


Leveraging Digital Health Technologies and Outpatient Sampling in Clinical Drug Development: A Phase I Exploratory Study

Marissa F. Dockendorf¹ , Gowri Murthy², Kevin P. Bateman¹, Prajakti A. Kothare¹, Melanie Anderson¹, Iris Xie¹, Jeffrey R. Sachs¹, Rubi Burlage³, Andra Goldman⁴, Matthew Moyer⁴, Jyoti K. Shah⁵, Rachel Ruba⁶, Lisa Shipley¹ and Jane Harrelson¹

Merck & Co, Inc (Kenilworth, NJ) is investing in approaches to enrich clinical trial data and augment decision making through use of digital health technologies, outpatient sampling, and real-time data access. As part of this strategy, a phase I study was conducted to explore a few technologies of interest. In this fixed-sequence two-period trial, 16 healthy subjects were administered 50-mg once-daily sitagliptin packaged in a bottle that electronically captured the date and time study medication was dispensed (period 1) and in a traditional pharmacy bottle (period 2). Dried blood spot samples were collected for sitagliptin concentration analysis on select study days, both in clinic and at home, with collection time recorded using an electronic diary in period 1 and by clinic staff in period 2. Study results demonstrated the feasibility and subject acceptance of collecting digital adherence data and outpatient dried blood spot samples in clinical trials and highlighted areas for future improvements.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ Digital health and outpatient sampling have the potential to enable enriched clinical trial data sets and transformation of the clinical trial paradigm towards a more patient-centric approach; however, more experience with such technologies in a clinical trial setting is needed before widespread adoption in clinical trials.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ Smart packaging and outpatient sampling technologies were tested in a phase I study for feasibility of implementation in clinical trials.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✔ The results highlight opportunities for leveraging digital health technologies and outpatient sampling in clinical trials and challenges that will need to be overcome to fully realize the vision of patient-centric clinical trials.

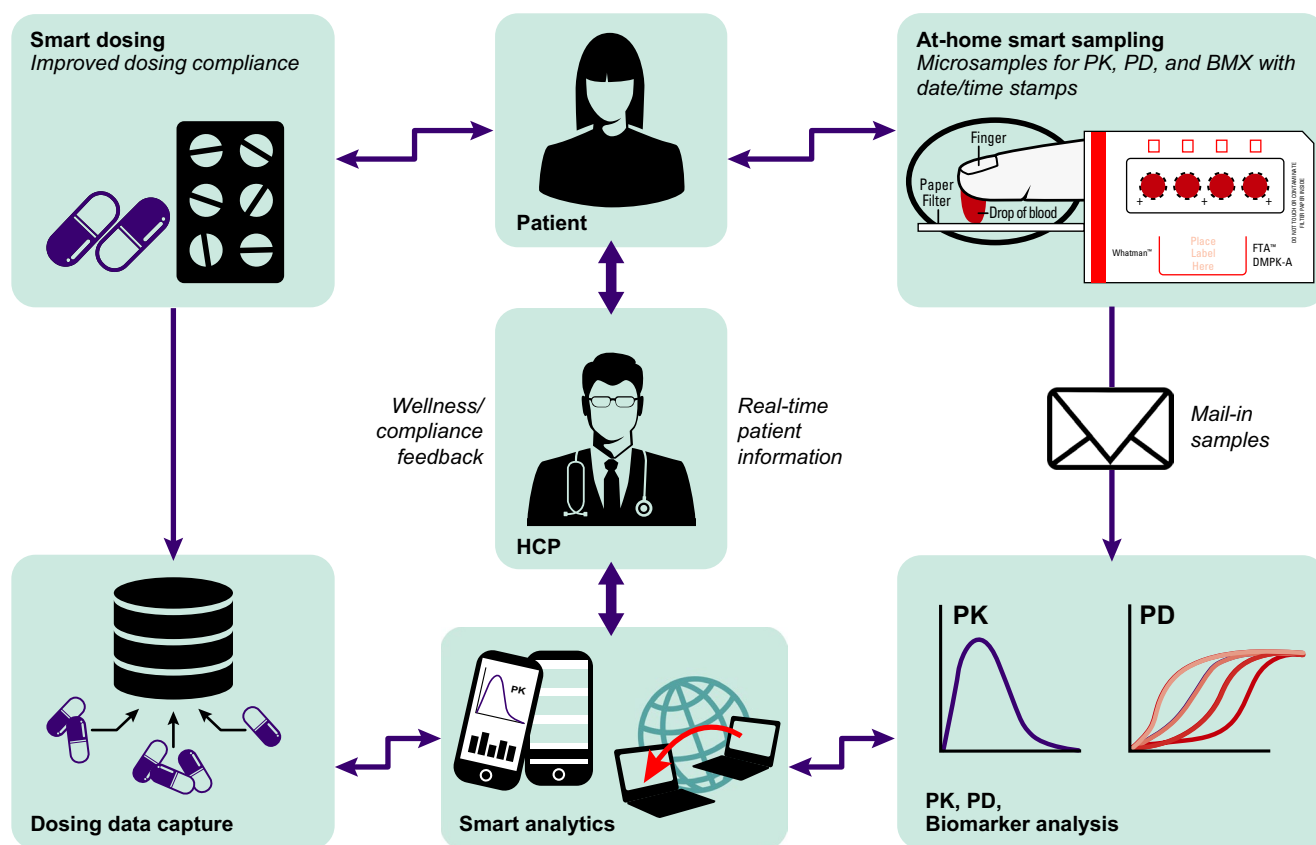
HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✔ Studies such as this one, which assess feasibility and subject acceptance of digital health and outpatient technologies in the phase I clinical trial setting, are important building blocks to understand the advantages and disadvantages of various digital health technologies and outpatient sampling approaches and ultimately drive toward more patient-centric late-stage clinical trials.

Advancements in digital health technologies have the potential to radically change the clinical trial paradigm from a site-centric to a patient-centric approach. The current site-centric model can be burdensome for the patient, provides only static snapshots of data (corresponding to the time of the clinical visit), and may limit patient enrollment to those who live near clinical sites. It

also results in lost opportunities to monitor disease progression, pharmacokinetics (PK), pharmacodynamics (PD), and safety and tolerability end points in between clinical visits. Furthermore, pill counts and subject-reported paper diaries are often relied on for dosing and adherence information in the current clinical paradigm, and inaccuracies in this information remain a significant source of

¹Pharmacokinetics, Pharmacodynamics, and Drug Metabolism, Merck & Co, Inc, Kenilworth, New Jersey, USA; ²Translational Medicine, Merck & Co, Inc, Kenilworth, New Jersey, USA; ³Preclinical Development, Formulation Sciences, Merck & Co, Inc, Kenilworth, New Jersey, USA; ⁴Global Clinical Supply, Merck & Co, Inc, Kenilworth, New Jersey, USA; ⁵Scientific Information Management, Merck & Co, Inc, Kenilworth, New Jersey, USA; ⁶Preclinical Development, Project Management, Merck & Co, Inc, Kenilworth, New Jersey, USA. Correspondence: Marissa F. Dockendorf (marissa.dockendorf@merck.com)



Disclaimer: These are just a few of the technologies/examples and not an endorsement of any product

Figure 1 Illustration of a trial leveraging Smart Trials components of smart dosing, smart sampling, and smart analytics. BMX, biomarker; HCP, healthcare practitioner; PD, pharmacodynamic; PK, pharmacokinetic.

variability in interpretation of PK/PD and dose–response information.^{1–5} Finally, the typical lack of real-time feedback and data access during clinical trials can delay clinical decision making because of protracted steps for data aggregation, source verification, database lock, and biostatistical/pharmacometric analyses. This limits the ability to make trials truly adaptive, to make real-time “right dose, right patient” decisions, or to intervene in situations of noncompliance efficiently during clinical studies.

Merck & Co., Inc. (Kenilworth, NJ) has launched a cross-functional multiyear “Smart Trials” initiative, aimed at leveraging digital health and other new technologies in clinical trials to make them more patient centric. For context in this article, the authors define digital health as the convergence of digital technologies with various elements of drug development to reduce operational inefficiencies, improve access to higher-quality data, reduce costs, and enable precision medicine. Components of Smart Trials include the following: (i) Smart Dosing: digital technologies to accurately monitor dosing information; (ii) Smart Sampling: technologies for use in the outpatient/home settings for collection of PK, safety, and/or biomarker data; and (iii) Smart Analytics: informatics platforms and tools for real-time data access, integration, and visualization (Figure 1). Application of these components in clinical trials is likely to lead to higher-quality information for clinical decisions,

access to data in an outpatient setting that were previously unattainable in the site-centric paradigm, and more rapid, timely clinical decision making through faster turn-around of integrated data during trials. A key part of the Smart Trials strategy is to conduct a series of phase I trials aimed at evaluating technologies and new methods that would potentially add value to clinical development programs. These trials provide a platform for rapid “learn and confirm” cycles to enable emerging technologies to become clinical trial ready.

The first of these phase I studies was a two-period fixed-sequence trial that included both “smart” and “traditional” periods in which 50-mg once-daily sitagliptin was administered to 16 healthy volunteers. The “smart” portion of the trial (period 1) included use of smart dosing technology (CleverCap PRO), at-home dried blood spot (DBS) PK sampling, and capture of self-reported event times (i.e., dosing and sampling) with an eDiary (writeresult). The “traditional” portion of the trial (period 2) used traditional dispensing bottles and included in-clinic dosing and PK sampling, with event times reported by clinic staff. Sitagliptin was selected as a probe drug because of its safety and tolerability profile and its amenability to DBS analysis.^{6,7} Selection criteria for a smart dosing device included study drug formulation, the type of technology (i.e., packaging devices vs. ingestion tracking), device capabilities, data

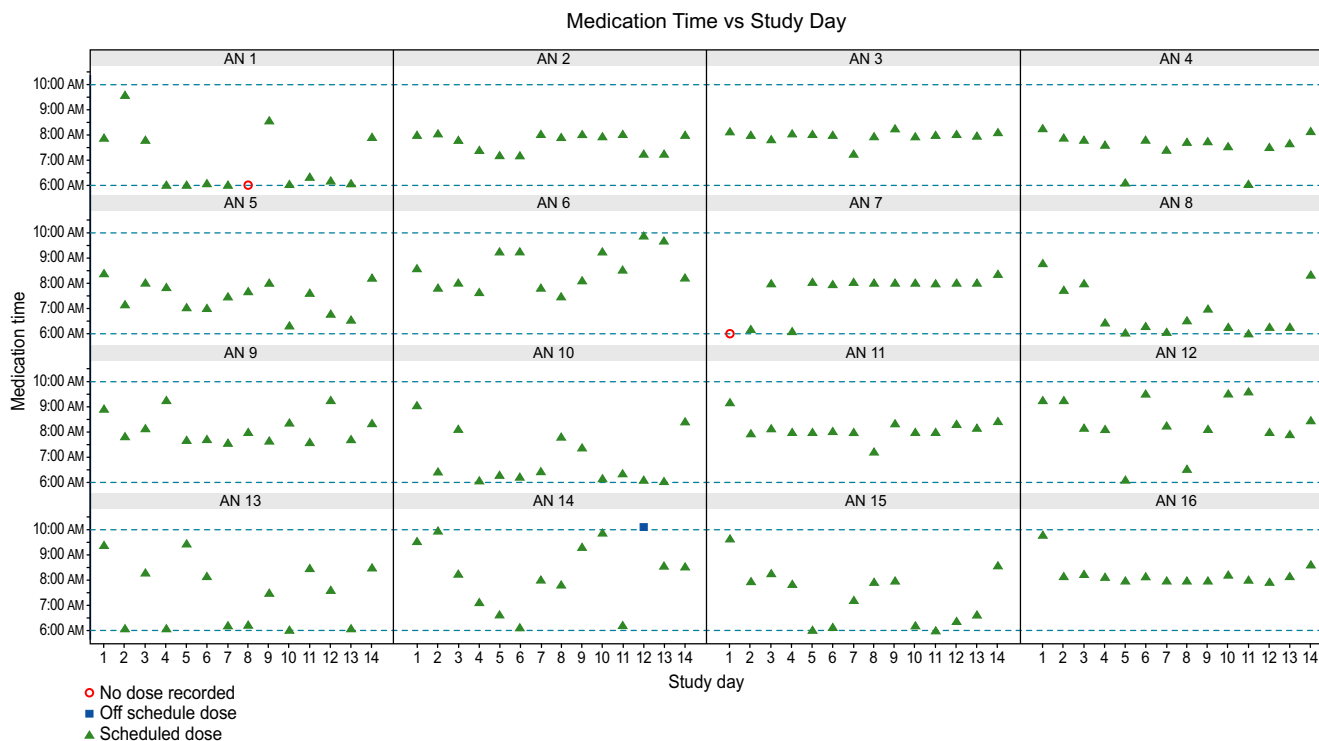


Figure 2 Time the dose was dispensed from CleverCap PRO vs. study day in period 1 for each subject in the trial. In cases in which no dose time was recorded from CleverCap PRO, the time was set to 6 AM for the purposes of plotting in this figure. Dashed lines indicate the minimum and maximum instructed dosing times of 6 and 10 AM. Off-schedule doses represent those that were recorded outside of the instructed 6–10 AM dosing window, whereas scheduled doses represent those that were recorded inside the instructed 6–10 AM window. AN, allocation number.

capture, and vendor maturity. CleverCap PRO[®], a smart packaging device, allowed the study drug to be dispensed by the pharmacy in its commercial formulation, provided subject dosing reminders, and enabled real-time monitoring of subject adherence (via a Web-based portal). A smart telephone electronic diary (writeresult eDiary[®]) was provided to study trial participants to record PK sampling and dosing times on PK sampling days and also provided reminders to subjects to collect their samples. Data from the eDiary were made available in real time via a Web-based portal. The results of this trial are presented in this article.

RESULTS

Sixteen healthy male and female subjects were enrolled into the study, and 14 subjects completed the trial. Subjects ranged from 20 to 55 years of age, with a mean age of ≈ 39 years. One subject was discontinued from the study on day 17 (day 3 of period 2), and one subject withdrew from the study on day 17; neither subject was replaced.

Smart dosing

Figure 2 shows the dosing pattern for 16 subjects during period 1 (days 1–14). At the end of period 1, 222 of 224 expected doses (99%) were recorded as dispensed by the CleverCap PRO. All but one of the 222 recorded dispensing events were in accordance with the protocol-specified dosing instructions of one dose per day between 6:00 and 10:00 AM, and the other fell just outside

the protocol-specified range (10:09 AM). Pill counts of the returned medication bottles at the end of period 1 indicated that all 14 doses were taken by each of the 16 subjects, suggesting that the two dosing events reported as missing by CleverCap PRO (subject 7, day 1; and subject 1, day 8) were not correctly recorded by the device, potentially as a result of sensor malfunction or an irregularity in tablet shape. In one of these cases, clinic staff confirmed the dose was administered in clinic. In the other case, the subject reported taking the dose in the eDiary, and this was confirmed by sitagliptin concentrations from PK samples. For the subset of days when self-reported dosing data were collected via eDiary (days 1, 3, 5, 8, 11, and 14), a high correlation ($R^2 = 0.88$) was observed between self-reported dosing time from the eDiaries and electronically captured dosing time from CleverCap PRO.

Data integration

Data integration from the bioanalytical, CleverCap PRO, eDiary, and clinical databases was performed after the study by the clinical research organization, Celerion (Lincoln, NE). Data merge of the eDiary and bioanalytical data identified 19 mismatches between the DBS sample barcodes scanned in the eDiary vs. what was expected on the basis of barcode assignment in the bioanalytical database (specific to subject and nominal day and time of collection). These mismatches were attributable to subjects not scanning the sample barcode or scanning the

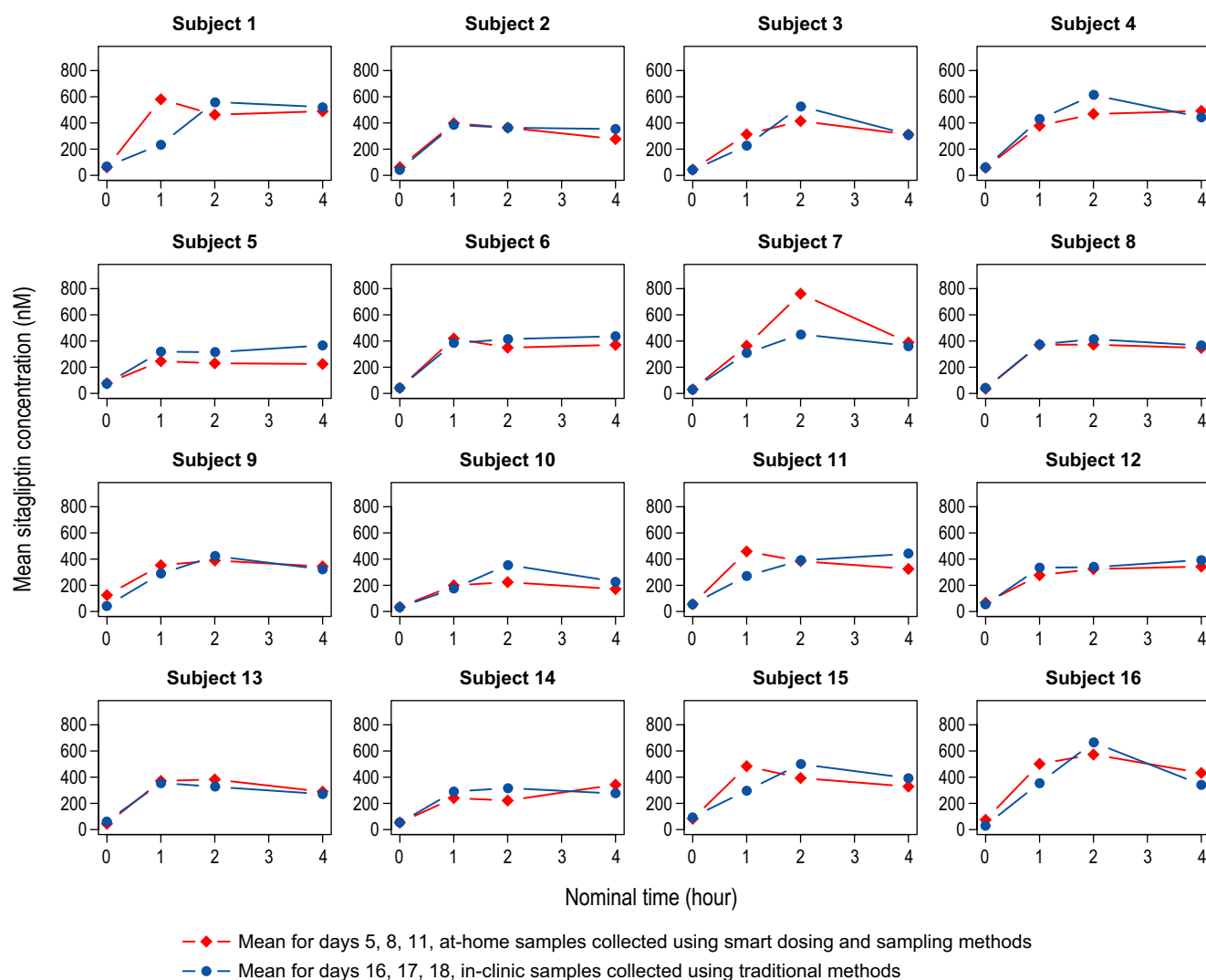


Figure 3 Individual fingerstick dried blood spot arithmetic mean sitagliptin concentration–time profiles (averaged across sampling days) on period 1 at-home sampling days (days 5, 8, and 11) and period 2 in-clinic days (days 16, 17, and 18) for each subject.

incorrect barcode, including cases in which the same barcode was scanned for multiple eDiary entries. These data integration challenges resulted in 11 fingerstick DBS samples being excluded from the PK analysis.

DNA fingerprints were determined for a subset of samples collected at home and compared with those measured from period 1 day 1 predose DBS samples (collected in clinic) to confirm subject identity for the at-home collected samples. In all measured cases, subject identity of the samples was as expected.

PK analysis

The primary PK comparison was considered to be the comparison of sitagliptin concentrations from fingerstick DBS samples collected on the three at-home PK sampling days in period 1 (days 5, 8, and 11, with date and time of dosing captured by CleverCap PRO and sampling captured by the eDiary) to those from fingerstick DBS samples collected on the three in-clinic PK sampling days in period 2 (days 16–18, with date and time of dosing

and sampling recorded by clinic staff). The arithmetic mean sitagliptin fingerstick DBS concentration–time profiles for the at-home PK sample collection days in period 1 were generally similar to the concentration–time profiles for the period 2 in-clinic PK sample collection days for each subject in the study (**Figure 3**). In addition, the period 1 at-home/period 2 in-clinic fingerstick DBS sitagliptin AUC_{0–4hr} GMR (90% confidence interval) was 0.93 (0.85–1.01), suggesting no relevant differences in sitagliptin exposure from at-home vs. in-clinic dosing and sampling.

Subject questionnaire

Of 16 subjects, 14 completed the questionnaire on day 18 of the study. Subject feedback on CleverCap PRO was generally positive (**Figure 4**). The average (SD) Net Promoter Score for CleverCap PRO was a 9 (1.41) of 10, which indicates the subjects were strong supporters of this technology. Questionnaire results for at-home sampling and the eDiary are displayed in **Figure 5**. Subjects indicated that the training video for the DBS sampling procedure was

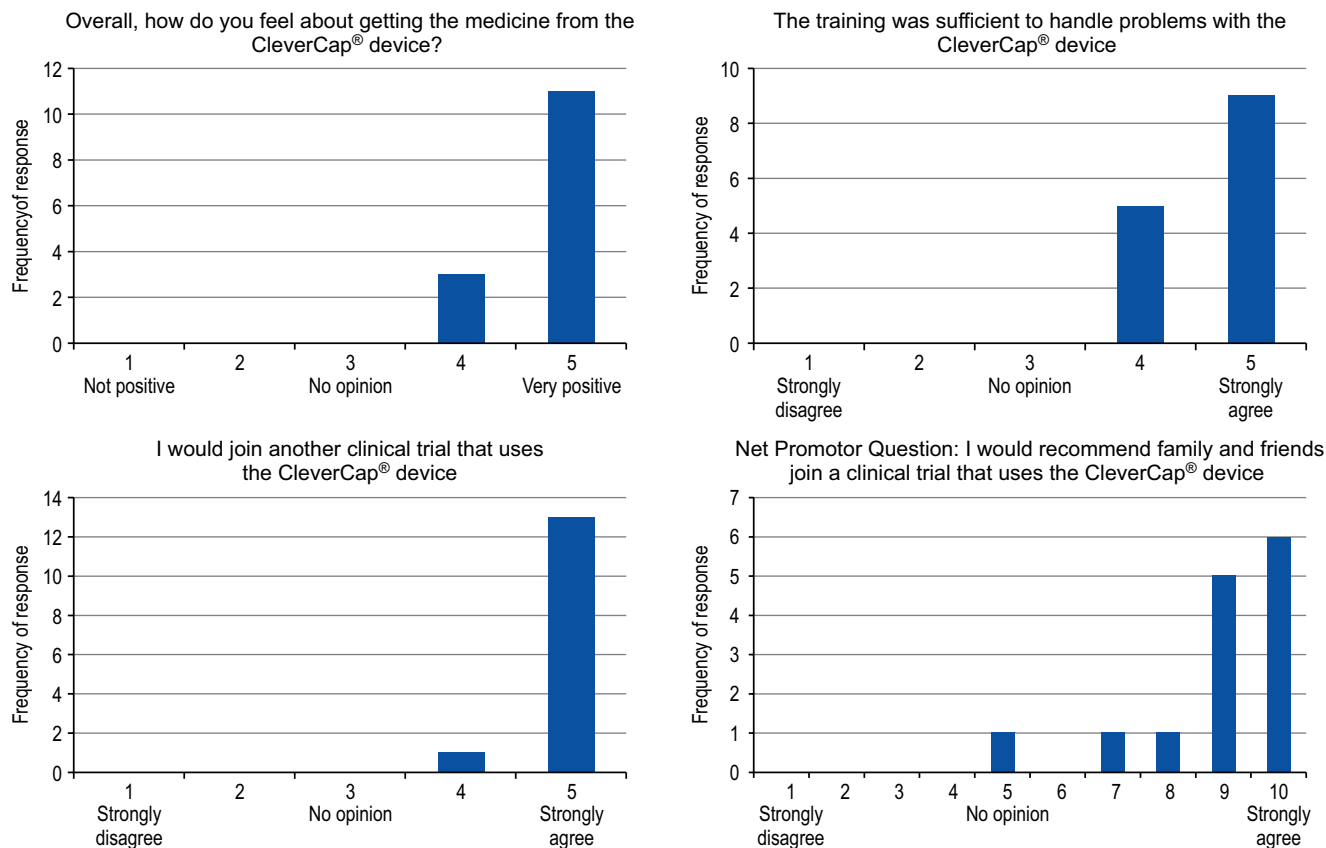


Figure 4 Subject questionnaire results on CleverCap PRO.

useful. In general, the subjects found fingerstick DBS sampling easy to do; although most (10/14) subjects indicated some pain associated with fingerstick sampling, when asked which method of sampling they would prefer for future clinical trials, 7 of 14 subjects indicated a preference for at-home fingerstick DBS sampling over in-clinic venous blood collections. The average (SD) Net Promotor Score for at-home DBS sampling was 8.1 (2.07) of 10, indicating the study participants were passive supporters.

DISCUSSION

In the study presented, the feasibility of at-home DBS PK sampling and commercially available digital health devices (CleverCap PRO and writeresult eDiary) for dosing and event time capture was explored in a phase I setting. Through phase I trials such as this, Merck & Co, Inc aims to build its experience with a broad range of approaches and understand their relative utility for clinical trial research. Adoption of a particular technology/approach is likely to be driven by understanding program needs, gathering more experience, tailoring for clinical research, and cost-benefit.

Electronic adherence solutions, such as CleverCap PRO, represent an opportunity to improve the reliability of dosing data from clinical trials, and the results from this study demonstrate the feasibility of using smart packaging in clinical trials. Although medication dispensing time from a smart package is not an ideal surrogate for time of medication ingestion, it is significantly more accurate than the currently accepted standard of paper diary⁸ and provides

a passive means of data collection that reduces the burden of self-reporting dosing times by the subject. Such technologies provide a means of obtaining richer, more accurate dosing information that can improve the quality of PK and statistical analyses, inform decisions on therapeutic forgiveness and tolerability if doses are missed or not taken as directed, and enable exploration of underlying predictors of poor adherence. Smart packaging also provides the opportunity to proactively remediate noncompliance in studies through the use of active intervention (reminders),⁴ which may ultimately lead to better outcomes for patients. Finally, use of smart packaging benefits study closeout activities by reducing the need for traditional dose reconciliation activities and eliminating transcription of patient dosing information by automating data transfer from package to electronic data capture system. This saves time and resources, eliminates the potential for transcription error in dosing data, and reduces investigations that may otherwise be triggered by discrepancies between patient-reported dosing and pill count by clinical site staff. Alternatives to smart packaging for non-paper-based dosing data capture include ingestible sensor-based formulations (e.g., Proteus), facial recognition technology (e.g., AiCure), and enhanced eDiary-based solutions, each of which has its advantages and disadvantages.

Outpatient PK sampling was another aspect of clinical trial conduct explored in this study. Although this article focused on outpatient sampling for PK analysis, this type of approach could also be used for measurement of PD, safety, or biomarker end points. Although in most cases, outpatient sampling is unlikely to

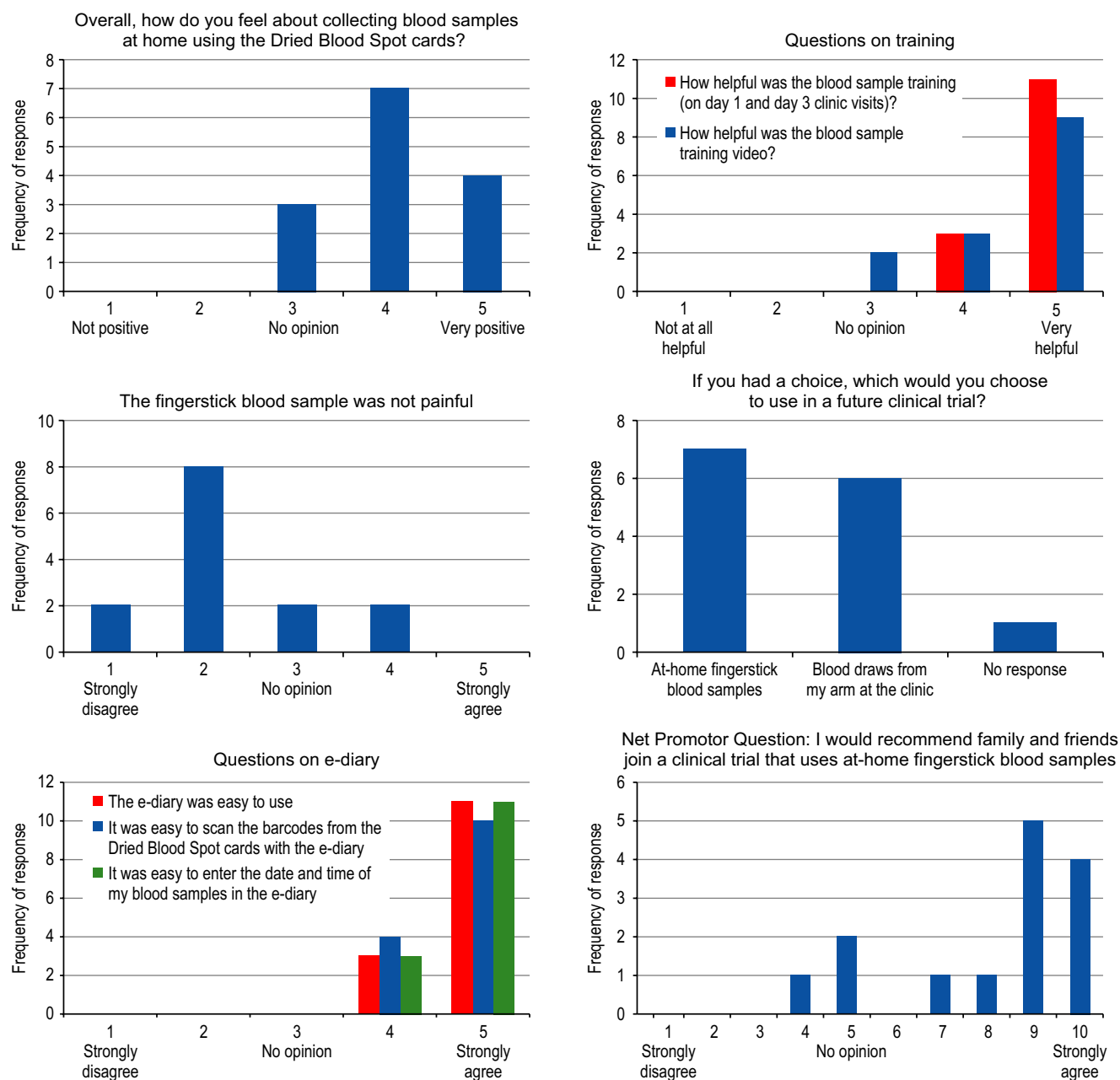


Figure 5 Subject questionnaire results on fingerstick dried blood spot sampling, training, and eDiary.

completely eliminate the need for clinical visits, its adoption can augment the in-clinic collected data, allow better understanding of adherence, and enable a more streamlined approach to clinical visits (potentially reducing the number of visits).

In general, population PK and PK/PD modeling in longer-term studies leverages sparse samples collected during clinic visits. Collection of samples in an outpatient setting provides an opportunity to enrich PK/PD information. A prior effort to access PK data in an outpatient setting through DBS samples showed much greater PK variability from outpatient vs. in-clinic data from the same cohort of patients.⁹ This was hypothesized to be partially attributable to inaccurate recording of dosing and sampling times by

patients via paper diaries. In this study, subjects were instructed to collect DBS samples at home and were provided with an eDiary to record dosing and sampling times. PK profiles from samples collected in an at-home setting were similar to those from samples collected in clinic, demonstrating feasibility of obtaining reliable PK information from such samples. However, several challenges were also revealed, including data reconciliation challenges because of subjects not scanning or incorrectly scanning sample barcodes with the eDiary. In future trials, Merck & Co, Inc plans to evaluate alternative approaches that would eliminate dependency on subject-reported sampling date/time data and the need for barcode scanning, such as sampling devices that include automated date

and time stamps, and is actively working with several technology companies to enable such an approach; no commercial devices exist, to our knowledge, that automatically collect date/time of sampling. In addition, DNA profiling was used in an exploratory manner in this trial as a means to confirm subject identity for a subset of samples collected at home and could serve as a useful tool to help reconcile sample discrepancies in future trials.

The feedback from subjects' questionnaire responses demonstrated a willingness to use smart packaging and the eDiary and to collect at-home DBS samples. Most subjects indicated some level of pain associated with fingerstick DBS sampling, with 7 of 14 subjects indicating a preference for at-home fingerstick DBS sampling compared with in-clinic venous blood collections in this trial (four samples per at-home PK sampling day). In contrast, unpublished data from another Merck & Co, Inc trial in which fewer at-home DBS samples were requested (one sample per at-home sampling day) indicated that subjects did not generally find fingerstick sampling painful, and 33 of 36 subjects in the trial preferred at-home fingerstick DBS sampling to in-clinic venous blood draws in that trial. Thus, reducing the number of samples requested and/or using more pain-free methods of sampling may help drive patient preference toward at-home sampling. Overall, the feedback from this small sample cohort of subjects supports moving towards a patient-centric approach in late-stage research that can minimize the burden on patients while still allowing collection of the robust clinical data sets required for informed drug development.

The broader vision for the Smart Trials initiative is to enable real-time integration and feedback of study information (smart analytics), so that clinical decisions can be made more rapidly. Although real-time analyses during study conduct may not be feasible in late-stage trials because of blinding, the implementation of advanced technologies is anticipated to reduce operational overhead for transcription of data records, data integration, and data reconciliation before database lock in the current paradigm. Coupled with smart dosing and smart sampling, smart analytics can offer transformative value to the conduct and decision making from trials. This exploratory trial offered insights into what will be necessary to realize this vision, including needed improvements in the process of integrating data sets across data sources. Furthermore, enabling real-time viewing of integrated device data will enable real-time data query generation, which may help minimize discrepancies between interdependent data collected.

The Smart Trials initiative is aimed at leveraging digital health technologies and outpatient sampling approaches in clinical trials to make them more patient centric. The initial focus of the initiative is on technologies that can provide greater confidence in dosing data, user-friendly methods of outpatient PK or biomarker sampling coupled with automated date/time stamps, and opportunities to evolve to real-time access to clinical trial data. The ability to rapidly sift through emerging technologies to identify which are useful for clinical research and to partner with developers to enable clinical trial-ready technologies is a critical component to realizing the vision of patient-centric trials. The study described in this article highlights the types of data and experiences that will be necessary building blocks to enable the transition to patient centricity.

METHODS

This phase I study (Study MK-0431-841) explored the use of dosing and sampling technologies that could enable at-home clinical evaluations. The study was fully outsourced to a clinical research organization, Celerion. The study protocol, informed consent, trial participant training materials, and questionnaire were approved by the Chesapeake Institutional Review Board. The study was conducted in accordance with Good Clinical Practice, and participants provided written informed consent.

Study design

This phase I trial was an open-label, fixed-sequence, two-period study. Sixteen healthy subjects were administered sitagliptin, 50 mg once daily. During period 1 (days 1–14), defined as the smart portion of the trial, subjects were instructed to take the study medication using a smart dispensing device (CleverCap PRO) once daily between 6 and 10 AM for 14 days and to self-collect fingerstick DBS samples on specified days and nominal times in the clinic (predose on days 1 and 3 and 1, 2, and 4 hours postdose on day 14) and at home (predose and 1, 2, and 4 hours postdose on days 5, 8, and 11). During period 2 (days 15–18), defined as the traditional portion of the trial, sitagliptin was packaged in a traditional pharmacy bottle, and dosing and sampling occurred in clinic during outpatient visits, with event times recorded by clinic staff in the electronic case report form of the electronic data capture system. In-clinic fingerstick DBS samples were collected on days 16–18 (predose and 1, 2, and 4 hours postdose). In-clinic venous DBS and plasma samples were also collected at select days and timepoints in both periods.

Study technologies and data integration

Study drug for administration in period 1 was packaged in CleverCap PRO (Compliance Meds Technologies, a.k.a. CMTCare, North Miami Beach, FL) smart packaging. CleverCap PRO is a tamper-resistant medical device combination bottle cap and medication dispenser. The cap is connected to a helix that inserts into the medication bottle and guides the medication out of an aperture in the side of the cap. The aperture is monitored by a sensor, which detects ejection of the medication from the bottle, logs the event within its internal memory, and automatically transmits it via a 2net Hub (cellular) to a server for secure aggregation in real time. Subjects received a 2net Hub and a CleverCap PRO filled with the study drug and were instructed to connect the 2net Hub to any electrical outlet, preferably close to where they kept the CleverCap PRO. The CleverCap PRO alerted subjects to take the study drug through sound reminders in period 1 during the predefined time window (6–10 AM). Reminders started at 8 AM and continued every 15 minutes until the dose was dispensed. If subjects missed taking their dose in the 6–10 AM dosing window, the dose could be dispensed by following additional instructions provided with the training material. Data from CleverCap PRO were viewable in real time via a Web portal.

In period 1, subjects were given all of the DBS cards needed for the period 1 PK samples. These cards were pre-labeled with a barcode, which uniquely corresponded in the bioanalytical database to a given subject and nominal study day and time. Therefore, subjects were asked to collect their DBS samples on a particular card at each study-specified time. Subjects were instructed to return all of their at-home-collected DBS samples to the clinic on their day 14 visit.

Subjects were provided with a smart phone preloaded with an eDiary app (writeresult) to record date and time of dosing and sampling on period 1 PK sampling days. The eDiary provided reminders via an alarm when it was time to complete activities on PK sampling days. Sample-related activities included collecting DBS samples at protocol-specified times, scanning the sample barcode, and entering and submitting the date/time of sample collection in the eDiary. Subjects were also asked to enter the date/time of dosing after the predose sample collection on PK sampling days (from which reminder times for subsequent 1-, 2-, and 4-hour samples were calculated). The eDiary allowed subjects to bypass barcode scanning to enter data if needed (e.g., in the event of barcode scanning issues) and also allowed subjects to enter their data at any point

in period 1 (i.e., data entry was not restricted to the expected date). Both the date and time of eDiary entry and the subject-reported date/time of dosing and sampling were captured in the data set. The data from the eDiary were viewable in real time through the vendor's Web-based dashboard, with access provided to the clinical site staff and Merck & Co, Inc. In period 1, collection of in-clinic dose and PK sampling date/time data was recorded by clinical staff at the site and entered into the clinical database.

Fingerstick DBS PK samples were assayed at Merck & Co, Inc. The sitagliptin concentrations from the bioanalytical database, dosing times from the CleverCap PRO Web portal, dosing and sampling times from the writeresult Web portal, and site-recorded data were integrated after the study by the clinical research organization.

Site and participant training

Clinical site staff were trained on the smart dosing and smart sampling devices selected for the trial, including an overview of the functionality and the clinician-required handling vs. subject-required handling. Staff training for CleverCap PRO included direct demonstrations with the pharmacy staff on how to close a standard pharmacy bottle with the CleverCap PRO closure, place the desiccant, and dispense study drug. Before study start, each subject was provided a demonstration of CleverCap PRO to understand the mechanism of dispensing a tablet from the bottle. The study coordinator observed each subject and addressed any questions or issues before dispensing from the assigned CleverCap PRO on day 1. The site staff were guided through a step-wise collection guide for fingerstick DBS sampling that was also provided to the subjects. A video was provided to both site staff and trial participants, with step-wise demonstration of blood collection on the DBS cards. The subjects (and staff) were also provided with a participant manual with day-by-day instructions outlining each activity to be conducted on days 1 through 14, the duration of the smart dosing and sampling period. Guides were also included in the manual on sample collection procedures, how to enter the collection data into the electronic diary, and the instructions for the CleverCap PRO bottle. The electronic diary included training modules that were accessible to subjects throughout the study.

Day 1 of period 1 was used as a training day for dosing and sampling, with the site staff observing each subject's dispensing of the study drug, collection of blood on the DBS card, and data entry in the electronic diary. The subjects returned to the clinic on day 3 for a repeated observation of collections and were provided additional training as required. The clinical site staff were available by telephone for the duration of period 1 to address subject questions, if any, on period 1 at-home activities.

DNA profiling

DNA profiling involved extracting DNA from the DBS samples and looking at small sections of DNA that vary between unrelated individuals, thus creating a "DNA fingerprint" for each individual, without generating individual genetic sequence data. DNA profiling was performed at Genetica DNA Laboratories (Burlington, NC). Punches (1.2 mm) from DBS cards were analyzed using Promega PowerPlex18D amplification kits without a DNA extraction step. A DNA fingerprint was generated for each subject in the study using the day 1 DBS sample collected in clinic. DNA fingerprints from a subset of subsequent DBS samples were generated to confirm subject identity by comparison with day 1 DNA profiles.

Participant questionnaire

A questionnaire was administered at the end of the trial to obtain subject feedback on the digital health devices and sampling methods used in this trial, the quality of the training provided, and participating in a clinical trial with at-home activities. The questions were grouped by smart dosing and smart sampling, using a five-point Likert scale. An assessment to capture the Net Promoter Score was also included

as a tool to assess participants' overall opinion of CleverCap PRO and fingerstick sampling with the eDiary, through their willingness to recommend the devices and sampling methods in a future clinical trial to family and friends using a 10-point scoring system (1 indicates strongly disagree; 5, no opinion; and 10, strongly agree). A score of 9–10 would indicate strong supporters or promoters, a score of 7–8 would indicate passive supporters (a willingness to participate themselves but not recommend), and a score of ≤ 6 would represent detractors (not willing to recommend or participate again). In addition, the questionnaire asked subjects for their preference between fingerstick and venous blood collections. Additional comments on the trial and devices were also captured.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (<http://www.cpt-journal.com>).

Appendix S1. Bioanalytical and Pharmacokinetic Methods.

Appendix S2. MK-0431-841-00 Protocol.pdf.

ACKNOWLEDGMENTS

The authors would like to acknowledge Tian Zhao and Yang Liu for statistical support; and Monali Sura for assistance with protocol authoring and study conduct. The authors would also like to thank Dana Gill, John Brejda, Natacha Benrimoh, and Ted Marengo (Celerion) for assistance with this study. Editorial assistance was provided by Michele McColgan (Merck & Co, Inc).

FUNDING

Merck & Co., Inc. (Kenilworth, NJ) provided financial support for the conduct of the study.

CONFLICT OF INTEREST

All authors are employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc (Kenilworth, NJ), who may own stock and/or hold stock options in the company.

AUTHOR CONTRIBUTIONS

M.F.D., G.M., K.P.B., P.A.K., M.A., I.X., J.S., R.B., A.G., M.M., J.S., R.R., L.S., and J.H. wrote the manuscript; M.F.D., G.M., K.P.B., P.A.K., J.R.S., R.B., A.G., M.M., R.R., L.S., and J.H. designed the research; M.A., I.X., and J.S. performed the research; M.F.D., G.M., K.P.B., P.A.K., J.R.S., R.B., A.G., M.M., J.S., and R.R. analyzed the data.

© 2018 Merck Sharp & Dohme Corp. *Clinical Pharmacology & Therapeutics* published by Wiley Periodicals, Inc. on behalf of American Society for Clinical Pharmacology and Therapeutics.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

[The copyright line for this article was changed on 04 July 2019 after original online publication].

1. Fossler, M.J. Patient adherence: clinical pharmacology's embarrassing relative. *J. Clin. Pharmacol.* **55**, 365–367 (2015).
2. Marrazzo, J.M. et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N. Engl. J. Med.* **372**, 509–518 (2015).
3. Shiovitz, T.M. et al. Mitigating the effects of nonadherence in clinical trials. *J. Clin. Pharmacol.* **56**, 1151–1164 (2016).

4. Vrijens, B. & Urquhart, J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. *Clin. Pharmacol. Ther.* **95**, 617–626 (2014).
5. Vrijens, B., Vincze, G., Kristanto, P., Urquhart, J. & Burnier, M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ* **336**, 1114–1117 (2008).
6. Kothare, P.A. *et al.* An integrated strategy for implementation of dried blood spots in clinical development programs. *AAPS J* **18**, 519–527 (2016).
7. Xu, Y., Woolf, E.J., Agrawal, N.G., Kothare, P., Pucci, V. & Bateman, K.P. Merck's perspective on the implementation of dried blood spot technology in clinical drug development: why, when and how. *Bioanalysis* **5**, 341–350 (2013).
8. El Alili, M., Vrijens, B., Demonceau, J., Evers, S.M. & Hilgsmann, M. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. *Br. J. Clin. Pharmacol.* **82**, 268–279 (2016).
9. Li, C.C. *et al.* Population PK analyses of ubrogepant (MK-1602), a CGRP receptor antagonist: enriching in-clinic plasma PK sampling with outpatient dried blood spot sampling. *J. Clin. Pharmacol.* **58**, 294–303 (2018).