Local Contact Details

to be printed on headed paper

A phase 2 study of the monocyte-targeted histone deacetylase inhibitor tefinostat (CHR-2845) in chronic myelomonocytic leukaemia (CMML)

Patient Information Sheet 1

Introduction

You are being invited to take part in a clinical trial (also known as a study). Before deciding if you want to take part, it is important that you understand why the research is being done and what it will involve. Please take the time to read this information sheet carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you feel you need more information. Take as much time as you need to decide if you wish to take part or not.

- Part 1 tells you the purpose of the study and what will happen if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Thank you for reading this information. If you decide to take part you will be given a copy of both this information sheet and your signed consent form.

This trial has been given ethical approval by Wales REC 3

Monocle Study Patient Information Sheet 1

Part 1

What is the purpose of the Monocle study?

Chronic myelomonocytic leukaemia (CMML) is a rare disease of the bone marrow that causes a build-up of a type of white blood cells called monocytes in the bone marrow and blood. Treatment options for the majority of people with CMML are currently relatively limited and there have been very few clinical trials addressing this disease.

Tefinostat is a new drug, taken by mouth as a capsule, which only becomes active after it is inside monocytes. It works by blocking enzymes which cells need to grow and divide. In a previous study, tefinostat was given to 18 patients with blood cancers (leukaemia and lymphoma). Very few of these patients experienced any significant side effects whilst taking tefinostat (greater detail is given in the table on page 8). Only 2 of the patients in this study, however, had CMML. We would therefore like to find out how effective tefinostat treatment is for patients with recently diagnosed or previously treated CMML.

The aims of the Monocle study are to see whether patients with CMML benefit from tefinostat treatment, while we also monitor for any previously unreported side effects of therapy. In the study, tefinostat therapy will be taken every day for 24 weeks. After 24 weeks, patients who are found to be benefitting from tefinostat will be given the option to remain on treatment for longer. This is a phase two trial.

What is a 'Phase 2' clinical trial?

Phase 2 trials involve 20-300 patients and are designed to see how well a drug works, once the initial safety of the study drug has been confirmed in smaller phase 1 trials. A phase 2 trial also aims to continue assessing the safety of the drug from the phase 1 trial in a larger group of patients. The safety of tefinostat has been assessed in a phase 1 trial in patients with blood cancers (leukaemia and lymphoma) and also in a continuing study in patients with liver cancer and we now want to test it in CMML patients in the Monocle study.

Why have I been invited to take part in the Monocle study?

You have been diagnosed with or have been previously treated for CMML and your haematology doctor has considered that you might be suitable for this study. There is currently no single effective treatment for CMML, so we are inviting patients like you to take

part in the Monocle study to test the effectiveness of tefinostat in this disease. In total, 40 patients in the UK, from up to 20 different hospitals, will take part in this study.

Do I have to take part in the Monocle study?

No, taking part in the Monocle study is entirely voluntary. It is up to you to decide whether or not you wish to take part. If you decide to take part you will be asked to sign a consent form, but you will still be free to withdraw at any time and without giving a reason. If you decide that you would rather not be in the study, your haematology doctor will be happy to talk through alternative treatment options, including the current standard treatment options, your care will not be affected in any way. If you decide to withdraw from the study because of side-effects it is important that you tell your haematology doctor about these. Your haematology doctor may also stop your involvement in the study if he/she feels that this is in your best interests.

What will happen to me if I take part in the Monocle study?

Before you take part in this study, you must read this Patient Information Sheet and Consent Form in full. You are encouraged to ask as many questions as you like. If you decide to take part in the study, you will need to sign and date this form (a copy will be returned to you for your records). You do not need to sign this form immediately and should take as long as you need (at least 24 hours) to consider the information provided and consult with your doctor, family and friends as you wish.

If you decide to take part in this study, you will be required to follow the schedule of study visits and procedures and to take the study medication (tefinostat) as directed. If you take part in the study, you should not be involved in any other drug study at the same time. You should tell your study doctor about any new medication that is prescribed for you in order to check whether it is safe to continue whilst taking the study medication. If you are admitted to hospital you should tell them that you are in the Monocle study and give the study team's contact details.

The table on page 6 summarises what will happen to you at each study visit. There is also a detailed text explanation of the study visits and procedures below:

- **Screening**

  The first part of the study is known as the 'screening' period. During this time a number of tests will be done to make sure you are suitable for the study and these will include: taking your medical history, a review of the medications you are taking, a

physical examination, taking blood, urine and bone marrow samples, an ECG recording (heart tracing) and a urine pregnancy test if you are a female who could become pregnant. You will also be asked to complete quality of life questionnaires. If the screening process confirms that you are suitable for the study, this information will be registered with the Cardiff Centre for Trials Research (CTR) and you will be able to start the first cycle of tefinostat treatment.

- **Treatment**

  During your treatment you will take tefinostat by mouth once daily after eating. To help us monitor the treatment you receive in the study, the period over which you take tefinostat is divided into 28-day (4-week) cycles which will run continuously with no gaps in between them. The tefinostat will be supplied every 4 weeks and you will need to store it in your fridge at home. Your doctor will tell you how many capsules you need to take; the dose may change depending on how your CMML responds to the treatment and on whether you develop any side effects. Your haematology doctor may suggest **increasing** your dose to try to improve the response of your CMML to tefinostat, or may need to **reduce** or **stop** your dose if you are experiencing side effects.

- **Tests and Procedures**

  During the first 24 weeks of tefinostat treatment you will need to come to the hospital to be seen every 2 weeks so that we can monitor your response to the treatment and its safety. At each of these fortnightly visits we will ask about any side effects you might be experiencing and take blood samples (about 2-3 teaspoons of blood will be collected at each of these routine visits). On alternate visits (every 4 weeks) you will also have a physical examination (including measuring blood pressure, pulse rate, temperature, body weight, liver and spleen size, lymph node enlargement, gum and skin examination), an ECG recording (heart tracing) and we will take a urine sample. We will also make note of any changes in your medications and any blood or platelet transfusions you have received and repeat a urine pregnancy test for women who could become pregnant.

  During the first and second cycles of tefinostat treatment some extra blood samples will be taken to enable us to measure the effects of tefinostat in blocking the targeted enzymes in blood cells and also to measure the levels of the drug in your blood. To do this, 2 extra teaspoons of blood will be taken on day 1 of therapy before your first dose of tefinostat and 1, 2 and 4 hours after it. Further samples will be taken on day

2 before you take the second dose of tefinostat and on days 15 and day 29 (day 1 of cycle 2).

After 12 and 24 weeks of tefinostat treatment (the end of cycles 3 and 6) we will more formally assess the response of your CMML to tefinostat treatment. At these times, further bone marrow samples will be taken and we will also ask you to repeat the quality of life questionnaires that you completed at your first visit after screening. If you should need to stop tefinostat treatment before the 24 week point due to either side effects or a worsening of your CMML then an additional bone marrow sample will be requested.

- **What happens after 24 weeks treatment?**

  If the assessment at the end of the sixth cycle (24 weeks) of tefinostat treatment shows that there has been an overall improvement in your CMML, and you have not experienced any significant side effects, your doctor will give you the option of continuing with the tefinostat therapy. Treatment can then be continued for as long as this improvement is maintained. If you decide to continue with the tefinostat treatment you will need to come to the hospital every 4 weeks. At these visits we will take blood samples (2-3 teaspoons), ask about any transfusions you have received or any changes in your medications, perform a physical examination, take an ECG recording and also repeat a urine pregnancy test for women who could become pregnant. If the overall improvement in your CMML is lost at a later point, tefinostat treatment will be stopped and your doctor will need to take a further bone marrow sample.

	Screening	Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6			Treatment can be continued as long as response is maintained - maximum follow-up interval 4 weeks	Loss of response / Disease progression / Intolerability
Week		**1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**		
Day	**Day -28 to 0**	**1**	**2**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**		
Informed consent	✓																
Screening - eligibility criteria	✓																
Medical and CMML history	✓																
Demographic data	✓																
Concomitant medications	✓	✓			✓		✓		✓		✓		✓		✓	✓	✓
Transfusion history	✓	✓			✓		✓		✓		✓		✓		✓	✓	✓
Physical Examination	✓	✓			✓		✓		✓		✓		✓		✓	✓	✓
Vital Signs, Weight	✓	✓			✓		✓		✓		✓		✓		✓	✓	✓
Performance score (ECOG)	✓														✓		✓
Haematology	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Biochemistry	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Coagulation screen	✓																
Urinalysis	✓	✓		✓	✓		✓		✓		✓		✓		✓		✓
Blood and bone marrow for central correlative studies	✓																
Pregnancy test [1]	✓	✓			✓		✓		✓		✓		✓		✓	✓	
ECG	✓	✓		✓	✓		✓		✓		✓		✓			✓	
Bone marrow assessment [2]	✓								✓						✓		✓
Quality of Life questionnaires	✓								✓						✓		
Dispensation of study medication		✓			✓		✓		✓		✓		✓		✓	✓	
Blood samples for enzyme studies [3]		✓	✓	✓	✓												
Blood samples for assessing levels of drug in your body (4)		✓	✓	✓	✓												
Adverse event assessment		Monitor during treatment and for 30 days after last dose of tefinostat															
Progression / AML transformation	Monitor from day of registration to end of trial																

1 Pregnancy test (urine) should be performed within 1 week of each study cycle in women of childbearing potential
2 Bone marrow examination should be performed at baseline, after 3 and 6 cycles of treatment and, for patients continuing beyond 6 cycles of tefinostat, at the time of topping drug if you are not benefitting from it or are experiencing too many side effects. Baseline bone marrow sample to be shipped for central biological correlative studies
3 Blood for enzyme studies will be taken pre-dose on day 1, 1hr, 2hrs and 4hrs post dose on day 1, pre-dose on day 15 and pre-dose on day 29 (day 1 of cycle 2)
(4) Blood for assessing levels of drug will be taken pre-dose on day 1, 1hr, 2hrs and 4hrs post dose on day 1, pre-dose on day 2, pre-dose on day 15 and pre-dose on ay 29

What are the alternatives to the Monocle study?

If you decide not to participate in this study, or your doctor feels you are not suitable, an alternative treatment plan will be made available. Alternative treatments might include a chemotherapy tablet (hydroxycarbamide) or a 'hypomethylating agent' (azacitidine) which is given by injections and/or transfusion with blood or platelets. Different patients with CMML will experience different features of the disease and not all of these treatments will be suitable for all patients. Sometimes a bone marrow transplant is considered for patients who are fit enough to get this treatment and who have a bone marrow donor, but this can only be done in a few patients. Your doctor will discuss the alternative treatment options with you before you decide whether or not to take part in this study.

What are the possible disadvantages and risks of taking part?

The Monocle study will involve more visits to hospital and more blood tests than might be needed in routine care. Blood tests may lead to some local bruising and discomfort. Also, because we want to see how the drug affects the bone marrow, at least 2 extra bone marrow tests will be done so that we can monitor you more closely. Some local discomfort is to be expected when the bone marrow tests are performed.

Being involved in a research study involves a degree of commitment to these extra hospital visits and additional tests. Although it is not expected that you will need to stay in hospital overnight, occasionally this might be necessary to treat side effects.

- ***Side effects of tefinostat***

All drugs can have side-effects and this includes tefinostat. Tefinostat has only been given to a relatively small number of patients before, so we may not yet fully know all of the potential side effects associated with it. Side effects that were experienced in the 35 patients that have been treated with tefinostat (18 patients with leukaemia and lymphoma that were treated in the first phase 1 study of tefinostat, and an additional 17 patients that have recently been treated in another early phase trial of tefinostat taking place in liver cancer) are summarised in the table overleaf:

	Number of Patients Experiencing Side Effects			
	Mild Symptoms	Moderate Symptoms	Severe Symptoms	Total
Nausea	9	5	1	**15**
Fatigue / Lethargy	5	8	2	**15**
Reduction in appetite	1	4	2	**7**
High creatinine levels (kidney function)	2	5	0	**7**
Constipation	4	0	0	**4**
Rash	4	0	0	**4**
Muscle Pain / Cramps	1	2	0	**3**
Vomiting	2	1	0	**3**
Proteinuria (protein in urine)	1	1	0	**2**

The liver cancer study is currently ongoing. During the Monocle study, the study team and the team at your local hospital will be kept informed of any significant new side effects that are identified. The local team will keep you updated of any significant new drug safety developments.

It is important that you tell your study doctor or research nurse about any new symptoms that you have at each hospital visit. You can telephone either of them between visits if you are concerned and you will find their telephone numbers printed at the end of this information sheet.

- ***Pregnancy during treatment - information for women and men***

If you or your partner becomes pregnant during this study then you will be asked to complete a separate consent form in order to collect information on the outcome of the pregnancy.

Female patients: We do not know the effect of tefinostat on an unborn child; therefore, if you are pregnant you cannot enter the study. Women who could become pregnant must agree to use at least 2 effective contraception methods during the study. Your study doctor will discuss this with you. You must also continue to use effective methods of birth control for at least 3 months after you stop taking tefinostat. Before the study, and before each 4-week cycle of tefinostat, a pregnancy test will be done for all women who are of child bearing potential. If you become pregnant during the study, these risks could affect you or your unborn child. If you think you may be pregnant, you must tell your study doctor immediately. Pregnancy will be a reason to stop study treatment. If you become pregnant, information on the outcome of your pregnancy will be requested.

Male patients: The effect of tefinostat on sperm is not known so male patients must also agree to use at least 2 effective methods of birth control during the study and for at least 3 months after stopping tefinostat treatment. Your study doctor will discuss this with you. If your partner thinks they have become pregnant during your participation in the study you must tell your study doctor immediately so that the pregnancy can be monitored.

What are the possible benefits of taking part?

We hope that the study treatment will help to control your CMML and make you feel better but, given that only 2 patients with CMML have received tefinostat in previous studies, it is not yet possible to predict exactly how patients will respond, so we cannot guarantee that you will benefit directly from taking part in the study. Research studies such as this are essential for progress in the treatment of diseases. The information we get from this study may help us to improve the future treatment of patients like you with CMML.

What happens when the study stops?

Patients may continue to receive tefinostat treatment for as long as it appears to benefit them. If the decision is made to stop study drug treatment (for example because of side effects or because the CMML is not responding sufficiently well) you will continue to see your haematology doctor and further treatment options will be discussed. You will remain under follow-up in the study for a period of at least 18 months following registration for the Monocle study to allow us to assess longer term outcomes. When the results of the study become available a summary can be provided to you upon request.

Will my travel expenses be covered?

Yes, we will refund any additional travel expenses and hospital parking costs that you may incur when attending Monocle study appointments that are considered over and above your routine care.

What if there is a problem?

Every care will be taken in the course of this study. If you have a concern about any aspect of this study you should ask to speak to the local research team who will do their best to answer your questions. If you remain unhappy and wish to complain formally you can do this through the NHS complaints procedure. More detailed information about this is given in Part 2.

Will my participation in the study be kept confidential?

If you decide to participate in the Monocle study, the information collected about you during the course of the study will be kept strictly confidential. Further details are included in Part 2 of this information sheet.

Your GP will be informed of your participation in the study. There is a space on the consent form for you to confirm that you are aware of this.

This completes Part 1 of the Information Sheet. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Monocle Study

Patient Information Sheet 1

Part 2

What if new information becomes available?

Sometimes during the course of a study, new information becomes available about the treatment or drug that is being studied. If this happens, your haematology doctor will tell you about it and discuss whether you should continue in the study. If you decide not to carry on, your doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form.

On reviewing new information, your haematology doctor might consider it to be in your best interests to withdraw you form the study. They will explain the reasons for this and arrange for your continuing care.

What will happen if I don't want to carry on with the study?

If you decide not to continue the study for any reason, you should discuss this with your haematology doctor so that they can make the best arrangements for your continuing care. If you withdraw consent for further study treatment, we will still need to use the information we have collected about the treatment you were given and your progress up to the time you withdrew. If you withdraw consent from the study, we will check whether you will still allow your Research Nurse or Doctor to update the study team from time to time on how well you are doing. You may withdraw consent for your blood and bone marrow samples taken during the study; in these circumstances we will arrange to have these destroyed so that none of your cells are kept. In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived for a minimum of 15 years after which arrangements for confidential destruction will be made.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of this study, you should ask to speak to one of your local research Nurse or Doctor or to the study organisers who will do their best to answer your questions. The Chief Investigator of the Monocle study is Dr Steven Knapper (Cardiff University) who may be contacted via Cardiff University Centre for Trials Research on 02920 687870.

- **Complaints:** If you remain unhappy and wish to complain formally you can do this through the NHS complaints procedure. Details can be obtained from your local hospital.

For sites in England you may also contact your local Patient Advisory Liaison Office. (Tel……..)

- **Harm:** There are no special compensation arrangements if you are harmed by taking part in this research project. If you are harmed due to negligence, you may complain through your local hospital complaints procedure or you may have grounds for legal action against the trial sponsor (Cardiff University).

Will my participation be kept confidential?

If you agree to take part in the Monocle study, your doctor will send information about you, your condition and your progress to the study trials unit (Centre for Trials Research) at Cardiff University. This information will be put into a computer and analysed by the Centre for Trials Research staff. All information will be held securely and in strict confidence. Your name will not be identifiable by the Sponsor or Trial team, within the study you will only be referred to by your trial number, initials and date of birth. All personal details will be treated as strictly confidential by these organisations.

If you consent to take part in the research, your medical records may be inspected by your hospital personnel or the Chief Investigator (or his nominee) on behalf of the trial Sponsor who is Cardiff University for purposes of analysing the results. Your notes may also be looked at by people from regulatory authorities to check that the study is being carried out correctly.

Authorised members of CRT Pioneer GP Limited, the commercial company that owns and supplies tefinostat, may review your study documents but will not have access to individual medical records. The data they review will be completely anonymised and will contribute to the understanding of the safety of the drug they may use if the company apply to license the drug.

When the study is complete, the results will be presented at haematological conferences and published in medical journals, but no individual patients will be identified. If you would like to obtain a copy of the published results, please ask your hospital doctor.

What happens to any samples I give?

Most of the blood and bone marrow samples taken during the Monocle study are for routine diagnostic tests and are part of the regular care of your CMML. These routine tests will be conducted by your local hospital. Additional study samples will be analysed by Cardiff University and a commercial company based in the UK. As such your samples will be sent outside of the NHS for testing, but they will not be sent outside the UK. All material that leaves your local hospital will have your name and personal details removed and will be identified by your trial number, DOB and initials.

There is a separate information sheet (Patient Information Sheet 2) that asks for your permission to allow us to store any blood or bone marrow that is left over after the tests specified in the study protocol have been completed so that this can then be used for future research such as new tests or scientific experiments designed to develop new CMML treatments. If, at any time, you inform us that you no longer want these extra samples to be stored for future research, we will arrange to have them destroyed. In these circumstances we will still retain any data that has already been gained from using the samples but no further work would be undertaken.

Will any genetic tests be done?

Haematological diseases such as CMML develop, in part, because of genetic changes (mutations) that arise in blood and bone marrow cells. The only genetic tests to be done using blood and bone marrow samples taken in the Monocle study will be to look for these genetic changes within leukaemia cells. The genetic changes which can cause leukaemia are not the sort of genetic changes that get passed on to children; we will not allow any tests for genetic diseases to be performed.

Who has organised, reviewed and funded the research and who will be supervising it?

The study is being organised by Cardiff Centre for Trials Research and is being sponsored by Cardiff University which is, in law, the responsible organisation. The lead individual responsible for the day to day running of the study, also known as the Chief Investigator, is Dr Steven Knapper of Cardiff University. The lead person at your local hospital, also known as the local Principal Investigator is Dr.(PERSON) who can be contacted on (TELEPHONE). The Monocle study is funded by Bloodwise (previously called Leukaemia Lymphoma Research). Tefinostat is being supplied for use in the study by CRT Pioneer GP Ltd. The Monocle study has been reviewed by Wales REC 3 and approved by the Research & Development department at your local hospital. There is an Independent Data Monitoring Committee (IDMC) who will be overseeing the study data on a regular basis.

This completes Part 2 of the Information Sheet. If you have any further questions, please ask a member of your local study team. If you are happy to take part in the study, your team will ask you to complete the attached consent form. You will be able to keep a copy of this. Thank you.

Monocle Study: Informed Consent Form

Name of Researcher: *Insert local researcher's name*

Chief Investigator: *Dr Steven Knapper*

Please initial boxes

1	I have read the attached Monocle Study Patient information Sheet 1 (v3.0 dated 19/12/2017) and received a copy to keep.	☐
2	I have had an opportunity to discuss this study and ask questions.	☐
3	I have received satisfactory answers to all of my questions.	☐
4	I have received enough information about the study.	☐
5	I have spoken with Dr / Mr / Mrs _____.	☐
6	I understand that I am free to withdraw from the study: • at any time • without having to give any reasons • without affecting my future medical care	☐
7	I understand that I will need to use two forms of contraception whilst participating in this study and inform you if myself or my partner becomes pregnant.	☐
8	I understand that my doctor will provide information about my progress, in confidence to the central organisers and the trials unit at Cardiff University and that all information will be held securely and in strict confidence..	☐

9 I understand that sections of my medical records, relating to my participation in the study, may be inspected by responsible individuals from the trial Sponsor (Cardiff University). All personal details will be treated as STRICTLY CONFIDENTIAL. The information will be used for medical research only and I will be identified by trial number, initials and date of birth. I will not be identified in any way in analysis and reporting of the results. I give permission for these individuals to have access to my records and to have my clinical details recorded in them. ☐

10 I understand that some of my anonymised data may be shared with the commercial company CRT Pioneer GP Ltd. ☐

11 I am aware that my GP will be informed of my participation in the Monocle study. ☐

Name of patient	Date (dd.mmm.yyyy)	Signature
Name of person taking consent (if different from researcher)	Date (dd.mmm.yyyy)	Signature
Name of researcher	Date (dd.mmm.yyyy)	Signature

(1 for patient; 1 for researcher (trial site file); 1 to be kept with hospital notes)