SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Ribociclib + Aromatase Inhibitor Advanced Breast Cancer

PROTOCOL REF: MPHARIBOBR
(Version No. 2.0)

Approved for use in:

Indicated for the treatment of previously untreated, oestrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy where the following criteria are met:

- Previous hormone therapy whether as adjuvant therapy or as neoadjuvant treatment is allowed as long as the patient has had a disease-free interval ≥ 12 months.
- Female patients are either post-menopausal or if pre- or peri-menopausal have undergone ovarian ablation or suppression with LHRH agonist treatment.
- ECOG status 0-2.

Note – Ribociclib contains peanuts and soya – contraindicated if patient has nut / soya allergy

*********BLUETEQ REGISTRATION REQUIRED***********

Dosage:

Drug	Dose	Route	Frequency	Duration
Ribociclib	600mg once daily	Oral	Days 1 to 21 followed by 7 days rest - 28 day cycle	Until progression or unacceptable toxicity
Letrozole or alternative Aromatase Inhibitor	See BNF for dosing	Oral	Days 1 to 28 continuously	Until progression or unacceptable toxicity

Aromatase inhibitor to be initiated at CCC, 1 month's supply given then further supply to be obtained from the GP.

Administration + Counselling Points:

Ribociclib can be taken with or without food. Patients should be encouraged to take their dose at approximately the same time each day, preferably in the morning. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Ribociclib tablets should be swallowed whole and should not be chewed, crushed or split prior to swallowing.

Ribociclib should be used together with letrozole or another aromatase inhibitor. The aromatase inhibitor is taken orally, once daily, continuously throughout the 28‑day cycle. Please refer to the Summary of Product Characteristics (SmPC) of the aromatase inhibitor for additional details.

Patients should be instructed to avoid pomegranates, pomegranate juice, grapefruit or grapefruit juice. These are known to inhibit CYP3A4 enzymes and may increase exposure to ribociclib.

Emetogenic risk:

Low emetogenic risk

Supportive treatments:

1st line antiemetic- Metoclopramide 10mg PO TDS to be prescribed as needed (maximum 5 days' supply)

2nd line antiemetic- Ondansetron 8mg PO BD to be prescribed as needed (Not recommended in cases of QT prolongation)

Loperamide 4mg at the onset of diarrhoea then 2mg when required (maximum of 16mg per day)

Extravasation risk:

Not applicable

Dosing in renal and hepatic impairment:

Renal	eGFR ≥ 30 ml/min/1.73m^2- no dose adjustment eGFR < 30 ml/min/1.73m^2 - Starting dose of 200mg once a day is recommended. Use with caution- monitor for signs of toxicity

Hepatic

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A).

Patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) can have increased (less than 2-fold) exposure to ribociclib and the starting dose of 400 mg once daily is recommended

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

Child-Pugh Class
A (5-6 points)
B (7-9 points)
C (10 or more points)

INR: International Normalised Ratio.
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

Interactions:

Ribociclib is primarily metabolised by CYP3A4. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter its pharmacokinetics.

For more detailed interactions please refer to the Ribociclib SmPC. For any interaction queries please contact Cytopharmacy.

CYP3A4 inhibitors	The concomitant use of strong CYP3A4 inhibitors must be avoided, list includes but is not exhaustive; **clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, verapamil and voriconazole**. Alternative concomitant medicinal products with less potential to inhibit CYP3A4 should be considered and patients should be monitored for ribociclib related adverse events. If co-administration of ribociclib with a strong CYP3A4 inhibitor cannot be avoided, the **dose of ribociclib should be reduced by one dose level** (see Table 1.0). In patients who have had their dose reduced to 200mg ribociclib daily and in whom initiation of a strong CYP3A4 inhibitor cannot be avoided, ribociclib treatment should be interrupted.
CYP3A4 inducers	The concomitant use of strong CYP3A4 inducers should be avoided, including, but not limited to, **phenytoin, rifampicin, carbamazepine and St John's Wort**. An alternative concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered. The concomitant use of moderate CYP3A4 inducers may lead to decreased exposure and consequently a risk for impaired efficacy, in particular in patients treated with ribociclib at 400 mg or 200 mg once daily.
CYP3A4 substrates	Ribociclib is a moderate to strong CYP3A4 inhibitor and may interact with medicinal substrates that are metabolised via CYP3A4, which can lead to increased serum concentrations of the concomitantly used medicinal product. Concomitant administration of ribociclib at the 600 mg dose with the following CYP3A4 substrates should be avoided: **alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam.**
	Caution is recommended in case of concomitant use with sensitive CYP3A4 substrates with a narrow therapeutic index including but not limited to **alfentanil, ciclosporin, everolimus, fentanyl, sirolimus and tacrolimus**. The dose of a sensitive CYP3A4 substrate with a narrow therapeutic index may need to be reduced as ribociclib can increase their exposure.

Substrates of transporters	Caution and monitoring for toxicity are advised during concomitant treatment with sensitive substrates of these transporters which exhibit a narrow therapeutic index, including but not limited to **digoxin, pitavastatin, pravastatin, rosuvastatin and metformin.**
Medical products with potential to prolong QT interval	Co-administration of ribociclib with medicinal products with a known potential to prolong the QT interval such as anti-arrhythmic medicinal products (including, but not limited to, **amiodarone, disopyramide, procainamide, quinidine and sotalol**), and other medicinal products that are known to prolong the QT interval (including, but not limited to, **chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron**) should be avoided.

Main toxicities:

The most common grade 3/4 adverse drug reactions (ADRs), reported at a frequency ≥ 20% and ≥ 2% respectively for the ribociclib and letrozole combination are listed below (this list is not exhaustive, please refer to SmPC for full details):

- Neutropenia
- Leukopenia
- Infections: UTIs very common
- Headache
- Back Pain
- Nausea and vomiting
- Fatigue
- Diarrhoea/ constipation
- Alopecia, rash (maculopapular), pruritis, **severe cutaneous reactions (see 'Special Warnings and Precautions' section below)**
- Hepatobilliary toxicity- raised LFTs (ALT, AST and serum bilirubin)
- Electrolyte disturbances- **hypocalcaemia, hypokalaemia, hypophosphataemia**

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D14	Cycle 2	Cycle 2 D14	Cycle 3	Ongoing
Informed Consent	X						
Clinical Assessment All patients on SACT should have **at least one F2F review during treatment.**	X		X	X	X	X	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)		X	X	X	X	X	Every cycle
FBC	X		X	X	X	X	Every cycle
U&E & LFTs	X		X (if prolonged QT seen on ECG)	X		X	Every Cycle
CrCl (Cockcroft and Gault)	X			X		X	Every cycle
CT scan	X						3 monthly or as clinically indicated
ECG/QTC ** (See below for ECG monitoring information)	X		X	X			Then if clinically indicated / previously abnormal ECG
Blood pressure measurement	X						Repeat if clinically indicated
Respiratory Rate							If clinically indicated
Weight recorded	X	X		X		X	Every cycle
Height recorded	X						

ECG Monitoring

6 – lead mobile ECGs will soon be available to use at each hub/centre to monitor QT through IQVIA technology for ribociclib patients only. This should not be used unless trained to do so. If this is not available, 12-lead ECGs should be utilized and reviewed

See Appendix 1 for details

Deferrals

Please note that it is ribociclib only that is being deferred – the aromatase inhibitor that the patient is taking (letrozole, anastrozole or exemestane) should be continued

Haematological toxicity:

Proceed rules for Cycle 1* day 1:

ANC ≥ 1.5 x 10^9/L	Platelets ≥ 100 x 10^9/L

*Based on MonaLEEsa 2 clinical trial inclusion criteria.

Continue with treatment if on day Cycle 1 Day 14:

ANC ≥ 0.5 x 10^9/L	Platelets ≥ 75 x 10^9/L

Proceed on day 1 of each subsequent cycle:

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 75 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Dose Modifications and Toxicity Management:

Special Warnings and Precautions

Neutropenia

- Based on the severity of the neutropenia, treatment with ribociclib may have to be interrupted, reduced or discontinued as described in Table 2.0.

Hepatobiliary toxicity

- Liver function tests should be performed before initiating treatment with ribociclib. After initiating treatment, liver function should be monitored.
- Based on the severity of the transaminase elevations, treatment with ribociclib may have to be interrupted, reduced or discontinued as described in Table 3.0. Recommendations for patients who have elevated AST/ALT grade ≥ 3 at baseline have not been established.

QT interval prolongation

- ECG should be assessed before initiating treatment. Treatment with ribociclib should be initiated only in patients with QTcF values less than 450 msec. ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. See Appendix A
- Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with ribociclib.
- The use of ribociclib should be avoided in patients who already have or who are at significant risk of developing QTc prolongation. This includes patients:
    - with long QT syndrome;

  - with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina and brady-arrhythmias;
  - with electrolyte abnormalities.
- The use of ribociclib with medicinal products known to prolong QTc interval and/or strong CYP3A4 inhibitors should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval. If treatment with a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 400 mg once daily.
- Based on the observed QT prolongation during treatment, treatment with ribociclib may have to be interrupted, reduced or discontinued as described in Table 4.0.

Severe Cutaneous Reactions

Toxic epidermal necrolysis (TEN) has been reported with ribociclib treatment. If signs and symptoms suggestive of severe cutaneous reactions (e.g. progressive widespread skin rash often with blisters or mucosal lesions) appear, ribociclib should be discontinued immediately.

Table 1.0: Dose modification guidelines

Dose level	Ribociclib dose	Number of 200 mg tablets
Starting dose	600 mg once daily	3
1st dose reduction	400 mg once daily	2
2nd dose reduction	200 mg* once daily	1
* If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.		

Table 2.0: Dose modification and management- Neutropenia

Toxicities	Grade 1 or 2* (ANC 1.0 x 10^9/L to ≤ LLN)	Grade 3* (ANC 0.5 to < 1.0 x 10^9/L)	Grade 4* (ANC <0.5 x 10^9/L)
Neutropenia	No dose adjustment is required.	Dose interruption until recovery to grade ≤2, then resume at the same dose level. If toxicity recurs at grade 3: dose interruption until recovery ≤ 2, then resume and reduce by 1 dose level***. For grade 3 febrile neutropenia**: Dose interruption until recovery to grade ≤2. Resume and reduce by 1 dose level***.	Dose interruption until recovery to grade ≤2, then resume and reduce by 1 dose level***.
* Grading according to CTCAE Version 4.03 (CTCAE=Common Terminology Criteria for Adverse Events). ** Grade 3 neutropenia with a single fever >38.3°C (or above 38°C for more than one hour and/or concurrent infection). ***See Table 1.0 for dose modification levels. ANC = absolute neutrophil count; LLN = lower limit of normal			

Table 3.0: Dose modification and management- Hepatobiliary toxicity

Toxicities	Grade 1* (>ULN - 3xULN)	Grade 2* (>3 - 5xULN)	Grade 3* (>5 - 20xULN)	Grade 4* (>20xULN)
AST and/or ALT elevations from baseline**, without increase in total bilirubin > 2 x ULN	No dose adjustment is required.	Baseline at grade < 2: Dose interruption until recovery to ≤ baseline grade, resume ribociclib at same dose level. If grade 2 recurs, resume and reduce by 1 dose level***. Baseline at grade 2: No dose interruption.	Dose interruption of ribociclib until recovery to ≤ baseline grade, resume and reduce by 1 dose level***. If grade 3 recurs, discontinue ribociclib.	Discontinue ribociclib.

Combined elevations in AST and/or ALT together with total bilirubin increase, in the absence of cholestasis	If patients develop ALT and/or AST >3xULN along with total bilirubin >2xULN irrespective of baseline grade, discontinue ribociclib.
*Grading according to CTCAE Version 4.03 (CTCAE= Common Terminology Criteria for Adverse Events). ** Baseline = prior to treatment initiation. ***See Table 1.0 for dose modification levels. ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal	

Table 4.0: Dose modification and management- QT Prolongation

ECGs with QTcF >480 msec	1. The dose should be interrupted. 2. If QTcF prolongation resolves to <481 msec, resume and reduce by 1 dose level. 3. If QTcF ≥481 msec recurs, interrupt dose until QTcF resolves to <481 msec and then resume and reduce by 1 dose level*.
ECGs with QTcF >500 msec	If QTcF >500 msec on at least 2 separate ECGs, interrupt ribociclib until QTcF is <481 msec then resume and reduce by 1 dose level. If QTcF interval prolongation to >500 msec or >60 msec change from baseline occurs in combination with Torsade de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue ribociclib.
* See Table 1.0 for dose modification levels. QTcF = QT interval corrected using Fridericia's formula	

Table 5.0: Dose modification and management of other toxicities*

	Grade 1 or 2**	Grade 3**	Grade 4**
Other toxicities	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to grade ≤1, then resume ribociclib at the same dose level. If grade 3 recurs, resume ribociclib and reduce by 1 dose level***.	Discontinue ribociclib.

* Excluding neutropenia, hepatotoxicity and QT interval prolongation.
** Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events).
***See Table 1.0 for dose modification levels.

References:

1. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL, André F, Winer EP, Janni W, Verma S, Conte P, Arteaga CL, Cameron DA, Petrakova K, Hart LL, Villanueva C, Chan A, Jakobsen E, Nusch A, Burdaeva O, Grischke EM, Alba E, Wist E, Marschner N, Favret AM, Yardley D, Bachelot T, Tseng LM, Blau S, Xuan F, Souami F, Miller M, Germa C, Hirawat S, O'Shaughnessy J (2016) Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med*. 3;375(18):1738-1748.

2. KISQALI® (ribociclib): Treatment Protocol Proforma1 .Novartis. September 2017

3. SmPC Ribociclib. Novartis. Available via electronic medicines compendium at https://www.medicines.org.uk/emc/product/8110 (accessed 25/7/23)
4. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
5. BNF available via: https://bnf.nice.org.uk/

APPENDIX 1

6 – lead mobile ECGs will soon be available to use at each hub/centre to monitor QTcF through IQVIA technology for **ribociclib patients only**. This should not be used unless trained to do so. Log-in and training will be provided for users by IQVIA Nurses / trained members of staff.

The ECG trace uploads automatically onto the Kardia dashboard where it is reviewed by the IQVIA Nurse team who will provide the QTcF reading within 30 minutes.

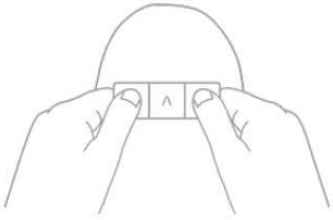
Helpdesk support shall be available 9-5pm, Mon- Fri excluding weekends, Bank Holidays and the period between 25th Dec- 1st Jan (incl)

Tel: 0800 032 1746 or via email at kisqaliECG@iqvia.com

If KardioPro is not available, 12-lead ECGs should be used

Process for recording an ECG using AliveCor Device

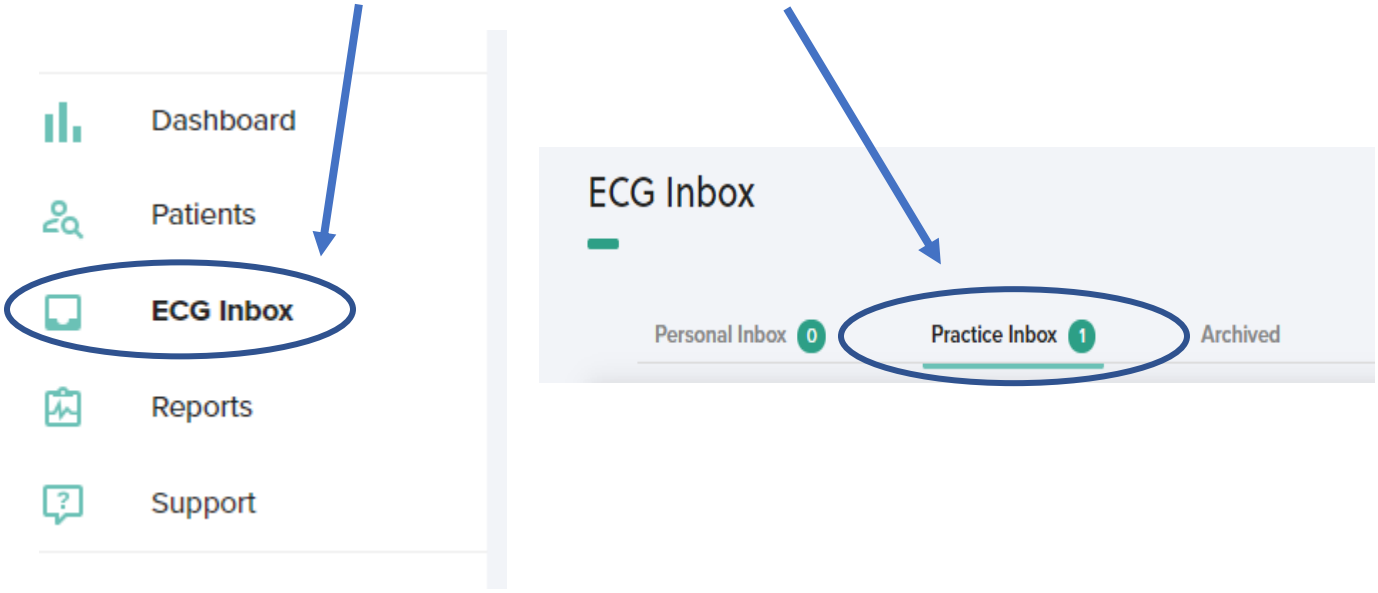
1. Ensure you have the correct iPad & matching device and that the iPad is charged and connected to the internet
2. Give the device to the patient, ensuring that they are sat with their feet to the floor. Expose the **LEFT** knee (preferable) or LEFT ankle if knee not accessible.
3. Ensure the patient is holding the device on the **LEFT** knee/ankle with the **" ^ "** pointing away from their body



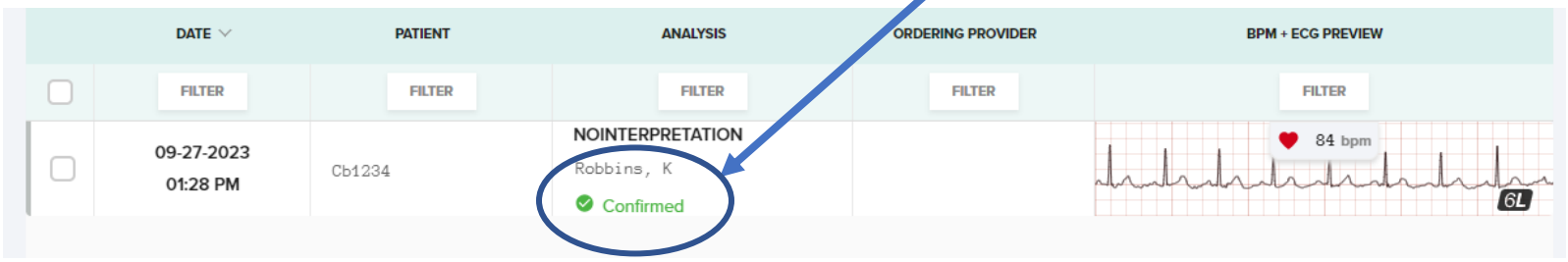
4. Open the Kardia Station App on the iPad
5. Enter the patients CB number
6. Record the ECG – this will take 30 seconds. Observe the trace to make sure the QT wave is facing upwards
7. If the ECG does not record, apply water to the knee/ankle to improve the connection with the device
8. Ensure completion of ECG – if you want to check if the ECG has been sent, click on the 3 horizontal lines, enter the password for the KardiaStation and select "KardiaStation Status"
9. If there is a green tick – the ECG has been sent to IQVIA
10. Keep the patient in clinic/waiting room until results are back

Process for accessing QTcF calculation

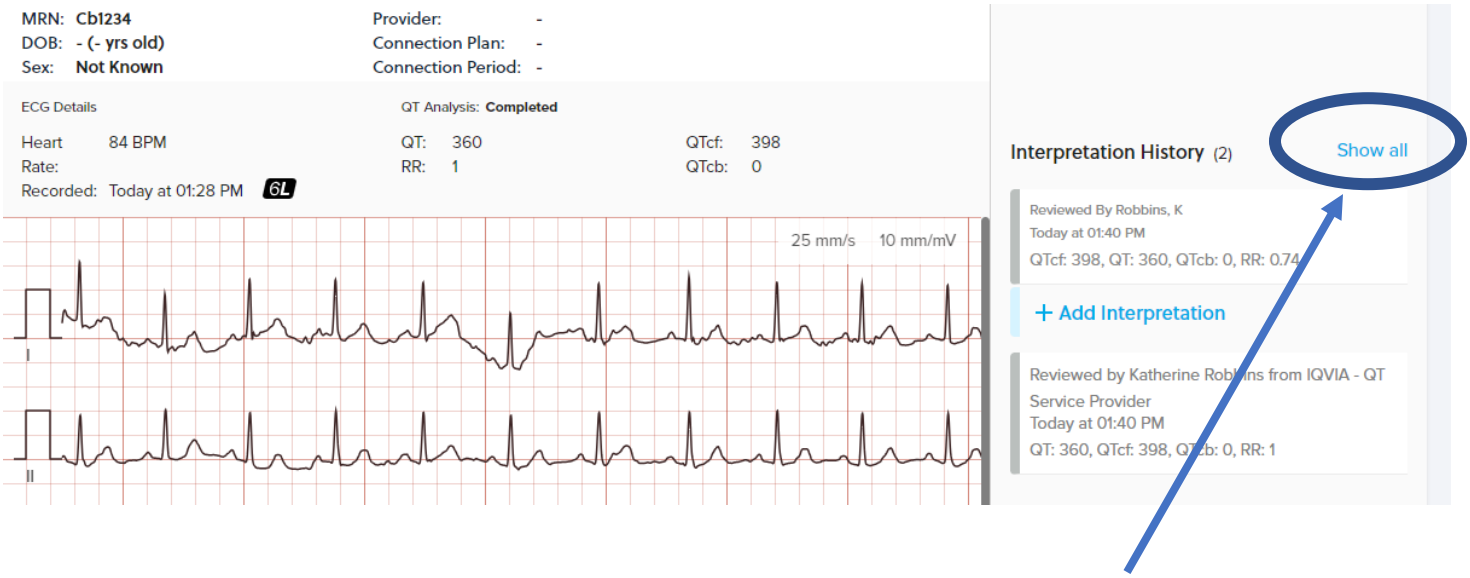
1. The QTcF will be calculated by IQVIA nurses within 30 minutes of recording
2. Go to website on a computer: https://www.kardiapro.com/login
3. Login to the KardiaPro platform using the login details that have been given (ensure using EU version)
4. Select ECG inbox on the left and then Practice inbox (as shown below)



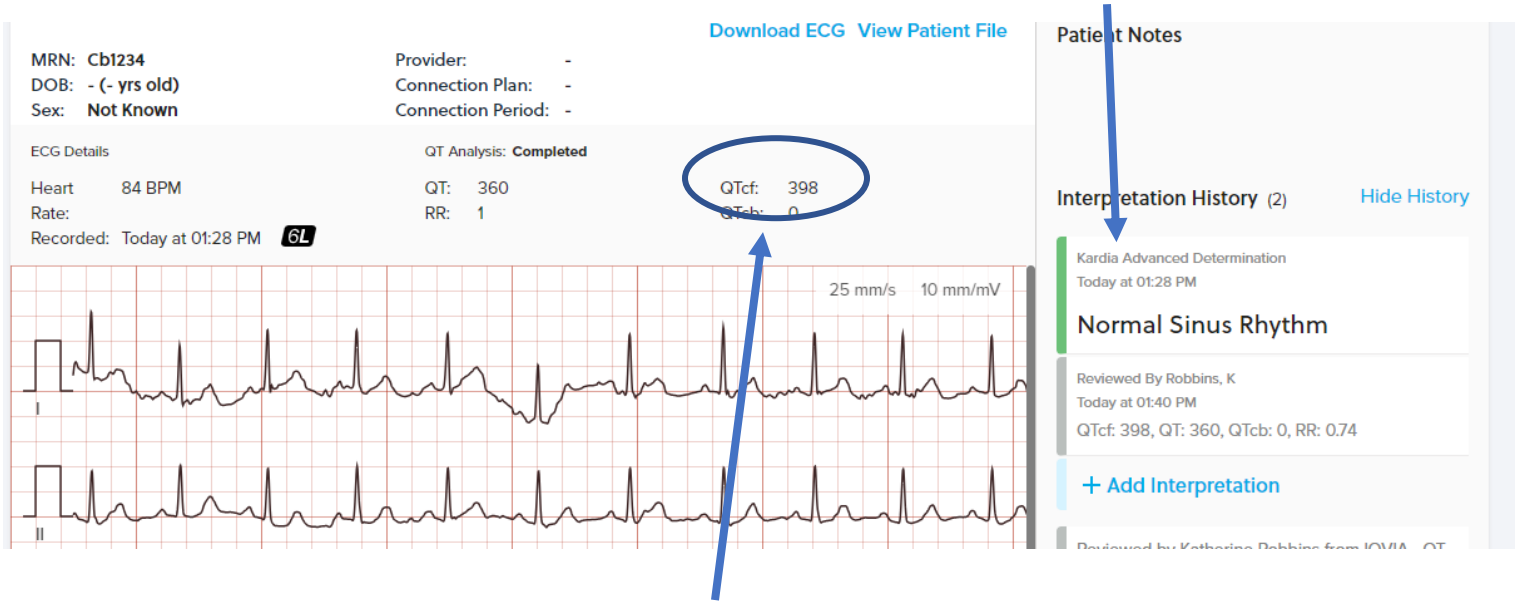
5. Ensure the analysis has been confirmed (shown below) and then click on the patient



6. Check if ECG has been interpreted as normal and QTcf is within limits:



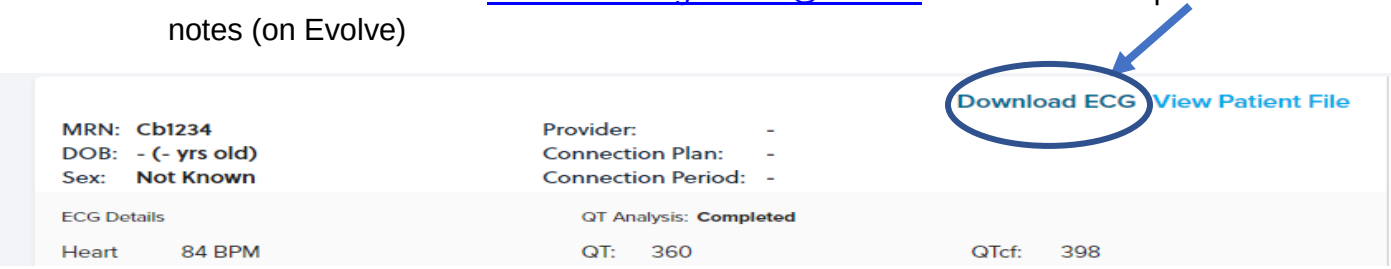
The “show all” button may have to be clicked to open up all information



Note: we are looking at the QTcF as shown.

7. If ECG rhythm results come back as amber or red (see below) then a 12–lead ECG should be taken and results reviewed by a professional trained to do so

8. If QTcF is >480msec treatment should be held and medical team informed (see table 4.0 above)
9. If all results are within range then the ECG can be downloaded as shown below, saved and then sent to ccf-tr.ScanningBureau@nhs.net who will scan to patients notes (on Evolve)



10. Ensure a Meditech note is entered to confirm the above results as per treatment plan

Housekeeping:

Security

Ipads and AliveCor devices should be stored together in a locked cupboard when not in use and should be signed in and out when in use.

Cleaning

1. Clean the electrodes by wiping with a soft cloth dampened with water or one of the following approved cleaners:

    a. Soap and water, or
    b. Bleach solution as recommended by the CDC:https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/disinfecting-your-home.html

2. To clean, spray the cleaner on a soft cloth and thoroughly wipe the device.
3. Ensure the device is sufficiently dried.

Precautions:
1. **Do not use disinfecting wipes or alcohol based products** as these products could adversely affect the product performance.
2. Do no immerse the device or expose the device to excessive liquid.

Batteries
The batteries should last for 200 hours of operational time or 12 months of typical use. Information for changing the batteries can be found at: https://alivecor.zendesk.com/hc/en-us/articles/1500005855261-How-do-I-change-or-replace-the-KardiaMobile-6L-battery-

Kardia Determinations

"Normal Sinus Rhythm"
Indicates normal sinus rhythm with no rhythm or heart rate abnormalities detected; your heart rate was 50-100 beats per minute (bpm).

"Bradycardia"
Atrial fibrillation was not detected and your heart rate was slow, at 40-50 bpm. This can be normal in some adults and athletes. Bradycardia can also be due to an arrhythmia.

"Tachycardia"
Atrial fibrillation was not detected and your heart rate was fast, at 100-140 bpm. This can be a normal response to conditions such as stress or exercise. Tachycardia can also be due to an arrhythmia.

"Unclassified"
Atrial fibrillation was not detected and your ECG does not fall under the algorithmic classifications of 'Normal Sinus Rhythm', 'Bradycardia' or 'Tachycardia'. An 'Unclassified' finding may be caused by other arrhythmias, unusually fast or slow heart rates or poor quality recordings.

"Possible Atrial Fibrillation"
Indicates atrial fibrillation, an irregular heart rhythm, was detected in the ECG. This finding can be detected at any heart rate.

"Unreadable"
The ECG could not be read, likely due to signal noise and/or incorrect recording technique.

TUTORIALS

"Too Short"
Your ECG recording must be at least 30 seconds to allow Instant Analysis algorithms to perform an analysis.

"No Analysis"
There is no Instant Analysis for this ECG.

These are potential findings and not diagnoses. The algorithms do not detect heart attack, blood clots, or stroke. Contact your doctor with any concerns.

Circulation/Dissemination

Date added into Q-Pulse	27TH February 2024
Date document posted on the Intranet	NA

Version History

		Author name and designation	Summary of main changes
		Gabriella Langton, Pharmacist, V2.0	Severe renal impairment dose 200mg (was 400mg in protocol) and addition of mobile ECG information