1	1			3
Creatinine increased	4	4	1			9
Decreased eGFR	1					1
Diarrhea	1	2				3

Table 14 (cont): Table of AEs experienced recorded as possibly related or probably related whilst on treatment by grade, grouped by episode - all patients

Episode	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
Dizziness		1				1
Dysgeusia	1					1
Dyspepsia	3					3
Dyspnea	1					1
Ear pain		1				1
Esophageal infection		1				1
Fatigue	1	6	1			8
Generalized muscle weakness		1	1			2
Hand spasm (intermittent)	1					1
Headache	2					2
Hiccups		1				1
Hot flushes	1					1
Hyperhydrosis		1				1
Hyperkalemia	11	2				13
Hypermagnesemia	4					4
Hypoalbuminemia	6	1				7
Hypocalcemia	4	2				6
Hyponatremia	9					9
Hypophosphatemia	1	1		1		3
Jaundiced					1	1
Laryngeal inflammation	1					1
Laryngitis		1				1
LDH decreased	1					1
LDH elevated	5	1				6
Leg weakness		1				1
Lymphocyte count decreased	4			1		5
Lymphocyte count increased		1	1			2
Mean Cell Haemoglobin concentration increased	2					2
Monocyte count increased	4					4
Monocytes Decreased	2					2
Mucositis oral		1				1
Myalgia		1	1			3
Nausea	1	2				3
Neutrophil count decreased		1	1	1		3
Neutrophil count increased	1					1
Pain		1				1
Paresthesia	1					1
Platelet count decreased				2		2
Pruritus	1					1

Table 14 (cont): Table of AEs experienced recorded as possibly related or probably related whilst on treatment by grade, grouped by episode - all patients

Episode	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
Rash	1					1
Reduced eGFR	1	1				2
Stiffness	1					1
Stomach pain		1				1
Tonsillitis		1				1
Total Protein increased	1					1
Urea decreased	1					1
Urea elevated	5	1				6
Vomiting	1					1
White blood cell increased	1		1			2

6.2.2.3. Definitely Related Adverse Events

Table 15: Table of AEs experienced recorded as definitely related whilst on treatment by grade, grouped by category - all patients

Episode	Grade 1	Grade 2	Grade 3	Grade 4	N/K	Overall
CPK increased	1					1
Edema limbs		1				1
Myalgia		1				1
Nausea		1				1

6.2.3. Adverse events that resulted in treatment discontinuation

Table 16: Table of AE categories that led to treatment discontinuation of of AML/MDS (RAEB2) patients

Adverse events that resulted in treatment discontinuation (AML)	n
Investigations	1
Metabolism and nutrition disorders	1
Gastrointestinal disorders	2
Musculoskeletal and connective tissue disorders	2
Nervous system disorders	1

The BNHL patient experienced no adverse events that led to treatment discontinuation however the patient in the CLL disease group experienced toxicities in categories gastrointestinal disorders, musculoskeletal and connective tissue disorders.

6.2.4. Serious Adverse Reactions (SARs)

1 SAR was reported on the BaP Trial.

Table 17: List of all SARs experienced on BaP trial

TNO	SAE Ref. No.	Sex	Age	Adverse Event Term	Grade	Outcome	Onset date of SAR	Suspect IMP	Dose; route; formulation	Treatment start date	Treatment end date
[redacted]	[redacted]	M	81	Creatinine increased	2	Resolved - with sequelae	02-Nov-2012	Bezafibrate standard release	1200 mg b.d; oral; tablet	24-Oct-2012	28-Oct-2012
								Medroxyprogesterone acetate	1000 mg o.d; oral; tablet	24-Oct-2012	28-Oct-2012

6.2.5. Suspected Unexpected Serious Adverse Reactions (SUSARs)

There were no SUSARs reported on the BaP Trial.

6.2.6. Serious Adverse Events

Full details of each SAE are listed in the CIOMS report in Appendix 1.

Table 18: Table of Serious Adverse Events (SAEs) experienced by patient grouped by category

CTCAE Category	Adverse event term	No Treatment Arm
Cardiac disorders	Sinus tachycardia	1
Sub Totals for Cardiac disorders		**1**
Gastrointestinal disorders	Abdominal pain	1
Sub Totals for Gastrointestinal disorders		**1**
Infections and infestations	Sinusitis	1
Infections and infestations	Skin infection	2
Sub Totals for Infections and infestations		**3**
Investigations	Creatinine increased	1
Sub Totals for Investigations		**1**
Musculoskeletal and connective tissue disorders	Back pain	2
Sub Totals for Musculoskeletal and connective tissue disorders		**2**
Renal and urinary disorders	Acute kidney injury	1
Sub Totals for Renal and urinary disorders		**1**
Respiratory, thoracic and mediastinal disorders	Dyspnea	1
Sub Totals for Respiratory, thoracic and mediastinal disorders		**1**
Report totals		**10**

6.2.7. Hospitalisations not reported as an SAE

Table 19: Table of hospitalisation not reported as an SAE

Reason for hospital admission	Number of admissions
Anaemia, difficulty passing urine, epigastric tenderness, fatigue, fever, swelling and erythema both forearms.	1
Deterioration of general condition	1
Disease progression	1
Epistaxis	1
Fever, falling Hb and rising WCC	1
Neutropenic sepsis	3
Upper GI bleed secondary to low platelets	1
Sepsis of unknown origin	1
Severe fatigue and general malaise	1

There were no hospital admissions for CLL or BNHL patients. Five patients in the AML/MDS (RAEB2) disease group had one hospital admission and three patients had two hospital admissions.

6.3. Compliance

Compliance was measured using the patient diaries and reflects the number of days that the patient took the medication that they were prescribed. This differs from the data in table 7 and 8 which show the number of weeks that medication was prescribed in comparison to the duration that the patient was on trial.

Table 20: Table of bezafibrate and medroxyprogesterone acetate of AML/MDS (RAEB2) patients. Patient [redacted] did not return any diaries and patient [redacted] did not start medication. N.B *Where a patient diary was unavailable it has been assumed that the patient was non-compliant for the duration of the missing diary.

TNO	Number of days prescribed BEZ according to patient diaries	% BEZ compliance	Number of days prescribed MPA according to patient diaries	% MED compliance	Number of missing diaries (days)
[redacted]	5	100	5	100	0
[redacted]	29	98	124	99	0
[redacted]	10	65	10	70	0
[redacted]	6	75	6	83	0
[redacted]	6	100	6	100	0
[redacted]	70	97	125	98	2
[redacted]	28	63	40	69	12
[redacted]	60	75	60	77	13
[redacted]	20	75	20	75	6
[redacted]	9	94	45	56	16
[redacted]	40	70	40	73	2
[redacted]	16	91	16	88	0
[redacted]	39	69	39	72	2
[redacted]	28	96	59	75	2
[redacted]	67	38	67	39	41
[redacted]	48	51	56	63	20

There was 100% compliance for one patient in the AML/MDS (RAEB2) disease group and one CLL patient. The median (IQR) compliance for bezafibrate for all patients was 75% (68 – 96) and 75% (70 – 91) for medroxyprogesterone acetate. The median (IQR) compliance for bezafibrate for patients with all patient diaries was 95% (79 – 100) and 94% (84 – 100) for medroxyprogesterone acetate.

6.3.1. Reasons for non-compliance derived from patient diaries

The following issues were listed as reasons for non-compliance in the comments section of the patient diaries:

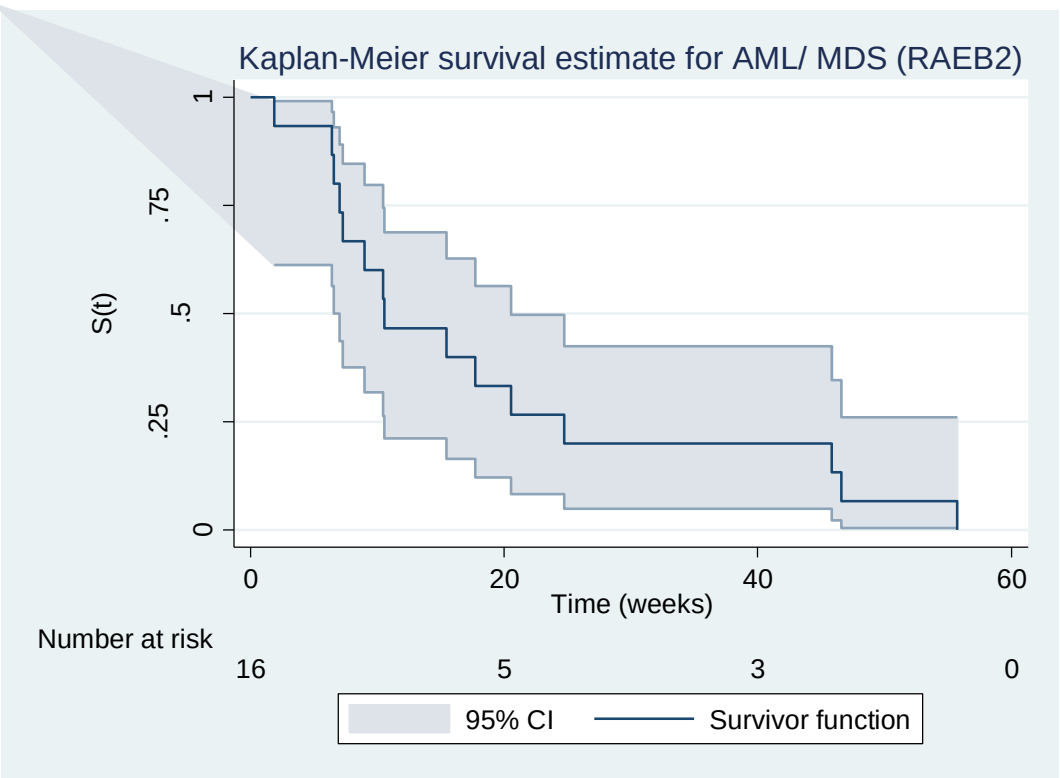
- Volume of tablets – two patients expressed difficulties with taking the number of tablets prescribed, especially in conjunction with other non-trial medications that they were prescribed. One patient on 4000 mg modified release bezafibrate (5 tablets twice a day) and 1000 mg medroxyprogesterone (5 tablets in the morning) stated that their morning dose of BaP (10 tablets) had taken them until the afternoon to take due to the large volume of tablets and so they had not taken their afternoon dose

- Nausea – three patients expressed difficulty in taking the tablets due to nausea
- Hospitalisation –four patients reported being unable to take their medication or complete the patient diary as they did not have the medications or diaries with them when they were admitted to hospital
- Medication supply – one patient ran out of medication before their next study visit

6.4. Anti-cancer activity

6.4.1. Overall survival

Figure 2: Survival plot of AML/MDS (RAEB2) disease group with 95% confidence intervals.



In the AML/MDS (RAEB2) group, 15 patients died and one was censored at their date of registration. The median survival in this group was 10.6 weeks (95% CI: 6.6, 20.6). The time from registration to death for the BNHL patient was 28.0 weeks and 27.7 weeks for the patient in the CLL disease group. Response in the AML/MDS (RAEB2) disease group

Haematological improvement was observed for one out of 16 (6%) patients in the AML/MDS (RAEB2) disease group. This patient had a platelet response for 14.0 weeks and an erythroid response for 20.0 weeks. This patient then progressed after 42.9 weeks of stable disease. Clinical disease assessment was not conducted in the patients in this group because there were no clinical indications to undertake the painful procedure of bone marrow aspiration.

6.4.2. Response in the BNHL and CLL group

The CLL patient had no clinical response, whereas the BNHL patient had disease progression after 9.9 weeks stable disease. Haematological response is not applicable for the patients in the BNHL or CLL disease group.

6.5. Change in Quality of Life for patients who have completed the baseline and/or week 18 diary.

Quality of life is recorded according to EORTC QLQ – C30 questionnaire. In order to interpret the scales, it is important to note that for the global health score and functional scores, high values represent a better quality of life for the patients. However for the symptom scores, a higher result represents a higher level of symptoms and therefore a lower quality of life. Functional scores include physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. Symptom scores consist of fatigue, nausea, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties.

Table 21: Table of QoL scores of AML/MDS (RAEB2) patients

Scales	Mean Baseline score (SD) n=14	Mean week 7-11 score (SD) n=3	Mean Week 18 score (SD) n=1	Average difference between baseline and week 7-11 scores n=3
Global Health score	53.0 (21.6)	78.0 (17.3)	83.0 (.)	-19.0 (35.2)
Physical functioning	60.0 (25.0)	56.0 (10.2)	73.0 (.)	-7.0 (13.2)
Role functioning	54.0 (38.8)	44.0 (25.5)	67.0 (.)	0.0 (44.0)
Emotional functioning	75.0 (21.4)	81.0 (17.3)	92.0 (.)	-17.0 (28.6)
Cognitive functioning	83.0 (20.7)	78.0 (25.5)	100.0 (.)	-11.0 (35.2)
Social functioning	65.0 (30.3)	56.0 (41.9)	83.0 (.)	-22.0 (35.2)
Fatigue	50.0 (23.8)	41.0 (12.8)	22.0 (.)	22.0 (22.0)
Nausea	18.0 (24.0)	0.0 (0.0)	0.0 (.)	11.0 (18.7)
Pain	18.0 (27.3)	22.0 (19.2)	33.0 (.)	6.0 (25.3)
Dyspnoea	40.0 (29.8)	44.0 (38.5)	33.0 (.)	0.0 (33.0)
Insomnia	36.0 (42.3)	33.0 (33.3)	0.0 (.)	11.0 (18.7)
Appetite loss	26.0 (35.0)	0.0 (0.0)	0.0 (.)	22.0 (38.5)
Constipation	17.0 (21.7)	0.0 (0.0)	0.0 (.)	22.0 (18.7)
Diarrhoea	2.0 (8.9)	0.0 (0.0)	33.0 (.)	0.0 (0.0)
Financial difficulties	24.0 (35.6)	33.0 (0.0)	33.0 (.)	0.0 (0.0)

The patient in the CLL disease group completed one QoL questionnaire at baseline. The BNHL patient completed QoL questionnaires at baseline, Week 7 – 11 and Week 18.

7. FURTHER INFORMATION

7.1. Substantial Amendments

Table 22: Summary of Amendments to the BaP Trial

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	27-Feb-2012	3.0	Substantial	Addition of mandatory CT scan at baseline for patients with BNHL
2	16-Apr-2012	4.0	Substantial	Any modified release form of Bezafibrate can now be used
3	09-Aug-2012	5.0	Substantial	Exclusion criteria changed from <60ml/min to <40 ml/min. Standard release bezafibrate to be given to patients with an eGFR 40-59.9 ml/min.
4	19-Sep-2012	5.0a	Non-substantial	Protocol updated to reflect that standard release and modified release Bezafibrate are two separate IMP's as dictated by the MHRA
5	25-Oct-2012	5.0a	Substantial	Update to GP letter to reflect the two formulations of BEZ that may be prescribed to the patient
6	24-Jan-2013	6.0	Substantial	Additional information added to dose modification according to results of renal function monitoring and to vigilance for and prevention of rhabdomyolysis. Clarification of statistical thresholds for continuing research post study.
7	30-Apr-2013	7.0	Substantial	Reduction in starting dose of Bezafibrate and implementation of dose escalations.
8	22-Jul-2013	7.0	Substantial	Update to GP letter to reflect the Bezafibrate dose escalation procedure
9	5-Aug-2013	7.0	Non-substantial	Update to clarify front page of patient diary
10	27-Feb-2014	7.0	Substantial	Update to the RSI to reflect new information provided in the Bezalip SPC

7.2. Trial Deviations

Table 23: Summary of the trial deviations reported throughout the trial

TNO	Date	Deviation
[redacted]	10-Oct-2012	Scheduled assessment not performed
[redacted]	31-Oct-2012	Other deviation
[redacted]	06-Dec-2012	Scheduled assessment not performed
[redacted]	11-Apr-2013	Patient deviated from trial treatment
[redacted]	.	Scheduled assessment not performed
[redacted]	04-Dec-2013	Other deviation
[redacted]	03-Jan-2014	Patient deviated from trial treatment
[redacted]	28-Nov-2013	Patient deviated from trial treatment
[redacted]	16-Apr-2014	Scheduled assessment not performed
[redacted]	07-May-2014	Patient found to be ineligible post registration
[redacted]	11-Jun-2015	Other deviation

7.3. Limitations and caveats

7.3.1. Formulation of bezafibrate

The trial opened to recruitment on 20-Jun-2012. However, it was difficult to identify patients with sufficient kidney function to be eligible for the trial. In Protocol v4.0, 16th April 2012, patients with an eGFR <60 ml/min were excluded from the study. This was amended in Protocol v5.0a, 19th September 2012 to allow patients with an eGFR of 40-59.9 ml/min to enter the trial, but to compensate for the reduced renal capacity by altering the formulation and dose of bezafibrate that these patients received.

The standard release bezafibrate tablets were half the strength of the modified release tablets, meaning that patients would have had to take 12 tablets twice a day to reach the same dose. In order to safeguard compliance, the dose of standard release bezafibrate was halved compared to the dose of modified release bezafibrate, meaning that patients would take the same number of tablets irrespective of the formulation they were prescribed.

This amendment allowed 5 patients to be recruited onto the trial with an eGFR of 40-59.9 ml/min. It was also instrumental in keeping patients on a form of bezafibrate following fluctuations in their eGFR levels (see section 7.3.3)

7.3.2. Rhabdomyolysis and creatine kinase monitoring

7.3.2.1. Initial dosing regimen – patients 1-6

The first four patients were recruited onto Protocol v5.0a, 19th September 2012. This version of the protocol required patients to take one of the following schedules of trial treatment:

- **eGFR level of ≥60 ml/min at baseline**:
  - 6 x 400 mg modified release BEZ tablets twice a day (a total of 4800 mg daily)
  - 5 x 200 mg MPA tablets (a total of 1000 mg daily)
- **eGFR level of 40-59.9 ml/min at baseline:**
  - 6 x 200 mg standard release BEZ tablets twice a day (a total of 2400 mg daily)
  - 5 x 200 mg MPA tablets (a total of 1000 mg daily)

One of these patients experienced serious muscle pains and was later discovered to be in the early stages of rhabdomyolysis. Although the Summary of Product Characteristics stated that rhabdomyolysis had occurred following overdose of bezafibrate before, it was not expected on the trial as it had not been detected in the 20 children receiving full dose bezafibrate in the Malawi study of endemic Burkitts Lymphoma (on the same dose of BaP on a dose per weight basis)[12].

In response to this the protocol was amended (Protocol 6.0, 24th January 2013) to mandate additional monitoring for signs of rhabdomyolysis (monitoring for increased creatine kinase(CK)) and to introduce dose modifications in response to rises in CK and reductions in eGFR levels. Two new patients were registered onto Protocol v6.0 and one of these also had a raised CK level, albeit without any symptoms of rhabdomyolysis.

In total six patients were recruited onto the full dose regime and three of these patients withdrew prior to completing their first week of treatment due to perceived toxicities. Of the other three patients, one was unable to take bezafibrate for more than 5.9 weeks due to a reduced eGFR level (despite staying on the trial for 42 weeks in total) and one patient died after less than a week due to disease progression. The final patient of the first six was on treatment at the point that the dosing regimen was altered and was able to restart bezafibrate at a lower dose. No patient took the full dose of BaP for more than 5.9 weeks.

7.3.2.2. Revised dosing regimen – patients 7-18

In response to the second detected indication of a correlation between BaP treatment and Rhabdomyolysis, the protocol was further amended (Protocol 7.0, 30th April 2013) to introduce a reduced starting dose of bezafibrate and a dose escalation procedure as follows:

- All patients commenced treatment on 2 tablets of BEZ (see below for dose) twice a day and 5 tablets of MPA once daily taken in the morning.
  - All patients had 200 mg MPA tablets
  - Patients with an eGFR level of ≥60 ml/min at baseline were administered 400 mg modified release BEZ tablets.
  - Patients with an eGFR level of 40-59.9 ml/min at baseline were administered 200 mg standard release BEZ tablets
  - Throughout the course of the study, if a patient's eGFR level changed significantly, their treatment course was adjusted accordingly (see section 6.6.1)
- The dose of BEZ could be escalated at the local investigators discretion taking into account biochemistry results and an assessment of symptoms, by a maximum of 1 tablet twice a day as long as the patient's CK level was confirmed to be within the normal range. Dose escalations could not occur more frequently than weekly and total dose must not have exceeded 6 tablets of BEZ twice a day.

- If a patient's CK went outside the normal range or ≥ 3 x baseline level their dose of BEZ was re-assessed.

Following this amendment there were six other instances of raised CK levels which prompted an interruption of the patients bezafibrate medication (Table 22). All instances resolved to below upper limit normal following this interruption and all patients were able to restart bezafibrate at a reduced dose. See appendix 2 for a table of CK readings for each patient throughout the trial.

Table 24: Instances where increased CK resulted in a change to the patients dose of bezafibrate – the first line in the table reflects the event which prompted the protocol to be changed.

TNO	CK prior to taking current dose of BEZ (U/L)	CK level which prompted change in dose (U/L)	Time until CK dropped back below ULN (days)	Related symptoms	Continuous dose of BEZ taken up until date of CK measurement
[redacted]	N/K	472	7	None reported	4800 mg MR - 14 days 2400 mg SR -1 day 0 mg - 7 days
[redacted]	N/K	N/K	6		1600 mg MR - 6 days 2400 mg MR - 7 days
[redacted]	21	497	7	Grade 2 myalgia resolving after 10 days	1600 mg MR - 7 days 2400 mg MR - 6 days
[redacted]	42	153	14	None reported	1600 mg MR - 12 days
[redacted]	42	N/K	6		800 mg SR - 26 days 1000 mg SR - 9 days
[redacted]	44	1358	35	Grade 2 oedema which did not resolve	1600 mg MR - 6 days
[redacted]	64	5357	14	Grade 2 thigh pain resolving after 29 days	1600 mg MR - 6 days 2400 mg MR - 6 days

7.3.3. Issues with consistent dosing

Patient's eGFR levels were monitored at baseline and throughout the study, and their treatment regimes were adjusted based on their renal capacity. The following dose modifications were required in response to changes in eGFR levels:

- **eGFR falls below 40**
  - BEZ (but not MPA) should be discontinued if the eGFR falls below 40 ml/min.
  - If the patient's eGFR has improved to ≥40 ml/min within 48 hours then the BEZ can be restarted following a discussion with the Clinical Coordinator via the trials office.
  - For patients who have had a treatment interruption of >48 hours, once the patient's eGFR has been demonstrated to be above 40 ml/min and stable by two separate measurements, BEZ may be restarted following discussion with the Clinical Coordinator via the trials office.
- **eGFR falls from ≥60 to 40-59 but is within 15% of baseline**
  If there is a decline in eGFR to 40-59 ml/min from ≥60 ml/min but the eGFR remains within 15% of the baseline measurement, the patient should be switched from Modified Release BEZ to Standard Release BEZ at the reduced dose.
- **eGFR falls from ≥60 to 40-59 and is decreased >15% from baseline**
  If there is a decrease in eGFR of >15% from baseline (confirmed on a follow-up eGFR within 48 hours) and the eGFR on the test is 40-59 ml/min the BEZ should be discontinued. The MPA can continue. The local PI should identify what follow-up requirements are needed for standard clinical care in this situation. If the eGFR on follow-up is stable or has improved, recommencement of BEZ may be considered following discussion with the Clinical Coordinator via the trials office.
- **eGFR decreased >15% from baseline but remains ≥60**
  If there is a decrease in eGFR of >15% from baseline (confirmed on a follow-up eGFR within 48 hours) and the eGFR on the test is ≥60 ml/min BEZ should be continued at full dose. However, as in routine clinical care, closer monitoring is required to ensure that eGFR does not fall below 60 ml/min. At the PIs discretion, patients can be switched to the standard release formulation of BEZ at the reduced dose if there is concern.

These dose modifications were put into place as bezafibrate is processed by the kidneys and the Trial Safety Committee were concerned that inadequate processing of bezafibrate could lead to the same problems as taking high doses of bezafibrate. However, it was common for patient's eGFR levels to fluctuate throughout the trial (see appendix 2 for a table of eGFR readings for each patient throughout the trial) causing their dose of bezafibrate to be continuously adjusted and interrupted. In fact, there were 10 recorded instances where the patient's treatment had to be changed in response to their eGFR level (Table 23). Without a control group, it is unclear if the changes in eGFR level were linked to taking BaP treatment or if they were a result of this group of patient's poor health.

Table 25: Instances where decreased eGFR levels resulted in a change to the patients dose of bezafibrate

TNO	eGFR prior to taking current dose of BEZ	eGFR level which prompted change in dose	Number of days on BEZ prior to drop in eGFR	Comments
[redacted]	88 ml/min	53 ml/min	4800 mg MR - 14 days	Switched to SR which was stopped 1 day later due to increased CK
[redacted]	68 ml/min	55 ml/min	1600 mg MR - 7 days	Restarted 1600 mg MR after a 7 day break and escalated to a maximum 2400 mg MR. eGFR stayed between 53 and 68 throughout trial duration
[redacted]	90 ml/min	56.1 ml/min	1600 mg MR - 12 days	Treatment stopped as CK was also raised
[redacted]	65.8 ml/min	53.4 ml/min	800 mg SR - 26 days followed by 1000 mg SR - 9 days	Treatment stopped as CK was also raised
[redacted]	52.2 ml/min	37.1 ml/min	800 mg SR - 8 days	
[redacted]	76.1 ml/min	56 ml/min	1600 mg MR - 7 days followed by 2000 mg MR - 14 days	Reverted back to 1600 mg MR
[redacted]	64.9 ml/min	55 ml/min	1600 mg MR - 13 days	eGFR level fluctuated throughout trial period with a range of 36.7 ml/min to 90 ml/min
[redacted]	69 ml/min	N/K	800 mg MR (Alt days) - 6 days	
[redacted]	76 ml/min	68 ml/min	800 mg MR (Alt days) - 15 days	
[redacted]	90 ml/min	57 ml/min	1600 mg MR - 44 days	Restarted 800 mg MR after a break of 7 days and re-escalated to 1600 mg MR

8. CONCLUSIONS

8.1. Conclusions from the AML/RAEB2 population

8.1.1. BaP dosing

MPA was tolerated well throughout the study with 9/16 patients taking MPA continuously throughout the trial. 14/16 patients took MPA for more than 80% of the trial duration. One of the 16 patients did not start treatment due to poor health. There were no occasions where the patient stopped MPA but not bezafibrate although patients frequently took MPA alone.

Only four patients took the full dose of modified release bezafibrate (4800 mg daily) and none of these for more than two weeks. These four patients were recruited onto Protocol v5.0a and v6.0 where the starting dose of bezafibrate was either 4800 mg modified release bezafibrate or 2400 mg standard release bezafibrate. Of the patients that were recruited onto Protocol v7.0 (which involved starting on 1600 mg of modified release bezafibrate or 800 mg standard release bezafibrate) and had more than four weeks of treatment, four patients had a mode dose of 1600 mg and one had a mode dose of 3200 mg (the mode dose was taken in these patients for a range of 3-7 weeks). No patient was able to escalate to the full dose of BaP therapy. Of all the patients recruited on protocol 7.0, only 2 patients were able to take bezafibrate for their whole trial duration which was 5.4 weeks for one patient and 8.6 weeks for another. All other patients had at least one period where their bezafibrate had to be interrupted.

Interruptions or changes in bezafibrate doses were largely due to either a rise in CK or a drop in eGFR. Toxicities were reported at higher grades and rates than in previous studies administering BaP [11, 12]. In one patient bezafibrate had to be stopped because they developed myalgia and had an elevated CK indicative of rhabdomyolysis. In a further five patients bezafibrate was temporarily stopped because of elevations of CK (in two patients associated with myalgia and one with oedema); all patients recommenced lower doses of bezafibrate. All patients experienced their first rise in CK within two weeks of starting modified release bezafibrate at a dose of 1600 mg (modified release bezafibrate starting dose).

In six patients (10 occasions) reductions in eGFR required a change in the dose of bezafibrate and in five of these patients (7 occasions) this also required a change in formulation. Bezafibrate is contraindicated in patients with an eGFR <40 ml/min. Patients have to be changed from modified bezafibrate to standard release bezafibrate if the eGFR drops below 60 ml/min. Because patients eGFR levels fluctuate (see appendix 2), future trials should consider only recruiting patients with an eGFR greater than 50 ml/min and only using the standard release formulation of bezafibrate.

Although high dose BaP was tolerated and efficacious in children with endemic Burkett's lymphoma [11] the patient group here have not tolerated high dose bezafibrate. This intolerance of high dose bezafibrate reflects multiple reasons that include reduced and fluctuating renal function and a propensity to develop myalgia with elevated creatine kinase. There has been no obvious benefit in improved haemopoiesis or overt anti-leukaemia activity from the attempts to escalate BaP dose over the previous published study [11].

8.1.2. Issues with the patient population

Since starting the BaP trial, a number of competing trials have developed in the AML setting in the UK. Due to this and the issues with establishing a continuous dose in this population, it would appear that further BaP based approaches in AML are not currently viable.

8.2. Conclusions from the CLL/BNHL population

No conclusions about the efficacy or safety of BaP in these settings can be drawn due to only 1 patient being recruited in each cohort. BaP therapy is not a competitive option in CLL at this time given the new drugs that have recently become available to these patients. Generically BaP is not attractive in BNHL at this time. However, given the efficacy seen in children with endemic Burkitt's lymphoma [12] and the lack of effective regimens for relapsed and refractory sporadic Burkett's lymphoma there is cause to consider a pilot study in this setting.

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