Abbreviated Clinical Study Report	
Drug Substance	Not applicable
Study Code	D9080C00001
Edition Number	1.0
Date	23 September 2022

A Non-Interventional Pilot Study to Evaluate a Machine-Learning Algorithm for Prediction of Blood Pressure, Glycated Haemoglobin and Estimated Glomerular Filtration Rate from Digital Retinal Images

Study dates:	First subject enrolled: 8 November 2021 Last subject last visit: 10 February 2022 The analyses presented in this report are based on a clinical data lock date of 24 March 2022
Phase of development:	Pilot study
Co-ordinating Investigator:	Not applicable
Sponsor's Responsible Medical Officer:	[redacted] AstraZeneca, Milstein Building, Granta Park, Cambridge, CB21 6GH United Kingdom

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centres

This pilot study was performed at two sites in Kenya to assess the feasibility of collecting digital retinal images in parallel with blood pressure (BP), laboratory, and point-of-care measures in resource-limited settings.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The study's main objective was to establish optimal and scalable methodology for concurrent retinal image acquisition, alongside collection of BP and laboratory assessments (Table S1). Following Food and Drug Administration guidance, this is an abbreviated Clinical Study Report (CSR), as the report is not intended to contribute to the evaluation of a product's effectiveness or provide definitive information on clinical pharmacology.

Table S1 Objectives and Endpoints

Objectives[a]	Endpoints
Primary	
• To assess successful use of methodology for retinal image acquisition, BP, glycated haemoglobin (HbA1c) and estimated glomerular filtration rate (eGFR) measurement	• Proportion of participants with completed study procedures and interpretable results including both retinal images, systolic and diastolic BP (ambulatory BP measurement [ABPM] or manual), HbA1c (laboratory-based or point-of-care test) and eGFR at Visit 1

BP: blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin

[a] Exploratory objectives are not reported in the Synopsis but can be found in Section 8.

Study design

This was a non-interventional pilot study to evaluate feasibility of collecting digital retinal images in parallel with BP, laboratory, and point-of-care measures. Its aim was to determine if the methodology could be scaled in a future larger validation study.

Over the course of two study visits, digital retinal images were collected from participants in parallel with BP, visual acuity, laboratory measures, point-of-care measures, medical history, and medication history. The data collected was used to establish whether an existing machine-learning algorithm accurately predicted BP, HbA1c, eGFR, and other clinical measures in the population under study. The results will be used to determine sample sizes required for full validation of a future algorithm.

Target population and sample size

This pilot study was performed in adults ≥ 35 years of age in Kenya with or without diabetes mellitus (DM) who were willing and able to provide written informed consent. Participants who had an eye condition known to preclude clear imaging of the retina (e.g., cataract) were excluded.

Approximately 300 participants were expected to be enrolled into the study. A formal sample size calculation was not performed, as this pilot study was intended to optimise methodology and provide data that would facilitate sample size estimation for a future larger study.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Not applicable.

Duration of treatment

Not applicable.

Statistical methods

No formal hypothesis testing was planned, and all analyses were intended to be descriptive.

Data collected during the study were described and summarised using standard statistics. Categorical variables were summarised as frequencies and percentages of the non-missing observations in each category. Continuous variables were reported as the number of observations, the number of missing, mean (and standard deviation), median, first and third quartile, minimum, and maximum. When missing data occurred, the number of missing observations for the variable was reported and missing observations were excluded from denominators when calculating percentages.

Study population

At two sites in Kenya, 317 individuals were screened for eligibility and 301 (95%) met the eligibility criteria and were enrolled (n=281 at the Kenya Medical Research Institute site and n=20 at the Aga Khan site). All 301 participants were included in the full analysis set. Over 92% (n=292) of participants in the full analysis set completed the study. The mean age of participants was 51.1 years and more men (n=164, 54.5%) than women (n=137, 45.5%) were enrolled. Approximately, 99% of the study population was Black. The median body mass index (BMI) for participants was 27.2 kg/m^2. Approximately 50% (n=147) of participants had either a Visit 1 HbA1c ≥ 6.5% or a known diagnosis of DM.

Summary of efficacy results

All study procedures had a very high level of completeness, ranging from 97.7% (for Visit 1 cystatin C-based eGFR completeness) to 100% (for Visit 2 systolic blood pressure [SBP] and

diastolic blood pressure [DBP]). For over 97% of participants, complete and interpretable images of both eyes were available for each visit. The large majority of images collected were rated as either 'excellent' quality (approximately 87% for both visits) or 'good' quality (approximately 5-10% for both visits). At both visits, 1.0% or fewer of images were rated as 'inadequate' or 'ungradable'.

Values for eGFR were stable across visits, with a mean creatinine-based eGFR (based on Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] equations) of 95-96 mL/min/1.73m^2. At Visit 1, overall mean SBP was 132 mmHg and mean DBP was 83 mmHg. At Visit 2, BP measurements were marginally lower, with an overall mean SBP of 128 mmHg and mean DBP of 79 mmHg.

At Visit 1, laboratory-based HbA1c measurements had a mean of 7.58%, while point-of-care-based HbA1c measurements yielded a slightly lower mean of 7.19%. A strong correlation was observed between the laboratory and point-of-care HbA1c measurements, with a Spearman's rank correlation coefficient of 0.98 (95% confidence interval: 0.98 to 0.99; p-value <0.001).

Summary of safety results

Two serious adverse events occurred during the study (including one death), and both were unrelated to study procedures. These findings support the safety of the study procedures used to collect digital retinal images, BP, laboratory, and point-of-care measures.

Conclusion(s)

- Collection of interpretable retinal images, BP, HbA1c, and eGFR was successful for the vast majority of participants at both visits, demonstrating the feasibility of the data collection methods in lower-resource settings.
- Laboratory and point-of-care measurements of HbA1c were highly correlated, though point-of-care results slightly underestimated the laboratory values.
- Predictive performance of the machine-learning models varied substantially by endpoint but were generally similar to performance metrics observed in the United Kingdom (UK) Biobank data the algorithms were originally trained on.