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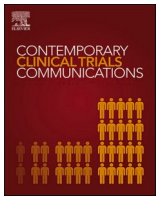

Conducting clinical trials with self-collection of pharmacokinetic samples: Experience from an exploratory, phase 1, open-label trial of centanafadine SR in healthy individuals

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ABSTRACT

Background: The COVID-19 pandemic accelerated a shift to decentralized clinical trials. We present the potential feasibility of this approach from a phase 1 pharmacokinetic (PK) trial.
Methods: Healthy adults (18–55 years) with a body mass index of 19.0–32.0 kg/m^2 were enrolled. The trial comprised a screening period, 2 clinic visits (visits 1, 2), 2 at-home visits (visits 3 and 4), and follow-up clinic visit (visit 5). Participants received a single 100-mg oral dose of centanafadine sustained release at visits 1, 2, and 4. Pharmacokinetic samples, electrocardiograms (ECGs; 6-lead [participant] and 12-lead [staff]), and vital signs were collected by clinical personnel (visit 1), under staff supervision (visit 2), and remotely (visit 4), facilitated by the Verily clinical trial application. Successful sample collection at visit 4 was reported descriptively. A survey assessed the utility of training, devices, and the Verily app, and ability to complete trial procedures.
Results: Among 20 participants enrolled, 90 % were female, mean (SD) age was 35.9 (11.1) years. Verily platform/procedures facilitated successful remote vital sign collection in at least 75 %, ECGs in at least 80 %, and blood microsamples in 65 %–70 % of participants at visit 4. Most agreed that training was adequate, and they were able to complete trial procedures on their own. Participants favored self-collection over staff collection, having visits in their own location, and would consider participation in similar future research.
Conclusions: Results from this decentralized PK trial, with remote, in-home sample collection and monitoring, demonstrated the potential feasibility of this study design.

1. Background

Accelerating and gaining efficiency in clinical development programs and clinical research in general could benefit patients in medical need as well as benefit society as a whole. Improving access to effective treatments and lowering the barriers to participation in clinical investigations will broaden the research landscape, ultimately improving treatments and patient outcomes. Traditional clinical trials represent a gold standard to ensure the development of safe and effective treatments, but they are costly and protracted, with high failure rates often due to failure in recruitment efforts (ie, operational reasons beyond "interventional failure") [1–4].

There is growing interest, therefore, in diversifying the avenues to generate clinical evidence. Available technologies provide all-encompassing arrays of tools and/or platforms for collection of data that can be leveraged to expand the scope of clinical research. This has unlocked study modalities complementary to traditional clinical trials [5,6]. One of these avenues is modernizing and boosting the agility of clinical studies, specifically by enabling the shift of trial operations to decentralized settings [7,8]. This diversification became even more relevant as the COVID-19 pandemic began [9,10], and its protracted course has further galvanized efforts supporting decentralized, patient-centric research, as many ongoing clinical trials struggled with site-based approaches during general quarantines and lockdowns [11–15]. As such, the remote, in-home collection of clinical trial data, in lieu of traditional site-based assessments, is gaining widespread

Abbreviations: ECG, electrocardiogram; HPLC-MS/MS, high-performance liquid chromatography with tandem mass spectrometry; PK, pharmacokinetic.

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acceptance, as evidenced by recent publications describing the incorporation of remote data collection into trial designs [16–18].

Decentralized, patient-centric trials have processes or procedures that take place based on the location and day-to-day living schedules of individuals participating. There are also other forms of patient-centricity, such as incorporating patients in the study design team [6]. Lowering participation burden can accelerate accrual timelines, and the immediacy of collection procedures can facilitate the capture of more comprehensive data [19]. In combination, these advantages have the potential to significantly improve efficiencies and representativeness in clinical development programs. Yet, there may be reservations about decentralizing certain types of studies. For instance, in phase 1 pharmacokinetic (PK) trials, reproducibility and methodologic compliance with blood sampling procedures are critical aspects that could be jeopardized if conducted outside clinical settings [11]. With the availability of volumetric, absorptive microsampling devices and the accompanying technology for training an individual for data capture, however, those challenges may now be addressed [20].

In this manuscript, we describe how decentralized sample collection was operationalized in the context of a phase 1 PK trial. The primary objective for this work was to assess the potential feasibility of conducting remote clinical trials utilizing at-home self-collection of PK samples and safety assessments consistent with procedures used in a traditional clinical trial setting.

2. Materials and methods

This trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, the Council for International Organization of Medical Science recommendations, and US Food and Drug Administration regulations. The informed consent form, protocol, and amendments for the trial were approved by an institutional review board (WCG IRB; IRB00000533) at the trial site, and all participants provided informed consent electronically before trial participation.

2.1. Trial design and training approaches

2.1.1. Participants

This exploratory phase 1, open-label, fixed-sequence trial was conducted at a single trial site in the United States (Diablo Clinical Research, Walnut Creek, CA, USA). The trial had a screening period, 2 clinic visits (visit 1 and visit 2), 2 at-home visits (visits 3 and 4), and a follow-up clinic visit (visit 5) (Fig. 1). The trial was designed to enroll healthy adults aged 18–55 years, with a body mass index from 19.0 to 32.0 kg/m^2. Detailed inclusion and exclusion criteria for the trial are provided in Table A1 (see Appendix).

2.1.2. Procedures

The trial had a screening period, 2 clinic visits (visit 1 and visit 2), 2 at-home visits (visits 3 and 4), and a follow-up clinic visit (visit 5) (Fig. 1). Participants received a single oral dose of centanafadine sustained release (SR) 100 mg at visits 1, 2, and 4. General health status was determined for each participant by medical history, physical examination, 12-lead electrocardiogram (ECG), and laboratory assessments (serum/urine chemistry, hematology, and serology). The specific procedures for each visit and evaluation were managed overall via a proprietary platform (Verily clinical research suite; Verily Life Sciences, South San Francisco, CA, USA).

Upon arrival for the screening visit, trial candidates registered online using the clinical research suite, and informed consent was provided electronically. After confirming participants' eligibility for enrollment, baseline demographics and health status assessments were obtained by site personnel.

At visit 1 and prior to any procedure, enrolled participants were provided with a set of mobile medical devices: a Model IR20b ear thermometer (ForaCare, Inc.; Moorpark, CA, USA) and a Model UA-651 upper-arm blood pressure monitor (A&D Medical; Boston, MA, USA) to collect and transmit data to the trial site wirelessly. In addition, participants were given a KardiaMobile 6-lead ECG device (AliveCor; Mountain View, CA, USA) and blood microsample kits (Neoteryx; Torrance, CA, USA), each of which contained a Mitra microsample device with volumetric absorptive microsampling (VAMS) technology, lancet, cotton gauze, bandage, and PK label. Trial personnel were responsible for loading the clinical trial app and the ECG device app (along with the associated registration for the ECG data-analyzing portal) on each participant's mobile phone. Trial personnel conducted test video visits and trained participants on remote trial procedures, including supervising participants while obtaining their own ECG recording. The clinical trial app was programmed to provide notifications to participants about

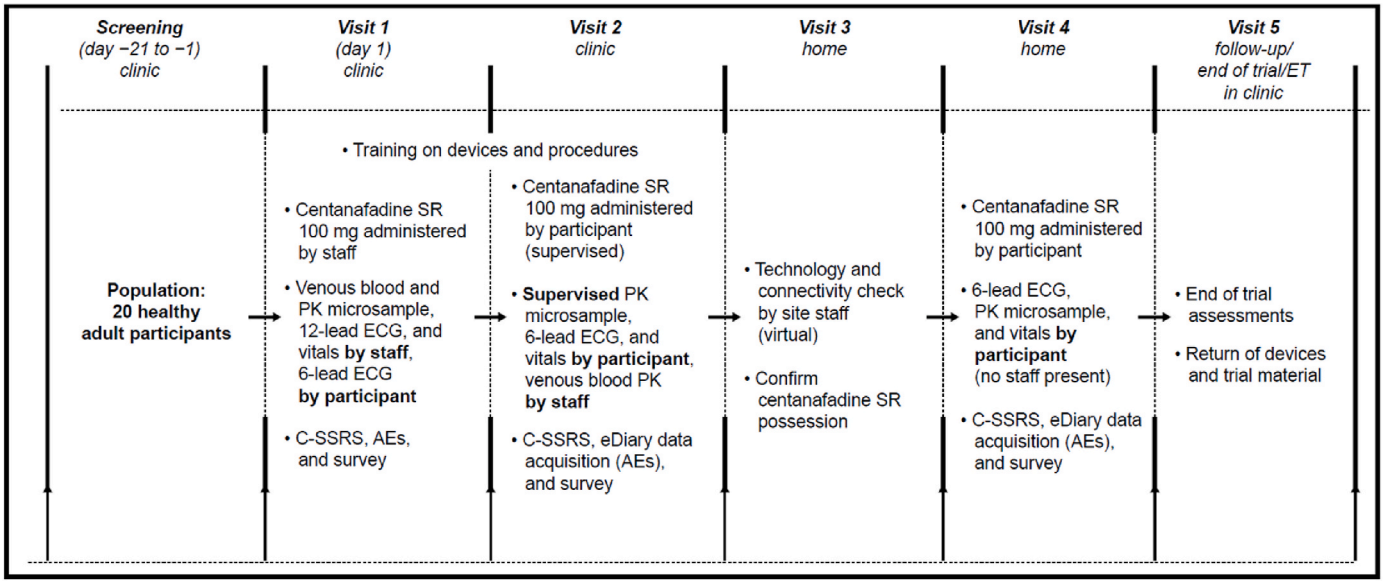

Fig. 1. Schematic of Trial Design.
AE, adverse event; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiograph; eDiary, electronic diary; ET, early termination; PK, pharmacokinetic; SR, sustained release.

upcoming procedures they were required to complete and provided acknowledgments as the procedures were completed.

At visits 1 and 2, trial staff provided direct participant training on trial procedures and devices (features and use for trial procedures) and recorded participants' ability to complete each trial procedure (supervised collection of the 6-lead ECG only at visit 1 and supervised collection of vital signs, 6-lead ECG, and microsample collection at visit 2). This direct training was supplemented by additional didactic material on the trial's app, available at any time throughout the trial. For those unable to complete any trial procedures, participants could be retrained up to 3 times per assessment, after which, if still unable to self-collect any remaining vital signs, ECGs, or PK microsamples successfully, they were discontinued from the trial. Site staff obtained vital signs, PK sampling (venous blood and microsampling), and a 12-lead ECG at visit 1 but collected venous blood only for PK analysis at visit 2.

At visit 3, participants and investigational site personnel conducted a video visit via the trial app to ensure that the mobile medical devices were properly connected, that participants received the appropriate supplies and trial drugs and had access to instructional materials. During this video visit, the trial site staff answered any questions that participants might have and collected other information as detailed in the protocol.

Visit 4 assessed the potential feasibility of performing remote procedures. During a video chat with investigational site staff, participants were asked to self-administer the investigational drug product at home and collect vital signs, 6-lead ECGs, and PK microsamples. Participants were allowed to contact site personnel via telephone or video chat at any time during the trial for extra guidance, if needed. Following all sample collections, site staff completed a follow-up telephone call to collect additional information per the protocol. Pharmacokinetic samples were returned to the clinic by the participants at visit 5. Direct shipment by the participant to the bioanalytical lab was originally intended; however, because of the logistical complications related to international shipments from the United States to Canada (where the bioanalytical lab is located) and the difficulty in having participants prepare the required international shipping documentation, this step was not successfully implemented.

Visit 5 was the final visit at the clinic. No procedures were performed by any of the trial participants; all protocol-required information was obtained by trial site staff. Participants who withdrew early or who were discontinued from the trial completed an early termination clinic visit identical to visit 5.

At the completion of visits 1, 2, and 4, participants completed a subject satisfaction survey to assess the training received by the site staff for self-collection of samples required of the trial procedures, the use of mobile medical devices and trial app that was provided, and the ability of participants to complete trial procedures according to the trial protocol requirements.

2.1.3. Training

Trial sponsor representatives provided training to site personnel before the start of the trial. This training included instructions on how to use each device during the trial, how to conduct technical troubleshooting should connectivity issues, battery failure, or device error codes occur, and how to remedy these situations.

2.1.4. Trial outcomes

The primary objective for this exploratory trial, ie, the potential feasibility of conducting remote clinical trials utilizing at-home self-collection of safety assessments and PK samples, was analyzed based on 3 endpoints assessed at visit 4. These were the percentages of vital signs and of ECGs collected within the ±15-min collection window that were deemed to be physiologically plausible by the investigator, and the percentage of PK microsamples with detectable centanafadine concentrations (except for predose samples) that were collected within the ± 5-min collection window.

2.2. Statistical analysis

The data in this trial were analyzed descriptively. The study was not powered for statistical comparisons of vital signs, ECG readings, or PK plasma or blood concentrations, and the sample size was chosen based on practical considerations. The target accrual of 20 participants was considered adequate for determining the potential feasibility and accuracy of self-collection of vital sign, ECG, and PK data.

3. Results

3.1. Demographics and baseline characteristics

In total, 23 individuals were screened and 20 were enrolled. Participants had a mean (standard deviation [SD]) age of 35.9 (11.1) years. Most participants were female (90.0 %) and White (60.0 %), and the mean (SD) body mass index was 25.6 (2.9) kg/m^2 (Table 1). All enrolled participants completed the trial.

3.2. Potential feasibility of conducting remote clinical trials utilizing at-home self-collection

The Verily platform and associated procedures facilitated the successful collection of remote data on vital signs in at least 75 % of participants, ECGs in at least 80 %, and blood microsamples in 65 %–70 % of participants at visit 4.

3.3. Participant satisfaction survey

Most participants (95 %–100 %) agreed or strongly agreed that the mobile medical device and trial app training received was adequate. Furthermore, 90 %–100 % of participants agreed or strongly agreed that they were able to use the devices and trial app to complete the trial procedures on their own. Overall, participants favored self-collection over staff collection and having trial visits in their own location and would consider participating in a similar research trial in the future.

4. Discussion

In this trial, we demonstrated that it is potentially feasible to conduct procedures for a phase 1 PK trial using a decentralized approach. Utilization of the proprietary clinical research suite and associated procedures facilitated the collection of remote data on vital signs, ECGs, and blood microsamples in the majority of participants at home at visit 4.

This is one of the first decentralized trials to report results specific to the potential feasibility of this approach. Despite the drive for decentralized trials, phase 1 and PK studies in particular pose a specific challenge owing to the sample collection procedures involved and the

Table 1
Participant demographics and baseline characteristics.

Parameter	Participants (N = 20)
Age, mean (SD), years	35.9 (11.1)
Sex, n (%)	
Male	2 (10.0)
Female	18 (90.0)
Race, n (%)	
White	12 (60.0)
Black	3 (15.0)
American Indian or Native Alaskan	1 (5.0)
Asian	3 (15.0)
Native Hawaiian or other Pacific Islander	0 (0.0)
Other	1 (5.0)
Ethnicity, n (%)	
Hispanic or Latino	7 (35.0)
Not Hispanic or Latino	13 (65.0)
Body mass index (kg/m^2), mean (SD)	25.6 (2.9)

need to yield reproducible and externally valid results for subsequent trials [11]. This imposes an extra layer of considerations in the design of studies such as this trial. In the present trial, we were able to deploy procedures in a unified, seamless fashion, using a single intuitive tool for participants and trial personnel that enabled monitoring and management for activities and data flows. This included onboarding and enrollment features, remote visit and monitoring tools to engage participants at their locations, and seamless data management across sponsor and site. While this trial design included only 2 at-home visits, future studies with extended durations and more at-home assessments could be designed, further reducing the patient burden.

Several features of the trial design optimized the reproducibility of at-home dosing relative to dosing in a clinical setting. At visit 4, participants self-administered a single fixed dose of centanafadine SR, employing the training they received from site staff at 2 earlier supervised clinic visit administrations (visits 1 and 2). Additionally, the administration of trial drug during a video chat allowed the staff to confirm completion of at least an 8-h fast and of all predose procedures. The video chat session with a site staff member along with app notifications received on the provided smartphone reminded participants to avoid drinking water for at least 1 h postdose. By witnessing trial drug administration, site staff could precisely mark the time of the first dose and define subsequent PK collection times.

Other features of the trial ensured that postdose PK samples were temporally accurate by setting a relatively stringent testing window (±5 min) for the participant's PK microsample collection at visit 4, as well as during clinic visits 1 and 2. At visit 4, participants received notifications on their smartphones via the trial app notifying them to prepare for and perform the at-home microsample collection. Prior training at visits 1 and 2 also included notifications on the smartphone, in combination with didactic materials available on the mobile app, enabling participants to perform the blood sampling within the designated time frame. The reliability of remote PK outcomes was analyzed at visits 1 and 2 by comparing plasma concentrations derived from participant samples (microsamples) versus trial site personnel–collected samples (venous blood draws) using a highly sensitive high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) assay method for centanafadine and will be the subject of a future manuscript.

Several limitations are associated with decentralized clinical trials, including the current trial. These include potential constraints for rapid management of treatment-emergent adverse events in participants who may be at distant geographic locations [7]. Several design features that were incorporated in the present trial may reduce the safety risks to acceptable levels, including utilization of a safe class of trial drug in a healthy adult population, 2 initial clinic visits to confirm the participant's tolerance of the trial drug, an at-home video visit during remote trial drug administration, and optional telephone or video visits at any time throughout the trial. However, these elements may not be fully generalizable to all studies conducted under substantially less favorable conditions than the present trial.

Another potential limitation is the reliance on 6-lead ECGs for the at-home cardiac timing assessments. Although sufficient for detecting clinically meaningful timing abnormalities in most cases [21], 6-lead traces may not be appropriate under all circumstances (eg, trials on antiarrhythmics where the 12-lead ECG would be widely used) [22]. It would be useful to develop remote 12-lead ECG approaches for these cases.

Another consideration could be the significant up-front investment of time and resources in participant training, which included 2 on-site visits and 1 at-home technology check visit. Thus, in the context of increasing efficiency through patient-centric approaches, it remains to be determined whether this type of platform may be more cost-effective for longer-term PK studies requiring data collection over longer periods of time. As participants were healthy and were young to middle-aged (range: 19–54 years), it is also unknown if their capacity to navigate the technology and procedures in this trial is generalizable to patients in a sick and/or elderly population; this is a broader issue for patient-centric trials.

Additionally, this trial was not designed to collect data on any reasons for unsuccessful participant collection of remote data within the specified time windows. While the participant satisfaction survey did assess if participants agreed that they were able to complete their assessments without difficulty, the survey did not collect reasons for success or failure. Moreover, the percentages of participants who agreed they could complete the procedures on their own (90 %–100 %) exceeded percentages of participants who collected remote data successfully (as low as 65 %–70 % for collection of blood microsamples), which may point to gaps in training. The results of this exploratory trial and further studies designed to examine reasons for unsuccessful data collection will help us improve procedures and training processes to achieve success rates necessary for submission to health authorities.

Nonetheless, notwithstanding these potential limitations, the results of the current trial should encourage remote PK studies in appropriate experimental settings, which could have benefits on the drug development process. Much of the training provided in the present trial was linked to sample collection for PK analysis; other trial designs may be less demanding on this front. Ideally, decentralized, patient-centric trial designs [7] will allow studies to balance factors, including the type of participants, intensiveness of surveillance, and adequate training, to minimize safety risks for participants. Future remote PK studies will need to incorporate design considerations particular to this approach, such as statistical plans that account for missing data when patients are unable to self-collect data and providing alternatives for participants who are unable to learn or perform complex procedures at home.

5. Conclusion

In summary, this phase 1 PK trial deployed a decentralized platform that enabled remote sample collection and monitoring procedures. While this trial demonstrated the overall potential feasibility of the study approach, the lessons learned will be valuable in designing and conducting future decentralized, patient-centric studies.

CRediT authorship contribution statement

Chelsea Ye: Writing – review & editing, Supervision, Software, Project administration, Methodology. **Tatiana Shablinski:** Software, Project administration, Methodology, Data curation. **Susan E. Shoaf:** Methodology. **Chris Chung:** Project administration, Methodology, Conceptualization. **Michelle Bullock:** Supervision, Software, Resources, Project administration, Methodology, Conceptualization.

Role of funding source

This study and manuscript were funded by Otsuka Pharmaceutical Development & Commercialization, Inc. Otsuka employees were involved in the study design, the collection, analysis, and interpretation of data, the review of the manuscript, and the decision to submit for publication.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Chelsea Ye, Tatiana Shablinski, and Michelle Bullock are employees of Verily Life Sciences, which received funding from Otsuka for the clinical trial management platform used in this trial. Susan E. Shoaf and Chris

Chung are employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101396.

Data availability

To submit inquiries related to Otsuka clinical research, or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit https://clinical-trials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

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