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SCIENCE MEDICINES HEALTH

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Product Development Scientific Support Department Qualification Opinion

Draft qualification opinion

Ingestible sensor system for medication adherence as biomarker for measuring patient adherence to medication in clinical trials

Draft agreed by scientific advice working party	March 2015
Adopted by CHMP for release for consultation	26 March 2015[1]
Start of public consultation	16 September 2015[2]
End of consultation (deadline for comments)	26 October 2015[3]

Comments should be provided using this template. The completed comments form should be sent to qualification@ema.europa.eu

Keywords	Qualification of novel methodologies , Ingestible Sensor System, Medication Adherence

1 Last day of relevant Committee meeting.
2 Date of publication on the EMA public website.
3 Last day of the month concerned.

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Background information as submitted by the applicant

Background information on the product

Proteus® Digital Health™ Inc. (Proteus) has developed an ingestible event marker (IEM, also known as ingestible sensor (IS)), a platform technology that can be co-formulated with active pharmaceutical compounds into drug/device combinations, integrating measuring of medication adherence into oral pharmacotherapy. The Proteus IEM is a CE-marked class IIa medical device (CE # 559373) indicated to time-stamp, via ingestion, any discrete event. The IEM communicates medication adherence to a compatible medical device, such as the proteus wearable sensor (Patch), CE-marked class IIa medical device since 2010 by BSI, Proteus Digital Health's EU notified body.

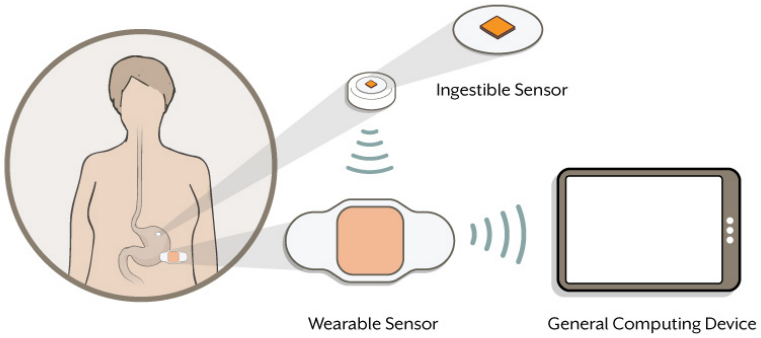
Proteus's ingestible event marker is approved for marketing in the EU and US as a medical device.

Proteus is submitting this briefing book to request EMA to issue a favorable opinion considering use of the proteus technology as a "qualified method" for measuring adherence and associating relevant physiologic and behavioral parameters, such as indications of therapeutic response. We believe that when medication is co-ingested with the IEM, proteus technology is fit-for-purpose of measuring medication adherence and associating other data useful in assessing therapeutic response. To date, hundreds of patients have used the proteus technology to measure adherence and associated physiological responses. Many of these cases have been published in peer-reviewed journals, and many more are conducted in commercial (post-approval) clinical settings. A summary of some of the major use cases is presented later in document (section 2). Detailed results of the studies can be found as an annex to this document.

Whether co-ingested with a drug dose, or taken as part of integrated (single entity) drug-device dose form, the IEM-drug combination is unique in that the drug component and device component function completely independently of one another - the drug provides its pharmacologic effect as it would if administered singly, while the device signals that it has been ingested just as would be the case if swallowed independently. The two components are mechanically associated at the time of ingestion to ensure that the dosing signal generated by the IEM accurately reflects ingestion of the associated medication.

The entire information chain from drug-device combination (IEM + drug) to compatible medical device is depicted in figure 1. Proteus intends to use already CE-marked compatible medical devices, such as the proteus wearable sensor, to complete the information chain of measuring adherence for the ingested medication and associated therapeutic responses. Data collected by proteus wearable sensor is displayed on a compatible computing device. Further data integration and analysis may be achieved through cloud-based computing applications.

Figure 1. Drug + IEM combination product

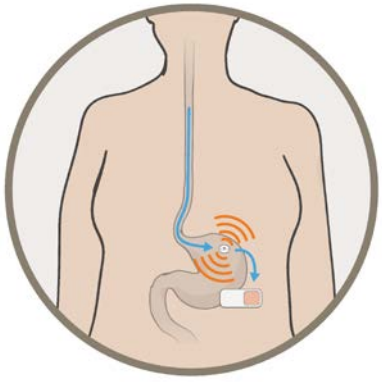


The ingestible sensor and the compatible medical device

The ingestible sensor a food-particle-sized device comprised of an integrated circuit (IC) with layers of minerals on two sides, was CE-marked in 2010 in EU as a class IIa medical device (CE # 559373) and cleared in 2012 for marketing in United States (DEN120011). Upon ingestion, the sensor IC produces a short-lived signal powered by a biogalvanic battery. Encoded in the signal is an identifier code unique to the IC. The signal propagates conductively through the body, where it is detected, recorded, and relayed by a compatible medical device such as the proteus wearable sensor (see figure 2).

Proteus wearable sensor, depicted in figure 2, is a wearable adhesive-backed device measuring approximately 10.2 cm x 5.6 cm x 0.98 cm that contains electronic sensors capable of detecting the ingestion of the IEM and measuring physiologic and behavioral metrics such as heart rate, activity, body angle relative to gravity, and time-stamped user-logged events generated by swallowing the proteus ingestible sensor. The proteus wearable sensor is capable of automatically forwarding recorded data via a secure Bluetooth connection to a compatible computing device. This sensor was CE-marked in 2010 in EU as a class IIa medical device (CE # 559373) and cleared by the FDA in 2012 (DEN120011). Proteus anticipates continued rapid technologic advancement in the field of ingestible sensor detection and corresponding rapid evolution in compatible medical device receiver/recorders.

Figure 2. This illustration shows the ingestion of the IEM and its detection by the proteus wearable sensor



Data received from the wearable sensor will be processed and displayed on a compatible computing device (e.g., tablet computer) paired with the wearable sensor. This display function can be in a standalone mode or tethered to a cloud database.

Cloud applications will enable users to review adherence and other physiological and behavioral data received from the wearable sensor and other devices, interact with caregivers, and provide data to health care providers in a safe and secure manner.

Proposed indication for proteus methodology

When the ingestible sensor is co-ingested with medication, the proteus technology is intended to log, track and trend drug intake times and thus measure medication adherence, permitting other measured physiologic and behavioral parameters to be assessed in light of medication adherence.

Meeting objectives

Proteus is submitting this briefing book in follow up to the meeting held with Spiros Vamvakas, MD, head of scientific advice, and Maria Isaac, MD, PhD, senior scientific advisor for EMA to discuss proteus's methodology for measuring patient adherence to medication and physiologic response.

In this meeting, EMA participants suggested that:

- The proteus technology is a candidate that most likely will qualify as a method "fit for purpose" of measuring and monitoring medication adherence and associating other measured parameters useful to assessing therapeutic response. This will be based on the facts that:
- The proteus device is already CE-marked, and
- Its safety and performance are supported by ample clinical evidence.
- Proteus will need to formally request the qualification opinion from EMA (letter of intent submitted on October 22, 2014)
- Proteus will submit a briefing book (this document).

Proteus is requesting EMA to issue a favorable opinion considering the proteus technology as a "qualified method" for measuring adherence and associating relevant physiologic and behavioral parameters, such as indications of therapeutic response. When granted, this opinion is expected to further streamline the approval process for integrated digital medicines using proteus technology within the European Union.

Safety and performance4

Summary

Proteus has secured CE marking of its medical device products through CE certificate # 559373 per MDD. Proteus has also secured approval of its ingestible sensor and wearable sensor from FDA under DEN120011 (K113070). Following is a summary of some of the safety data presented in Proteus's submissions.

To date, all of the clinical investigations of the proteus system components in the United States have been designated as non-significant risk (NSR) studies, as they have met the established regulatory criteria for a NSR device study. Specifically, the system components are not:

- An implant used to support or to sustain human life
- Being used for substantially diagnosing, curing, mitigating or treating disease or preventing impairment of human health, or

4 See Annex 3 for a complete copy of Investigational Brochure (IB)

- A potential serious risk to the health, safety or welfare of subjects.

No serious adverse events (SAEs) and no unanticipated adverse device effects (UADEs) have been reported. The vast majority of the non-serious, device-related adverse events that have been reported in completed studies have been categorized as mild in severity.

Non-Clinical Studies

To facilitate the development of the IS and to help validate its safety and technical performance, Proteus has performed a comprehensive series of computer simulations, bench-top testing, and in-vitro and in-vivo non-clinical studies.

The following sections summarize three safety topics, which were reviewed as part of existing regulatory clearances:

- Biocompatibility
- Electrical safety
- Mechanical safety

Biocompatibility

To ensure biocompatibility of its products, Proteus looks to the international organization for standardization (ISO) document 10993-1: 2009 for guidance regarding the assessment of device biocompatibility. Proteus uses this standard to inform the design and performance of relevant in-vitro and in-vivo biocompatibility tests for the IS. In addition, Proteus obtained expert advice from respected medical device testing laboratories and toxicology consultants to ensure that the assessment of biocompatibility would be appropriate and sufficiently comprehensive. Once testing requirements were established for the IS, they were fulfilled in the following ways:

- Theoretical analysis, based upon the materials and their use
- In-vitro chemical characterization
- In-vitro biological characterization
- In-vivo biological characterization

An extensive set of biocompatibility tests have been performed and the results are highly supportive of the biological safety of the IS. Notable biocompatibility information for the IS and its placebo dose forms is presented below. Summary and details of these studies are presented in the table 1 below and annex 4, respectively.

Table 1. Summary of the biocompatibility studies performed on IS

Phase of assessment	**Evaluation**	**Conclusions**
	Canine oral toxicology study	No evidence of IS toxicity, based upon clinical observations and GI tract histopathology. No changes in blood levels of RIS inorganic materials following exposure.
	Rodent oral toxicology study	No evidence of IS toxicity—even in highest dosing group, which received the weight-

		adjusted equivalent of 30,000 RISs/day—based upon clinical observations, hematology, coagulation tests, blood chemistries, necropsy, and comprehensive histopathology.
	IS copper human health assessment5	Practical-use scenario (15 ISs ingested simultaneously, daily or twice-daily) poses no risk of copper toxicity. Extreme-use scenario (30 RISs ingested simultaneously, daily) poses no risk of systemic toxicity, but transient, non-systemic gastric upset could result at this dose. This concentration-dependent effect would be mitigated by intake with a meal.
	Quantitative cytotoxicity	Corroborates conclusion of IS copper human health assessment.
	Additional chemical characterizations	No unintended compounds detected above reporting threshold for new drug substances, a stringent standard that was adapted for analysis of the IS device.

ISs: Proteus has conducted a 14-day, repeat-dose oral toxicology study in rats (annex 5). IS test sample was extracted in simulated gastrointestinal fluid and administered via gavage. Doses ranged up to a weight-adjusted human equivalent of 30,000 ISs per day. There was no evidence of toxicity, even in the highest dosing group, based upon all observations and tests (clinical observations, animal weights, hematology and chemistry panels, gross necropsy, organ weights, and histopathology).

Placebo material in the IS dose forms: the placebo materials used in all dose forms of the ingestible sensor are manufactured under GMP from commonly used pharmaceutical excipient materials.

Electrical Safety

The FDA recognizes international electrotechnical commission (IEC) 60601-1 (EN 60601-1 for MDD), namely medical electrical equipment – Part 1: general requirements for safety, as its cornerstone for addressing key hazards associated with electrical medical equipment. IEC 60601-1 aims to protect both patients and users by reducing the likelihood of such hazards. Proteus Digital Health, Inc. therefore uses this standard as its primary guideline to design and test its devices from an electrical safety perspective. Where appropriate, IEC 60601-1 has been applied to components of the proteus system, in order to ensure conformance with critical safety requirements.

Furthermore, theoretical analysis and empiric in-vivo testing confirmed that the IS is not capable of causing near- or far-field tissue stimulation, due to the very small amount of, and nature of, the current created by ISs. In-vivo testing also demonstrated that the IS does not cause electrochemical damage to the lumen of the gastrointestinal tract. Further electrical safety information is available upon request.

5 Conducted by Gradient Corporation (Cambridge, MA, USA), a firm with expertise in metals toxicology.

Mechanical Safety

Mechanical safety tests were performed in a canine model, which indicated that ISs: 1) cause no mechanical injury to the lumen of the gastrointestinal tract and 2) are excreted reliably. Additional mechanical safety information is available upon request.

Food and IS Co-Ingestion: A clinical study has demonstrated that food and beverages including alcohol do not affect IS function in any clinically significant manner. The IS has been ingested in other studies with no limitations placed upon the co-ingestion of capsules, tablets, gelatin tabs, foods of any kind, and beverages of any kind and quantity including alcohol. The IS has been deliberately developed with elements that are consumed in the human diet, and to represent very small amounts (0.3% to 0.003%) of what is considered allowable for daily consumption of these elements (see gastrointestinal absorption of chemical elements of the IS, below).

Gastrointestinal absorption of materials in the IS: the IS has been deliberately developed to consist of minute amounts of materials already consumed in the human diet. The potentially absorbable quantities of these materials have been chemically characterized using IS extracts. The IS's extractable materials are present in quantities well below acceptable daily levels, even if 100% absorption is assumed. Details of the IS chemical analysis can be found in annex 6. A summary of this analysis is presented below.

IS chemical characteristics: chemical characterization of ISs produced by a medium-to-high-volume manufacturing process was performed.[6]

The extraction vehicles and extraction times used in these analyses were designed to simulate gastrointestinal conditions in the stomach and the intestines.[7] Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was used to quantify inorganic compounds and gas chromatography-mass spectrometry (GC-MS) was used to quantify organic compounds. To frame the analysis of the chemical characterization results, ICH guidance for industry Q3A impurities in new drug substances (July 2008), a key guideline for pharmaceutical compounds, was applied to the IS device.[8]

Inorganic Compounds

Table 2 quantifies inorganic materials obtained under different extraction conditions.

6Chemical characterization of SA003117 (an IS that contains the DP4.x integrated circuit) was conducted by Catalent, RTP Facility, P.O. Box 13341, Research Triangle Park, NC 27709.

7 ISs were incubated in pH 1.2 and pH 7 aqueous extraction vehicles at 37°C for 72 hours.

[8] Impurity identification and qualification thresholds have not been defined for ingestible medical devices. However, such thresholds are well established in the pharmaceutical industry. The reporting, identification, qualification, and thresholds specified in *Guidance for Industry Q3A Impurities in New Drug Substances* (July 2008) are 0.05%, 0.1%, and 0.15%, respectively, if the maximum daily dose of drug substance is ≤2g/day. Since each IEM weighs 5 mg (the unit dose), and we assume an upper daily intake of 30 IEMs/day, the maximum daily dose is 150 mg, well below 2g/day.

Table 2. Inorganic materials detected above the ICH Q3a reporting threshold (≥2.5 µg/IS)

pH	Mean copper extract (µg/IEM)	Mean Mg extract (µg/IEM)	Maceration time (hrs)
1.2	5.30	5.63	72
7.0	0.130	5.11	72
1.2 adjusted to 7 after 4 hours[9]	2.72	5.63	72

Table 3 compares single-IS and calculated 30-IS/day (projected extreme use scenario) quantities of copper and magnesium to common references for each material. To place these quantities in context, the extractable copper quantity is compared to Permitted Daily Exposure (PDE),[10] and extractable magnesium is compared to dietary reference intakes (DRIs).[11] One hundred percent absorption of the extractable copper and magnesium is assumed for these comparisons.

Table 3. Extractable quantities of IS Cu and Mg relative to permitted daily exposure (Cu) or to dietary reference intake (Mg), using the most conservative case (pH 1.2 results).

Element	Amount extracted (µg/device)	DRI or PDE (µg/day)	% of DRI or PDE (single IS)	% of DRI or PDE (30 ISs/day)
Copper	2.72	2,500	0.1%	3%
Magnesium	5.6	310,000	0.002%	0.05%

As can be seen, the estimated amounts of absorbable copper and magnesium, both essential minerals, are very low compared to common permissible levels.

Organic Compounds

Quantities of organic materials obtained from ISs under the different extraction conditions are shown in table 4.

Table 4. Organic materials detected above the ICH Q3a reporting threshold (≥2.5 µg/IS)

	(µg/IS)	
Element	**pH 1.2**	**pH 7**
Ethyl Citrate	263	231

[9] The highest (the worst-case) mineral extraction, 5.3µg/IS, was achieved after a full 72-hours under pH 1.2 conditions. Food generally passes out of the stomach to the higher-pH small intestine within minutes to a couple of hours. Our closest simulation of this physiologic reality—pH 1.2 for 4 hours adjusted to pH 7 for the remaining 68 hours—yielded a 49% reduction in the amount of Cu extracted per IS to 2.72 µg /IS. A value of 2.7 µg/IS extractable copper assumes 100% absorption in the human GI system.

[10] Copper PDE level derives from EMEA/CHMP/SWP/446/2000, *Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents*, September 2008

[11] Magnesium DRI derives from *Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Elements.* National Academy of Sciences, Institute of Medicine, 2004

The ethyl citrate species are breakdown products of triethyl citrate, one of the inert materials used to form the IS skirt. Triethyl citrate is an excipient material (i.e., an “inactive ingredient”) on the United States pharmacopeia - national formulary that is commonly used in solid-dosage form oral pharmaceutical products, such as ranitidine (Zantac®), omeprazole (Prilosec®), diltiazem (Cardizem®), and lamotrigine (Lamictal®). Triethyl citrate is also used as a food additive.12 Per the US Food and Drug Administration listing of food additives generally regarded as safe (GRAS), “the ingredient is used in food with no limitation other than current good manufacturing practice.”13

Assessment

Extractable copper, magnesium, and the citrate species are in quantities below, but near, the ICH Q3a qualification threshold (0.15%, or 7.5 µg/IS). To be conservative, they were therefore tested in the rodent toxicology study noted in section 1.4.1.1, “Biocompatibility.” No evidence of toxicity was seen in that study, even in the high-dose group that received a weight-adjusted human equivalent of 30,000 extracted ISs per day. Hence, these compounds are considered fully qualified for human use.

In summary, the IS is designed to consist of materials encountered in the human diet. The IS’s extractable materials (copper, magnesium, and triethyl citrate) are present in quantities well below acceptable daily levels, even when 100% absorption is assumed.

Gastrointestinal safety: The IS has been deliberately developed only with those elements that are consumed in the human diet. The size of a single IS at the time of ingestion is similar to a single grain of sand. No mechanical injury has been observed pre-clinically or reported in human studies. A total of 120 ISs (delivered within gelatin capsules) have been administered (40 ISs/day for 3 days) orally to an animal model, and no mechanically-related injuries to the GI tract were observed upon pathological analysis. IS device excretion has been assessed in an animal model; ingested ISs were reliably excreted, with a total gut transit time comparable to that reported in literature.

General safety: users of the proteus system who experience clinical worsening or new clinical symptoms should seek medical attention.

Medication and IS co-ingestion: ISs have been ingested in clinical studies with no limitations placed upon the co-ingestion of capsules, tablets, or gelatin tabs. There have been no reported losses of drug efficacy associated with the co-ingestion of any medication and an IS.

The IS has been deliberately developed with elements that are consumed in the human diet, and to represent very small amounts of what is considered allowable for the daily consumption of any of the elements (see gastrointestinal absorption of materials in the IS, above). Proteus is unaware of any warning or precaution in any patient package insert for any approved drug against the co-ingestion of these elements in these quantities.

Magnetic resonance imaging (MRI) and proteus system safety: The IS does not represent a magnetic imaging risk as there are no ferrous metals (such as nickel, iron, cobalt) or other magnetic materials in the IS. The wearable component of the product should be removed before magnetic imaging.

pH and IS performance: The IS has been demonstrated to function appropriately in normal human volunteers and patients with various diseases (see section 1.4.2). In vitro studies have demonstrated that the IS does not depend upon gastric pH for activation, and IS performance is unaffected across the pH range from gastric pH to neutral pH.

12 For instance, triethyl citrate is used to stabilize foams, such as the whipping of egg whites. William J. Stadelman, Owen J. Cotterill (1995). Egg Science and Technology. Haworth Press. ISBN 1560228555.
13 21 Code of Federal Regulations Part 184. Direct Food Substances Affirmed As Generally Recognized As Safe, Section 1911, “Triethyl Citrate”

Roentgenography (X-ray imaging), computerized tomography (CT), and IS visualization: The IS is not radiopaque. The IS has been found pre-clinically to be difficult to visualize with gastrointestinal roentgenography (X-ray imaging) in canines.

Clinical studies

The clinical study program for the proteus system was initiated in January 2008, aimed to characterize the safety and technical performance. Study subjects have included healthy volunteers, as well as patients with tuberculosis, heart failure, hypertension, diabetes, schizophrenia, advanced BMI, bipolar disorder, renal transplantation, seniors with fragile skin, tuberculosis, and bipolar disorder as their primary disease.

The proteus system measures and delivers data accurately & reliably with a low rate of AEs, no SADEs, and no UADEs.

IS performance

As noted previously, the IS has been cleared via the 510(k) pathway and has received the CE mark in the EU. The following is an excerpt from the FDA-cleared device label,14 which summarizes the technical performance:

- A total of 412 study subjects have participated in pill ingestion studies representing 20,993 ingestible sensor ingestions. In comparison with direct observation, the ingestible sensor was detected in 97.3% of ingestions, with correct identification in 100%.

IS Safety

The following is an excerpt from the FDA-cleared device label,15 which summarizes the clinical experience:

The ingestible sensor was extensively tested in preclinical studies prior to use in clinical studies. A total of 412 study subjects have participated in pill ingestion studies representing 20,993 ingestible sensor ingestions. Table 5 below summarizes adverse events (AEs) observed in the clinical studies of the ingestible sensor. None of these adverse events were considered serious and all resolved spontaneously.

Table 5. List of IS-related or –possibly related adverse events, quantified by subject (subjects counted only once if same AE occurred multiple times in an individual subject).

Adverse events related or possibly related to the IS	**Number of AEs**	**AE rate as % of all subjects (n=412)**
Nausea/vomiting	4	1.0%
Constipation	2	0.5%
Asthma attack	1	0.2%
Abdominal cramping	1	0.2%
Non-cardiac chest pain	1	0.2%
Bitter taste in mouth	1	0.2%

14 LBL-0111 Global CMD RP4 Instructions for Use (Annex 7)
15 ibid

Table 6 presents AEs quantified by AE rather than by subject.

Table 6. List of IS-related or –possibly related adverse events, quantified by AE (subjects counted more than once if same AE occurred multiple times in an individual subject).

Adverse events related or possibly related to the IS	**Number of AEs**	**AE rate as % of all subjects (n=412)**
Nausea/vomiting	5	1.2%
Constipation	2	0.5%
Asthma attack	1	0.2%
Abdominal cramping	1	0.2%
Non-cardiac chest pain	1	0.2%
Bitter taste in mouth	1	0.2%

Non-clinical and clinical data support the conclusion that the Proteus system performance and safety are satisfactory for its intended use. System sensitivity for detecting ISs is 99% for the latest configuration of the system. There have been no serious adverse events related or possibly related to the device, and there have been no unanticipated adverse device effects. The adverse event rate is very low and all AEs have been self-limited.

Conclusion

Non-clinical and clinical data support the conclusion that the proteus system performance and safety are satisfactory for its intended use. System sensitivity for detecting ISs is 99% for the latest configuration of the system. There have been no serious adverse events related or possibly related to the device, and there have been no unanticipated adverse device effects. The adverse event rate is very low and all AEs have been self-limited.

Clinical Experience

Problem statement: in a publication by world health organization (WHO) in 200316 the following issues were raised:

- Poor adherence to treatment of chronic diseases is a worldwide problem of striking magnitude.
- Adherence to long-term therapy for chronic illnesses in developed countries averages 50%.
- The impact of poor adherence grows as the burden of chronic disease grows worldwide.
- The consequences of poor adherence to long-term therapies are poor health outcomes and increased health care costs.
- Improving adherence also enhances patients' safety.
- Adherence is an important modifier of health system effectiveness.

The following graphs (figures 4 and 5) illustrate the gradual declines of medication adherence in heart failure17 and multiple sclerosis18. In both studies medication adherence drops roughly about 50% in the first year of the treatment.

16 Sabate E, WHO 2003, pp xiii-xiv.
17 Hauptman J, Heart Fail rev 2008;13:99

Figure 3. Medication adherence in heart failure

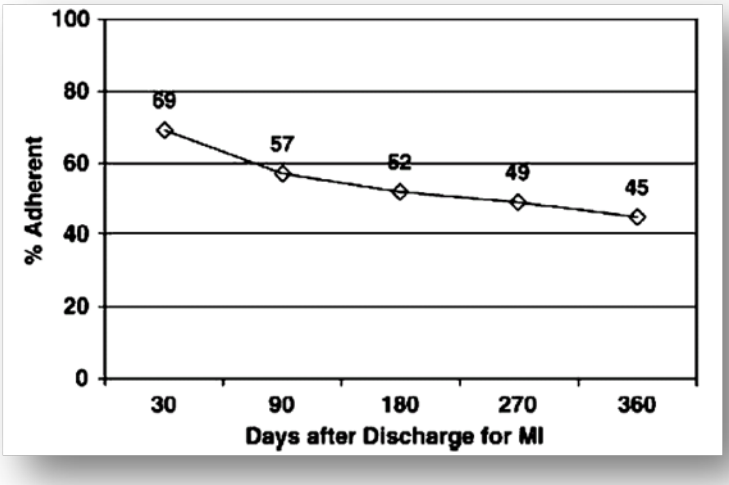
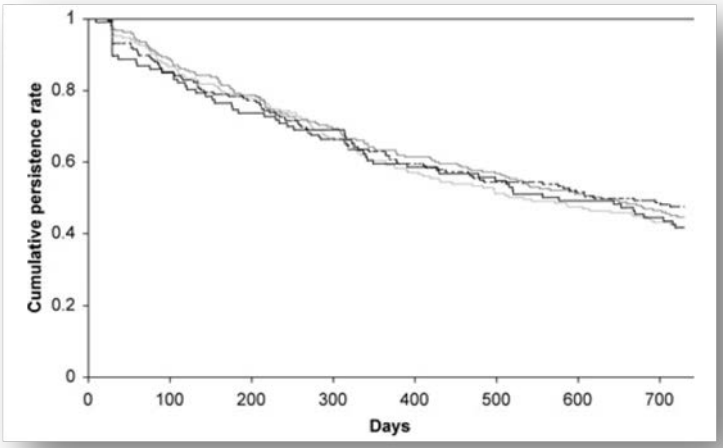


Figure 5 Medication adherence in multiple sclerosis



Summary of early clinical experience with proteus system for promoting patient self-management19: prospective, observational clinical studies were conducted to gain early experience with the commercially available proteus system (ingestible sensor, wearable sensor, and a personal monitor) designed to assess patient's adherence to oral medication and physiologic metrics in an ambulatory, at-home setting. The following highlights of the study design and results:

- 111 ambulatory patients studied across 3 disease states (CHF, HTN, tuberculosis) over 42 days
- Subjects took their medications along with ingestible sensors (co-ingested with their medications or as part of a capsule containing their medications).
- Medication adherence was >85%

18 Wong J, Can J Neurol Sci 2011; 38: 429
19 Au-Yeung KY, Moon GD, Robertson TL et. Al American J Managed Care. 2011;17(7):e277-e287 [#6 in Compendium]

- System showed 100% accuracy in identifying medication ingestions and differentiating 3 medications / dosages – Furosemide 20mg, Valsartan 80mg, Valsartan 160mg (2641 ingestions)
- 97.1% positive detection accuracy (3298 ingestions)
- 97.7% negative detection accuracy (221 ingestions)
- Ingestion detection unaffected by BMI or food content
- System was safe. Only adverse event was mild skin rash in 45 subjects due to adhesive used for the wearable sensor (prior generation of adhesive)
- System successfully integrated blood pressure and weight data from connected devices.

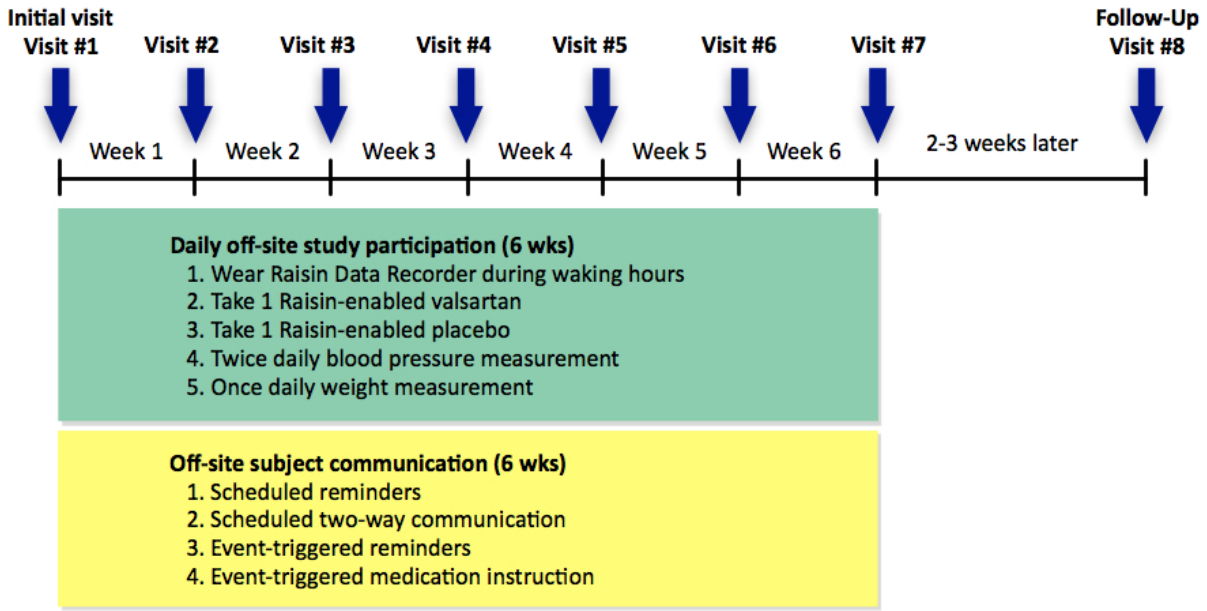
What follows are highlights from selected Proteus clinical trials. Study details can be found in the relevant clinical report or the proteus compendium of publications and abstracts attached as annexes.

Event marker ingested to trigger event recorder (EMITTER) 3.0 CV-HTN clinical trial

This was a 2009 six-week observational feasibility study (N=43) that validated the medication adherence and physiologic data gathering and communication capabilities of the proteus ingestible and wearable sensors—then referred to collectively as the raisin system—in a cardiovascular outpatient population prescribed valsartan for hypertension. Study participants were supplied valsartan contained within an over-encapsulation vehicle together with the proteus ingestion sensor, ensuring one-to-one correspondence between drug and sensor. Physiologic metrics were recorded in the cloud database from the wearable sensor and third-party telemetric weight scales and blood pressure cuffs, demonstrating the feasibility of the proteus methodology.

The complete study report is attached as annex 8 to this document.

Figure 6: overview of EMITTER 3.0 CV-HTN study procedures



26 males and 17 females were enrolled in this study with an average age of 61.7 ± 8.8 years.

Based on the statistical analyses of selected metrics, the primary objective of EMITTER 3.0 CV- HTN was met.

- The raisin system was capable and reliable in collecting data on raisin-enabled pill ingestion events. The positive detection accuracy (PDA) was 98.0%, when each IEM event was treated as independent. When a mixed model for repeated measures was used to account for the fixed effects of clinic visit day and the random effect of subject, the PDA was 96.7%. Both results exceeded the historical objective success criterion of 95%.
- The raisin system was able to collect daily activity data. The activity data availability (ADA) was 100% across 40 subjects per study metric definition.
- The raisin system communication process was robust and reliable. The event-triggered reminder reliability was 100% across 31 subjects.

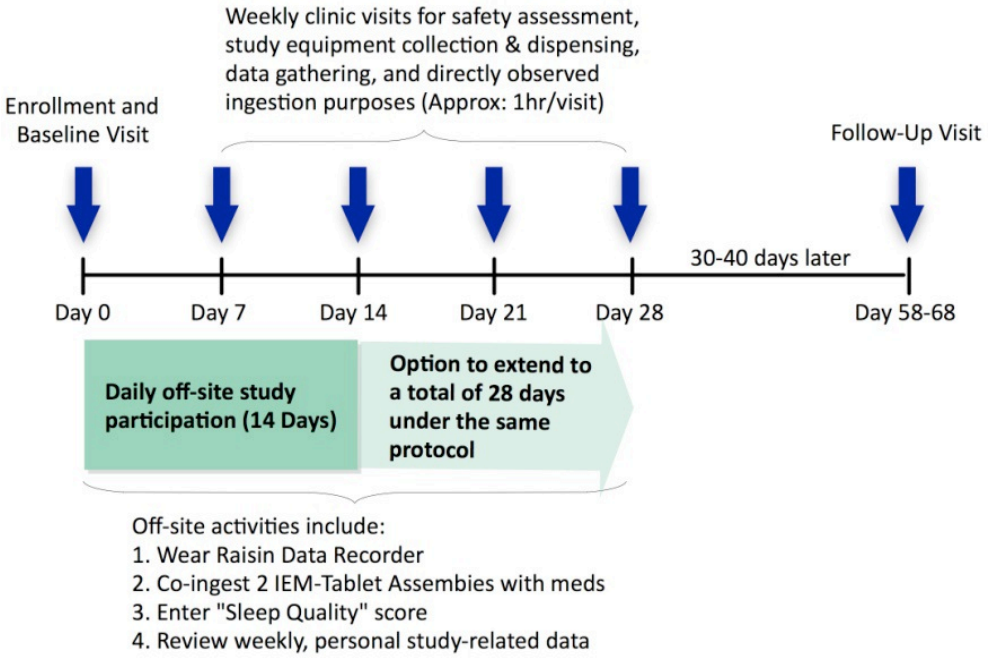
Based on the statistical analyses of selected metrics plus the responses from the post-study questionnaire, the secondary objectives of EMITTER 3.0 CV-HTN were met.

- Using the raisin system, taking and scheduling adherence rates were effectively quantified, monitored, and analyzed. The mean taking and scheduling adherence across subjects were 90.0% and 82.8%, respectively.
- Third-party telemetric weight scales and sphygmomanometers were successfully incorporated in the Raisin system to monitor subjects' weight and blood pressure. The mean weight reported was 89.2 ± 20.9 kg, ranging from 31.3 kg to 136.0 kg. The mean morning systolic/diastolic blood pressure reported was 131.4/78.1 mmHg; that in the evening was 127.3/72.6 mmHg.
- The mean activity level across subjects was 2.0 ± 1.5 hours/day, with a 95% CI of 1.9 to 2.1 hours/day. The activity identification accuracy (AIA) across subjects was 79.3% when each activity sequence was treated as independent. When a mixed model for repeated measures was used to account for the fixed effects of clinic visit day and the random effect of subject, the AIA was 82.3%. The low AIA was attributed to a combination of device data sampling settings and procedural issues.
- Feedback gathered from subjects and subjects' family members, friends and caregivers was overall positive and encouraging, while also providing valuable and constructive inputs for future system enhancement.

Event marker ingested to trigger event recorder 3.0 psychiatry study (EMITTER 3.0 PSY)

This was a 2010-2011 fourteen-to-twenty-eight day observational, multi-site, two-arm feasibility study (N=29) that validated the detection capability of the ingestible sensor against direct observation and characterized medication-taking behavior in bipolar or schizophrenia patients using a co-ingestion model (ingestible sensor-containing placebo tablet ingested together with prescribed medication). physiologic metrics including heart rate, activity, and sleep were also collected.

375 Figure 7: overview of EMITTER 3.0 PSY study procedures



376

377 **Table 7.** Taking and scheduling adherence across sites and by site

OVERALL	%	N	95% CI
Taking adherence Scheduling adherence	73.7 ± 24.9 67.1 ± 30.6	28 28	64.1, 83.5 55.2, 78.9
SITE 1 (Zucker Hillside Hospital, schizophrenic cohort)	%	N	95% CI
Taking adherence Scheduling adherence	80.3 ± 18.8 76.3 ± 26.5	16 16	70.2, 90.3 62.1, 90.4
SITE 2 (Massachusetts General Hospital, bipolar disorder cohort)	%	N	95% CI
Taking adherence Scheduling adherence	65.0 ± 29.9 54.8 ± 32.5	12 12	46.0, 84.1 34.1, 75.4

378

379 Physiologic parameters were recorded (HR, sleep, activity), as was subjective patient evaluation of the
380 system. All primary and secondary objectives were achieved.

381 The complete study report is attached as annex 9 to this document.

382 Medication adherence assessment: high accuracy of the new ingestible sensor system in kidney
383 transplants

384 Proteus pharma partner Novartis conducted a 12-week study assessing the Ingestible Sensor when
385 over-encapsulated with an immunosuppressive agent used for maintenance of renal transplant
386 recipients.

The abstract appears below and the complete publication is found together with other published Proteus materials in the compendium of Proteus publications and abstracts appearing as annex 10 to this document.

Figure 8: Novartis-sponsored study of Proteus methodology in renal transplant patients

Medication Adherence Assessment: High Accuracy of the New Ingestible Sensor System in Kidney Transplants

Ute Eisenberger,[1,11] Rudolf P. Wüthrich,[2] Andreas Bock,[3] Patrice Ambühl,[4] Jürg Steiger,[5] Allison Intondi,[6] Susan Kuranoff,[7] Thomas Maier,[8] Damian Green,[9] Lorenzo DiCarlo,[6] Gilles Feutren,[7] and Sabina De Geest[10]

Background. This open-label single-arm exploratory study evaluated the accuracy of the Ingestible Sensor System (ISS), a novel technology for directly assessing the ingestion of oral medications and treatment adherence.
Methods. ISS consists of an ingestible event marker (IEM), a microsensor that becomes activated in gastric fluid, and an adhesive personal monitor (APM) that detects IEM activation. In this study, the IEM was combined to enteric-coated mycophenolate sodium (ECMPS). Twenty stable adult kidney transplants received IEM-ECMPS for a mean of 9.2 weeks totaling 1227 cumulative days.
Results. Eight patients prematurely discontinued treatment due to ECMPS gastrointestinal symptoms (n=2), skin intolerance to APM (n=2), and insufficient system usability (n=4). Rash or erythema due to APM was reported in 7 (37%) patients, all during the first month of use. No serious or severe adverse events and no rejection episode were reported. IEM detection accuracy was 100% over 34 directly observed ingestions; Taking Adherence was 99.4% over a total of 2824 prescribed IEM-ECMPS ingestions. ISS could detect accurately the ingestion of two IEM-ECMPS capsules taken at the same time (detection rate of 99.3%, n=2376).
Conclusions. ISS is a promising new technology that provides highly reliable measurements of intake and timing of intake of drugs that are combined with the IEM.

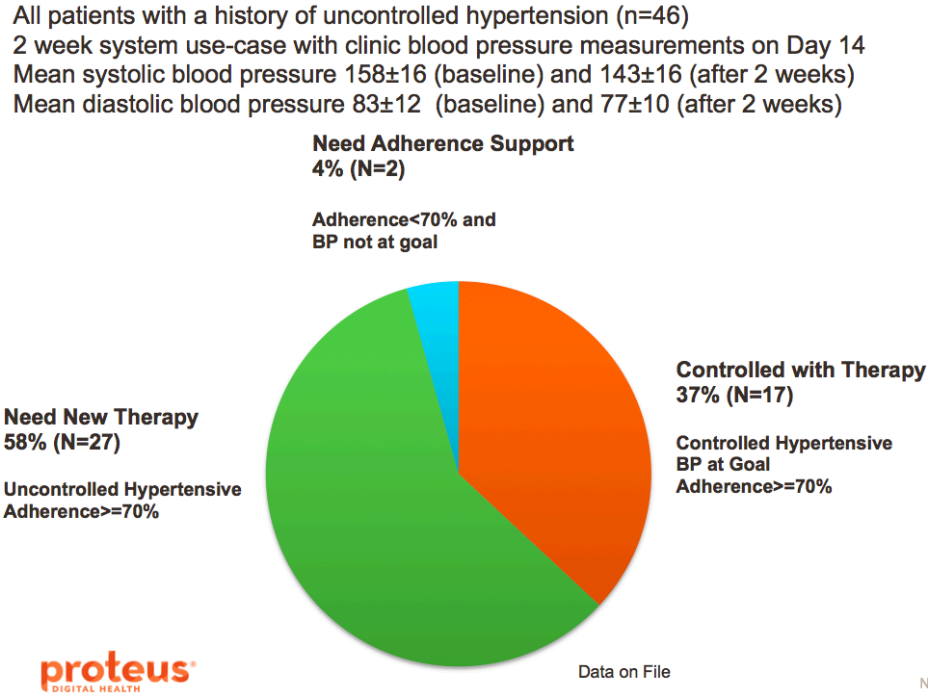
Keywords: Treatment adherence, Kidney transplantation, Ingestible sensor system, Telemedicine, Enteric-coated mycophenolate sodium.

(*Transplantation* 2013;96: 245–250)

Commercial validation

Proteus is working with the UK National Health Service to conduct an ongoing multi-center evaluation of uncontrolled hypertensive patients prescribed the proteus methodology for a two-week diagnostic period to assess anti-hypertensive medication adherence, therapeutic response, and likely cause. interim results from this study are summarized in figure 9 below.

397 Figure 9 Interim results of ongoing Proteus-NHS hypertension study



398

399 *Other Use Cases*

400 Table 8 below is a list of Proteus's publications as of April 2014. As presented in above use cases and
401 summarized in table below, proteus technology has demonstrated to be fit-for-purpose of measuring
402 medication adherence and associated physiological and behavioral responses. Details of these clinical
403 use cases can be found in annex 10 of this document.

404 **Table 8.** Summary of Proteus publications as of April 2014

PUBLICATIONS	SUMMARY
• Kane JM, Perlis RH, DiCarlo LA, et al. First experience with a wireless system incorporating physiologic assessments and direct confirmation of digital tablet ingestions in ambulatory patients with schizophrenia and bipolar disorder. Journal of Clinical Psychiatry 2013; 74: e533-e540	This study demonstrated the feasibility and safety of a wireless networked system incorporating physiologic assessments and direct confirmation of digital tablet ingestions in ambulatory patients with schizophrenia and bipolar disorder.
• Belknap R, Weis S, Brookens A, Au- Yeung KY, Moon G, et al. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. PLoS ONE 2013; 8(1):	This feasibility study demonstrated that electronically observed therapy may be an effective alternative to directly observed therapy, and could be a particularly attractive option when used with fixed-dose combination medications for the treatment of tuberculosis.

e53373.doi: 10.1371/journal.pone.0053373 http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0053373	
• Zdeblick M. How Wireless Therapy Will Change Health Care Delivery. International Electron Devices Meeting Technical Digest 2012.	The miniature supercomputer with high resolution screen we carry in our pocket to make phone calls will help bring modern health care to all corners of the world. Instead of building expensive hospitals throughout the developing world, low cost, high volume devices wirelessly networked together will help deliver health care to the billions of people who have none today.
• DiCarlo LA, Moon G, Intondi A, et al. A digital health solution for using and managing medications. IEEE Engineering in Medicine and Biology (Pulse) September/October 2012, pages 23-26.	Proteus Digital Health has developed a digital health technology that definitively determines when medications have been ingested, and can provide this information wirelessly in a confidential way to patients and designated caregivers, health providers, and researchers. The purpose of this system is to document and to communicate medication use and activities of daily living to assist in the care of patients, and to support clinical trials of pharmaceuticals.
• Au-Yeung KY, Robertson T, Hafezi H, et al. A networked system for self- management of drug therapy and wellness. Proceeding WH '10 Wireless Health 2010, pages 1-9.	A networked wellness system has been developed to record and to communicate medication use and activities of daily living. It consists of an ingestible marker made from food materials and a wearable, personal monitor. The system records and displays actual ingestions of oral medications, differentiating types/doses of drugs taken simultaneously, and providing these data to patients and providers along with biometrics such as heart rate, sleep, and activity for individually tailored care.
• Au-Yeung KY, Moon GD, Robertson TL, et al. Early clinical experience with a networked system for promoting patient self-management. American Journal of Managed Care 2011; 17: 277-287.	Initial experience in humans using the Proteus networked system to assess medication use and physiologic metrics in an ambulatory at-home setting is summarized. Tested in human volunteers, and patients having chronic diseases such as heart failure, hypertension, and tuberculosis, the system was found to be safe and effective in capturing and integrating adherence and physiologic data.
• Au-Yeung K, DiCarlo LA. Cost comparison of wirelessly versus directly observed therapy for adherence confirmation in tuberculosis treatment. International Journal of Tuberculosis and Lung Disease 2012; 16: 1498-1504.	Directly observed therapy (DOT) represents the tuberculosis treatment standard recommended by the World Health Organization, however, its implementation is commonly attenuated due to its cost. Some tuberculosis treatment programs in the United States do not use DOT at all, or use DOT only for high-risk patients. Under several potential cost scenarios, the immediate cost of TB treatment using wirelessly observed therapy appears to be substantially less than DOT. Further WOT development for TB treatment is warranted.

• Eisenberger U, Wüthrich RP, Bock A, et al. Medication Adherence Assessment: High accuracy of the new ingestible sensor system in kidney transplants. Transplantation 2013; 96: 245-250.	This was 12-week open-label single-arm exploratory study conducted in collaboration with Novartis, and evaluated the accuracy of the ingestible sensor system in directly assessing treatment adherence in 20 kidney transplant patients. The ingestible sensor system was demonstrated to be a promising new technology that provides highly reliable measurements of intake, and timing of intake, of drugs that are combined with the ingestion event marker.
• DiCarlo LA. Role for direct electronic verification of pharmaceutical ingestion in pharmaceutical development. Contemporary Clinical Trials 2012; 33: 593-600.	Identifying a dosing regimen for recommended use is one of the more difficult tasks in pharmaceutical development and has major therapeutic and economic consequences. The Raisin System provides a direct measure of pharmaceutical utilization in pharmaceutical studies provides the means to examine the temporal patterns of drug response that are engendered by patients' actual dosing patterns.
• Godbehere P, Wareing P. Hypertension Assessment and Management: Role for Digital Medicine. Journal of Clinical Hypertension 2014: 16 (3): 235	Dr. Godbehere describes the first use of the commercially available digital health feedback system to assess hypertension therapy. The system provided support for clinical decision and management by helping to discriminate between inadequate medication utilization and pharmacologic unresponsiveness. The system provided useful information for individualized treatment decisions regarding dose adjustment, the addition or discontinuation of medications, or medications use review (including adherence counseling) to improve blood pressure.

Overview of Regulatory History (IEM-drug combination products)

BSI

A summary of Proteus interactions with BSI are given below in table 11.

Table 9. Summary of Proteus/BSI interactions

CE #	Timing of interactions	Type of interactions	Key outcomes of meeting
559 373	August 5 2010, March 29 2011, January 17 2013	Certification	BSI certification for full quality assurance
559 373	May 6, 2014	Techfile audit	No major nonconformity found

Quality and CMC Elements

Description of Digital Dose Forms

To facilitate ingestion and handling, ISs are assembled in conjunction with excipient material as a pill. The IS can also be incorporated with active pharmaceutical ingredients (APIs). Previously, the ISs have been physically separated from any active pharmaceutical involved, either utilizing co-ingestion or over-encapsulation methods.

The IS-carrier formulation methods are versatile enough so that in final marketed forms, the IS can be combined with the desired active pharmaceutical so that both the activation profile of the IS as well as the dissolution profile of the API are maintained with no drug-device interaction expected.

Manufacturing Options

IS Tablet Dose Forms

The miniature IEM tablet (MIT) and the IEM tablet assembly (ITA) are inert tablets composed of commonly used pharmaceutical excipients. In the case of the MIT, an IS is placed inside the tablet; in the case of the ITA, an IS is attached externally on the tablet.

MITs and ITAs are formulated and manufactured using good manufacturing practices and pharmaceutical-grade materials.

The ITA and the MIT can be over-encapsulated alone or with other excipient tablets for cosmetic or technical purposes.

MITs, ITAs, and over-encapsulated MITs or ITAs may be swallowed alone or co-ingested with drug products (with the drug products being physically separate from these dose forms) to mark a medication dosing event.

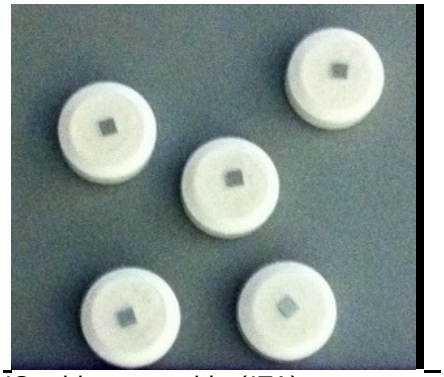
The excipient materials in ITA and MIT tablets may also be replaced by drug product(s). Such pharmaceutically active dose forms are currently in development.

Complete over-encapsulation

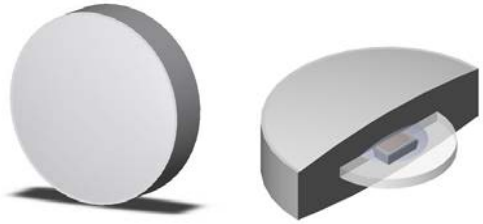
Over-encapsulation (OE) provides a vehicle to combine any solid-dosage drug product inside a capsule with an IS tablet dose form. A drug product of various form factors (for example a tablet, a capsule, or a powder) can be placed inside the capsule along with the IS tablet dose form. The capsule is then closed and locked by inserting and pushing the capsule cap over the capsule body. With the OE method, the IS, the drug product, and the standard excipient materials are completely contained within the capsule. Over-encapsulation provides an IS-enabled dosage form with a familiar appearance to patients or consumers.

Illustrations of form factors are presented below.

IS tablet dose forms



IS tablet assembly (ITA)

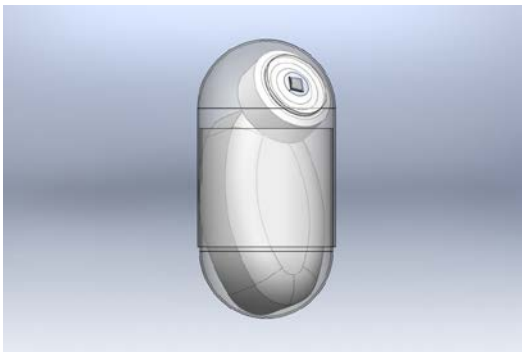


Miniature IEM tablet (MIT) or active pharmaceutical product (under development)

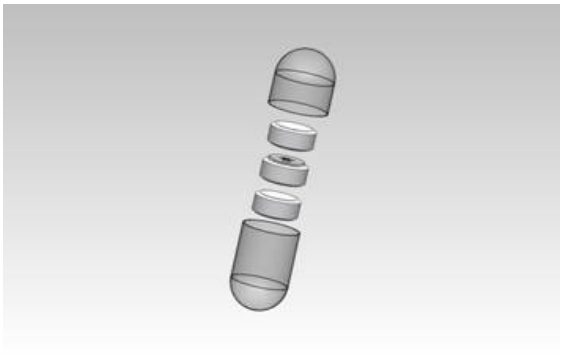
Tablet materials
Microcrystalline cellulose (MCC), NF

Croscarmellose sodium, NF (Ac-Di-Sol)
Magnesium stearate, NF

Complete over-encapsulation (OE)

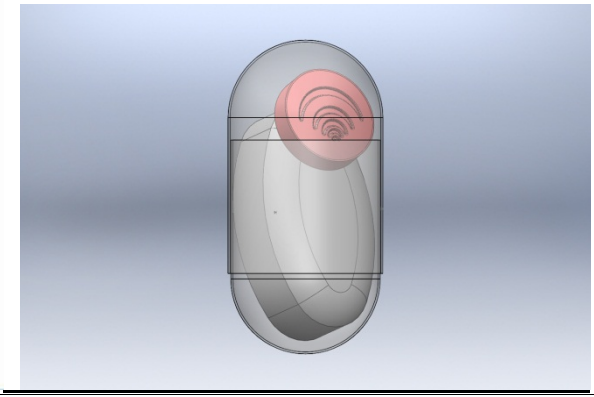


OE, drug product with ITA

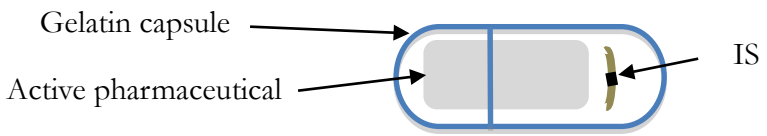


OE, excipient tablets with ITA

OE



Drug product with MIT



Capsule materials	**IS tablet materials (when present)**
Hard gelatin, NF OR Hydroxypropylmethylcellulose (HPMC), NF Colorant, NF	Microcrystalline Cellulose (MCC), NF Croscarmellose Sodium, NF (Ac-Di-Sol) Magnesium Stearate, NF

Analytical tests

Digital dose forms will be tested at release and on stability per EUP (when available) and/or USP and in-house specifications. Dosage form activation test (DFAT) is conducted utilizing IEM test system (ITS). The ITS is a test set-up designed to test the functionality of dosage forms integrated with IEM. The ITS test is performed by submerging an IEM enabled dose form into a phosphate buffered saline of

a set conductivity (7.0 mS/cm) at a set temperature (37°C), allowing the dose form to disintegrate and the IEM to discharge, and measuring the ensuing electrical signal with an adaptation of the proteus wearable sensor electronic module. The measurement data are acquired by the ITS software installed on a computer and transformed and displayed as meaningful IEM functionality data. A Distek brand dissolution system is used as the base platform for the ITS, along with custom fixtures and electronics.

Stability and Shelflife

When appropriate, prototypes will be manufactured from small scale development batches and packaged for stability testing at one or more of the following storage conditions and time points:

- Long term conditions at 25°C/60%RH: 0, 1, 3, 6, 9, 12 months
- Accelerated conditions at 40°C/75%RH: 1, 2, 3, 6 months
- Intermediate conditions at 30°C/65%RH: 1, 3, 6, 9, 12 months

Testing of samples stored at intermediate conditions will only be required when there is a significant change at the accelerated conditions. Tablets will be evaluated against their proposed specifications.

Primary batch stability program (if needed)

Three batches from each tablet strength will be manufactured at a scale of 100,000 units per batch. The tablets will be packaged in appropriate container closures. A total of 6 packaged lots will be placed on stability study under ICH conditions:

- Long term conditions at 25°C/60%RH: 0, 1, 3, 6, 9, 12, 18, 24, 36, 48 months
- Accelerated conditions at 40°C/75%RH: 1, 2, 3, 6 months
- Intermediate conditions at 30°C/65%RH: 1, 3, 6, 9, 12 months

Testing of samples stored at intermediate conditions will only be required when there is a significant change at the accelerated conditions.[20] Tablets will be evaluated against their final specifications.

Additional information provided by the applicant

The proteus ingestible sensor (IS) has received and renewed CE marking from BSI, Proteus' notified body, since August 2010 (CE # 559373). Data reviewed by BSI includes safety and toxicity reports as summarized in Proteus' briefing book submitted for the current request. The labeling for the BSI certified CE-marked product allows consumption of up to 30 IS per day with no limitation in duration of use.

Toxicity concerns of Proteus IS

Impurity identification and qualification thresholds have not been defined for ingestible medical devices. However, such thresholds are well established in the pharmaceutical industry. According to Attachment 1 of the guidance for industry Q3A impurities in new drug substances (July 2008), an impurity above 0.05% needs to be reported for the above mentioned metals. With respect to the ingestible sensor, only copper and magnesium were detected above the ICH Q3A's threshold.

As mentioned in the safety section of the Proteus briefing book, the highest (i.e., worst-case) mineral extraction was achieved after a full 72-hours under pH 1.2 conditions. Food generally passes out of the stomach to the higher-pH small intestine within minutes to a couple of hours. Our closest simulation of

20 Guidance for Industry, Q1A(R2) Stability Testing of New Drug substances and Products, November 2003, ICH revision 2

this physiologic reality is pH 1.2 for 4 hours adjusted to pH 7 for the remaining 68 hours. This method yielded a 49% reduction in the amount of copper extracted per IS, but the amount of magnesium extracted remained the same.

The extractable amount of magnesium is 5.63 µg/IEM which is less than 0.002% of the recommended dietary reference intake (DRI) for adults. For the maximum allowable intake of IS (30 IS/day), the magnesium intake amounts to less than 0.06% of the recommended daily DRI. Therefore, there is no safety concern for magnesium toxicity due to the extended use of IS.

The extractable amount of copper is 2.72 µg/IEM which is 0.1% of the permitted daily exposure (PDE) amounts for adults derived from EMEA/CHMP/SWP/4446/2000, Guideline on the Specification limits for residues of metal catalysts or metal reagents, 2008. For the maximum allowable intake of IS (30 IS/day), the copper intake amounts to 3.0% of the PDE. Therefore, there is no safety concern for copper toxicity due to the extended use of IS.

Both copper and magnesium are essential dietary minerals.

Pre-clinical reports

Proteus Digital Health assessed the potential effects of metal and mineral absorption in two animal studies using canines and rodents.

Canine study: in a toxicity study conducted by the Toxikon Corporation laboratory (Bedford, US) on beagle dogs, a group of 2 male and 2 female dogs received 24 IEMs per day, and a group of 2 male and 2 female dogs received 48 IEMs per day, for 7 consecutive days orally. Study showed no evidence of IS toxicity based upon clinical observation and GI tract histopathology. No change in either the presence or blood levels of inorganic materials between the treated group and control group were detected.

Rodent study: in a toxicity study conducted by the Charles River test facility (Edinburgh, UK) on sprague-dawley rats, five groups of 6 males and 6 females received extracts of the IEMs at 0.7, 2, 21, 214 or 2143 mg/kg/day for 14 consecutive days by oral gavage. The dosages assumed an IEM weight of 5 mg, human weight of 70 kg and animal weight of 300 g. Another group of 6 males and 6 females received the extract vehicle, simulated gastric and intestinal fluids. To act as controls, a further group of 6 males and 6 females received only water. The dose volume was 10 mL/kg. All animals received a necropsy on day 15 with a wide range of tissues collected for histological examination.

There were no signs indicative of systemic toxicity in any animal during the observation period. There were no differences in body weight and food consumption that were considered to be related to treatment and there were no eye changes that were considered to be related to treatment.

On day 14, there were no differences in hematology, coagulation or blood chemistry that were considered to be related to treatment. There were no organ weight differences and no necropsy or histological findings that were considered to be related to treatment.

In conclusion, after oral administrations of ingestible sensor extracts to rats, equivalent to a human dose of 30,000 ingestible sensors per day, there was no evidence of systemic toxicity in simulated gastric and intestinal fluid.

The only organic material detected above the ICH Q3A reporting threshold is the ethyl citrate which is an inactive ingredient and can be used in food with no limitation other than the cGMP (EU guide to good manufacturing practice and ICH question 7).

Additional information on Proteus technology data protection

Data originating with the proteus ingestible sensor is communicated conductively through the body to the patch or wearable sensor. This raw data is secure since detection requires direct skin contact and built-for-purpose amplifiers and decoders. The patch uploads data to a paired computer, typically a mobile phone or tablet, using the bluetooth protocol. Bluetooth links are secured using CCM (counter with cipher block chaining-message authentication code), a link layer encryption and authentication scheme built into bluetooth low energy (BLE), as defined in bluetooth Spec 4.0. In addition, bluetooth is a short range (10m) protocol and patch transmissions are intermittent and brief, making intentional interception difficult.

The core medical device software on the mobile phone or tablet stores and displays data locally. A user logs into this application using an email/password combination. Data is stored in an encrypted local MySQL database (SQLCipher 256-bit AES encryption).

The patient will typically elect to further uplink data from the phone to a cloud-based personal health record (PHR) under the patient's control. Data is communicated with the server using secure sockets layer (SSL) encryption. PHR data is encrypted at rest and in transit, and personally identifiable data is further segregated to decrease the likelihood of inadvertent or malicious disclosure of identifiable patient information.

The patient has the ability to enable sharing of PHR data with health care professionals, family members, or other individuals. The patient can reverse the data sharing arrangement at any time using the PHR interface.

To facilitate the access and review of data collected by patient-authorized physicians and other caregivers, it is important that the data and reports be transferred-to/accessible-from servers (cloud or physical) that integrate the data and generate reports for the users. To ensure patient privacy, Proteus is committed to complying with the data protection act of 1998.

In summary, the proteus technology is engineered to protect user information from interception or unintentional disclosure. Proteus has also taken appropriate business steps to further protect inappropriate access to personally identifying information.

Based on the co-ordinators' report, the scientific advice working party held that before opinion can be provided the applicant should discuss the following points:

Question 1

Qualified method

Does EMA agree to issue a favorable opinion considering the proteus technology as a "qualified method" for measuring adherence and associating relevant physiologic and behavioral parameters?

CHMP answer

The issue of low/undetectable medication adherence is considered of clinical relevance in several therapeuticl areas such as, for example, in cardiology, neurology and psychiatry. Indeed, when medication is co-ingested with the Ingestible Sensor (IS), such a technology directly confirms date and

time of ingestion and therefore qualifies as an accurate (around 97% accuracy) measure of medication adherence.

It is also an unmet need necessary to optimize clinical trial efficiency and evaluate the magnitude of the placebo effect (e.g. clinical trials for antidepressants).

During the discussion meeting the applicant gave examples of the intended clinical use for confirmation of therapeutic adherence outside the context of clinical trials for confirmation of adherence:

- in the management of uncontrolled cardio metabolic diseases (type 2 diabetes, hypertension, and/or hypercholesterolemia)
- for remote monitoring of medication ingestion by patients after their transition to convalescent care or to home following hospital discharge
- for confirming consistent utilization of high-cost treatments for diseases such as hepatitis C
- for assessment of a patient with Alzheimer's disease to aid in determining whether the patient remains capable of continuing to live alone.

For detecting associated relevant physiologic and behavioural parameters, such as activity, blood pressure and weight or other data useful in assessing therapeutic response, it is unclear if proteus technology shows advantages over peripheral mobile devices blue-tooth linked technologies (such as smart phones) without the need of an IEM. During the discussion meeting, the applicant clarified that the proteus software development (portal and app) allow for data integration from other peripherals.

The clinical development program presented for the scope of the qualification opinion request, included various types of utilization in different clinical settings. The EMITTER 3.0 and EMITTER 3.0 PSY are both feasibility studies aiming at validating the capabilities of the IS to monitor adherence and physiologic data gathering. The diagnostic value can be assumed, however it was not confirmed by clinical studies. The prospective evaluation of outcomes in patients with uncontrolled cardio metabolic diseases or patients with bipolar disorder or Alzheimer's disease, for instance, has not been performed and therefore a conclusive opinion referred to a specific diagnostic value, cannot be issued by the CHMP.

During the discussion meeting the company clarified that the rate of all AEs has been less than 1% in all subjects that have taken the IS so far. Disintegration and dissolution of the tablet will not be affected, although a risk assessment will be performed on a case by case basis.

If the IS is intended to be marketed with a specific medicinal product, a relevant benefit/risk assessment will be carried out at time of marketing authorization application depending on the dossier.

The applicant should be aware that the intended mode of administration of the oral medications reformulated as "digital medicines" in routine clinical practice will depend on the data presented in the MAA dossier.

In conclusion: The CHMP qualification opinion procedure is referred to the "acceptability of a specific use of a method, such as the use of a novel methodology or an imaging method in the context of research and development. The method can apply to non-clinical or to clinical studies, such as the use of a novel biomarker. The opinion is based on the assessment of data submitted to the Agency".

The CHMP agrees in considering the use of the proteus technology (IS) as a qualified method for measuring adherence in clinical trials.