Using Artificial Intelligence Platforms to Monitor and Identify Early Nonadherence Activity Based on Visual Confirmation of Medication Ingestion

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Background

- To date, most clinical trials have relied on scheduled pill counts and self-reported data to monitor drug compliance, even though these data are unreliable and tend to overestimate adherence. Pill counts routinely indicate levels of adherence above 95% across therapeutic areas.[1-3]
- One alternative has been measurement of concentrations of a drug or its metabolite; however, between-person variability in pharmacokinetics (PK) and limits on the frequency of blood sampling prevent this approach from providing accurate day-to-day information on adherence.
- When an investigational drug fails to demonstrate a beneficial effect in a clinical trial, it is difficult to determine whether the drug is truly ineffective or whether the drug worked suboptimally in the trial because subjects in the trial were nonadherent. Nonadherence results in reduced signal level and diminishes the ability to detect an effect.[4]
- The artificial intelligence (AI) platform (AiCure, New York, NY) uses software algorithms on smartphones to visually and automatically confirm participant identity, the medication, and medication ingestion (**Figure 1**). Participants receive automated reminders and precise dosing instructions. Study teams have access to real-time data for review and intervention.
- A recent phase 2 study (ClinicalTrials.gov identifier NCT02477020) was completed in the United States that evaluated the efficacy, safety, and tolerability of treatment for 6 weeks with TAK-063 compared with placebo in subjects with acutely exacerbated schizophrenia. Study subjects were required to remain confined for the first 3 weeks of the study. At any time after the week 3 visit and if deemed to be clinically stable by the investigator, subjects were allowed to complete the study as an outpatient (**Figure 2**). The outpatient segment from this phase 2 clinical trial provided an opportunity to investigate study drug compliance in subjects discharged from the hospital and followed up in the outpatient portion of the study using the AiCure platform.

Substudy Objectives

- The main objective was to evaluate the potential ability of the AI platform to identify suspect behaviors that may be related to lack of adherence to dosing of study medication and to assess the impact of early interventions on dosing behavior.
- A secondary objective was to compare 3 measures of adherence in subjects who were stable and completed the study as outpatients. The primary adherence measure for the study was based on scheduled pill counts (number of pills returned vs. number expected). A secondary measure of adherence was based on PK data collected at week 6 during the outpatient portion of the study. A third measure of adherence was based on adherence data collected by the AI platform.
  - Date and time stamps were collected for each individual pill. Adherence data fell into the following 5 categories: visual confirmation of ingestion using the AI platform application ("app"), self-reported dose via the "self-report" button on the app (no visual confirmation), self-reported dose over the phone to the study coordinator, missed dose, and dose taken in clinic.
  - Dosing data were transmitted to Web-based dashboards in real time. Missed doses or no data transmission triggered alerts to allow for study site interventions, either by SMS text or phone. Adherence data from the AI platform were evaluated for exploratory purposes.

Trial Design

- Clinically stable subjects with schizophrenia were discharged to the outpatient portion of the study and followed up for the remainder of the 6-week treatment period.
- Study subjects discharged to the outpatient portion of the study used the AiCure app to monitor study drug compliance. The smartphone app was installed with Health Insurance Portability and Accountability Act (HIPAA)–compliant AI software (**Figure 1**).
- Subjects used the app for each drug administration during the outpatient portion of the study.
- Adherence data are described for all subjects who were discharged to the outpatient portion of the study (**Figure 3**). The data summarized need to be interpreted descriptively and used to generate future hypotheses.

Figure 1. AI Platform Used in the Study

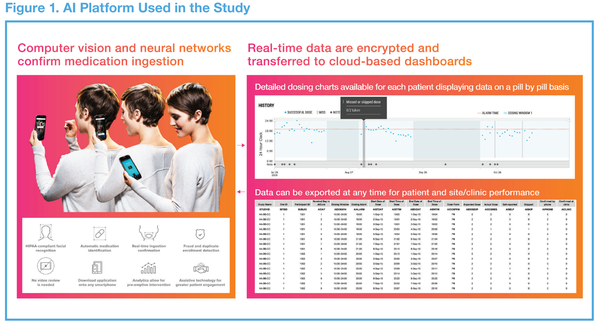
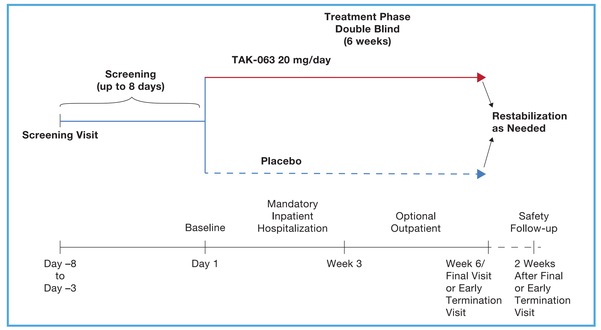


Figure 2. Schematic of Study Design



Results

- A total of 164 subjects were randomized for treatment (**Table 1**):
  - Completed trial: n=106 (64.6%)
    - Subjects discharged from the study site: n=26 (24.5%)
      - Completed trial using AiCure app: n=21 (80.8%)
      - Early termination (ET) during outpatient portion of the study using AiCure app: n=5

Table 1. Baseline Demographic Characteristics: Outpatient Segment and Overall

		TAK-063-2002	
		Overall (N=164)	Outpatient Segment (n=26)
Age, years	Mean (SD)	41.8 (10.38)	41.4 (10.36)
	Median	42	42
	Min, Max	22, 65	22, 61
Sex, n (%)	Female	32 (19.5)	3 (11.5)
	Male	132 (80.5)	23 (88.5)
Race, n (%)	American Indian or Alaska Native	1 (0.6)	0
	Asian	2 (1.2)	0
	Black or African American	108 (65.9)	17 (65.4)
	Native Hawaiian or Other Pacific Islander	2 (1.2)	0
	White	49 (29.9)	9 (34.6)
	Multiracial	2 (1.2)	0

SD, standard deviation; Min, minimum; Max, maximum.

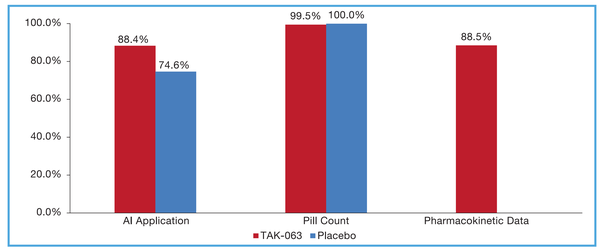
Results for Subjects Who Were Discharged as Outpatients (n=26)

- Baseline demographics were similar between the overall study population and the subjects in the outpatient portion of the study using the AiCure app (**Table 1**).
- 16/26 subjects received TAK-063 during the outpatient period.
- Data on AI platform adherence parameters were collected for 372 subject-days.
- Data on 744 adherence parameters were collected.
- 14.3 = average number of days spent in outpatient segment of the trial.
- 147 alerts were noted on internal databases. Alerts included self-reported doses (as recorded on app or by phone), missed doses, late doses, and no dose taken. A total of 22 interventions were made by study coordinators using the AI dashboard. Interventions were made for 7 subjects by 6 of 10 sites that discharged subjects to the outpatient portion of the trial.

Adherence

- The results are for adherence and data from the AI platform.
- Mean cumulative adherence rate based on visual confirmation of drug ingestion (AI app) was 75.9% from week 4 or week 5 (depending on when subjects were discharged) through week 6. Average adherence rate based on pill count was 99.7%.
- For subjects receiving TAK-063, mean cumulative adherence rate based on the AI app was 81.4% compared with 67.2% for subjects receiving placebo.
- Subjects who completed the trial (n=21) (**Figure 3**):
  - For subjects receiving TAK-063, mean cumulative adherence rate based on the AI app was 88.4% compared with 74.6% for subjects receiving placebo.
  - On the basis of PK sampling, mean adherence at week 6 was 91.7% (11 of 12 subjects) for subjects receiving TAK-063. PK adherence was defined as TAK-063 levels greater than the lower limit of quantification (LLOQ) (0.5 ng/mL).

Figure 3. Adherence as Measured by the AI Application, Pill Count, and PK Data at Week 6 by Treatment Group (n=21)*



*PK samples were marked as compliant if they were above the LLOQ. PK adherence was defined as TAK-063 levels greater than the LLOQ (0.5 ng/mL).
AI, artificial intelligence; LLOQ, lower limit of quantification; PK, pharmacokinetic.

Interventions and Subject Behavior (Table 2)

- 6 of 10 sites intervened using the AI dashboard (text messages and phone calls were logged on the AI dashboard) (**Table 2A**).
- 11 of 26 subjects demonstrated 100% compliance with the AiCure device (**Table 2B**). 8 of these subjects were in the TAK-063 subgroup. 6 of these subjects were found to be compliant based on PK sampling. 1 subject in this subgroup had a missing sample and the other subject had levels below the limit of quantification (BLQ) but had taken the last dose 2 days before the PK sample was drawn.
- Interventions were not recorded through the AiCure platform for 8 subjects. The number of site interventions for these subjects and the impact of these interventions are unknown. 5 of these subjects were ≥70% compliant on the AiCure device. 4 of the 5 subjects were in the TAK-063 subgroup and 3 were found to be compliant based on PK sampling. The remaining subject was flagged for incorrect use of the app prior to day 11 (total time in the outpatient portion was 15 days). This subject had an undetectable plasma concentration at week 6. This subject was the only subject (out of 26 subjects) to be flagged for suspect behavior (**Table 2C**).

Table 2. Interventions and Subject Behavior for All Subjects Discharged to the Outpatient Portion (Total n=26)

A. Subjects Receiving Documented Site Interventions (n=7)

Subject #	Treatment Arm	# Interventions	Pre-Intervention (adherence), %	Post-Intervention (adherence), %[a]	AiCure, %[b]	PK Week 3*	PK Week 6	Suspicious Activity	Days Using AiCure	Completed
1	TAK-063	2	100.0	100.0	100.0	Compliant	Compliant		6	Yes
2	Placebo	5	66.7	100.0	95.0				20	Yes
3	Placebo	2	77.8	100.0	85.7				14	Yes
4	TAK-063	1	50.0	38.5	40.0	Compliant	Compliant		15	Yes
5	Placebo	3	20.0	43.8	38.1				21	Yes
6	TAK-063	4	25.0	ET	25.0	Compliant	BLQ		2	No
7	TAK-063	5	33.3	ET	16.7	Compliant	Sample missing		6	No

B. Subjects 100% Compliant With AiCure Device; No Documented Site Interventions (n=11)

Subject #	Treatment Arm	# Interventions	Pre-Intervention (adherence), %	Post-Intervention (adherence), %	AiCure, %[b]	PK Week 3*	PK Week 6	Suspicious Activity	Days Using AiCure	Completed
8	Placebo				100.0				14	Yes
9	TAK-063				100.0	Compliant	Compliant		15	Yes
10	TAK-063				100.0	Compliant	Compliant		20	Yes
11	TAK-063				100.0	Compliant	Compliant		22	Yes
12	Placebo				100.0				14	Yes
13	TAK-063				100.0	Compliant	Compliant		14	Yes
14	TAK-063				100.0	Compliant	Compliant		20	Yes
15	Placebo				100.0				23	Yes
16	TAK-063				100.0	Compliant	Compliant		21	Yes
17	TAK-063				100.0	Compliant	Sample missing		1	No
18**	TAK-063				100.0	Compliant	BLQ		1	No

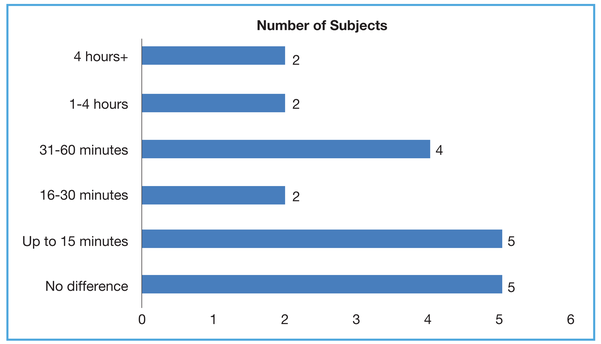
C. Subjects <100% Compliant With AiCure Device; No Documented Site Interventions (n=8)

Subject #	Treatment Arm	# Interventions	Pre-Intervention (adherence), %	Post-Intervention (adherence), %	AiCure, %[b]	PK Week 3*	PK Week 6	Suspicious Activity	Days Using AiCure	Completed
19	TAK-063				93.3	Compliant	BLQ	Yes	15	Yes
20	Placebo				90.9				22	Yes
21	TAK-063				85.7	Compliant	Compliant		21	Yes
22	TAK-063				71.4	Compliant	Compliant		7	Yes
23	TAK-063				70.0	Compliant	Compliant		20	Yes
24	Placebo				61.9				21	Yes
25[c]	Placebo				0.0				14	Yes
26[d]	Placebo				0.0				3	No

*Dose taken before week 3 PK results was during inpatient portion of the study. **Date of last dose for this subject was several days before the final visit and PK sampling (date of last dose 10/28; PK draw 11/4). BLQ, below the limit of quantification; ET, early termination.
[a]The post-intervention adherence is the cumulative average adherence in the period following the intervention until the end of the outpatient segment for the subject.
[b]The AiCure adherence is the cumulative average adherence across the entire outpatient segment for the subject.
[c]Subject 25: subject self-reported 50% of doses but did not go through required visual confirmation steps, so adherence is 0%.
[d]Subject 26: missed doses for 3 days; ET.

- The time of dose ingestion as reported at the time of PK sampling during the week 6 clinic visit on the electronic case report form (eCRF) differed from real-time recording by the AiCure device for 15 of 20 subjects (**Figure 4**).
- The remaining 6 subjects had dosing data that were either missing (missed dose, n=1), self-reported dose (subject confirmed dosing to study coordinator by phone, n=3), or missing PK sample (n=2).

Figure 4. Difference in Minutes Between Start Date/Time as Recorded by AI Platform and eCRF



Discussion

- The study used an AI platform as an additional measure of adherence to assess and increase dosing compliance in a phase 2 clinical study of subjects with an acute exacerbation of schizophrenia.
- The clinical study subjects who were eligible for discharge from the inpatient setting and who completed the study (n=21) demonstrated high rates of adherence using a mobile AI application. The cumulative average adherence rate for subjects receiving TAK-063 was 88.4% compared to 74.6% for subjects receiving placebo. Adherence based on PK data at week 6 was 91.7%.
- Site interventions for 7 subjects were recorded on the dashboard, and 5 of those subjects (71.4%) improved after intervention or had ET within 6 days. Early identification of non-adherence could be a useful tool in improving data quality.
- Suspect behavior was confirmed in 1 subject whose plasma concentration at week 6 was BLQ. This suggests that suspect behavior on the AiCure device could be indicative of intentional noncompliance.
- The date/time of last dose taken as recorded on the eCRF at the time of PK sampling (to assess the interval between the start time of the PK sample relative to the last dose taken) and that logged on the AI platform was at least 30 minutes apart for 40% of subjects (8 of 20). These discrepancies could have implications when determining the PK profile of a drug. Furthermore, this could have implications for drugs that must be taken during a narrow window.
- Because of the relatively low number of subjects participating in the outpatient portion of this study, additional data are needed to further understand the utility of the AiCure platform in clinical studies. Data from this study suggest that the AI platform could be useful to identify nonadherence and suspect behaviors in real time.

References

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DISCLOSURES

Adam Hanina and Laura Shafner are employees of AiCure, New York, NY, USA, and consultants to Takeda. Xinxin Dong, Elizabeth Hanson, Thomas A. Macek, Atul Mahableshwarkar, and Maggie McCue are employees of Takeda Development Center Americas, Inc., Deerfield, IL, USA. Anne Rubin* was an employee of Takeda at the time of this study.

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