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ORIGINAL RESEARCH

Cost-Effectiveness Analysis of a Prescription Digital Therapeutic in Type 2 Diabetes

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ABSTRACT

Introduction: BT-001 (AspyreRx™) prescription digital therapy, a form of personalized cognitive behavioral therapy, has demonstrated clinically meaningful and durable hemoglobin A1c reductions in patients with type 2 diabetes (T2D). The current study examined the cost-effectiveness of BT-001 plus standard of care (SoC) versus SoC alone in T2D over a lifetime horizon from a healthcare payer perspective.

Methods: We modeled the T2D pathway using an individual patient-level simulation; clinical data were sourced from the intention-to-treat subset of the BT-001 randomized clinical trial (RCT). SoC across both arms included the composition of oral and injectable treatments for T2D. Events were simulated using the United Kingdom Prospective Diabetes Study Outcomes Model 2 risk equation. A 3-month model cycle length was used in the first year, then annual model cycles were used in line with the original risk engine specifications. Patient characteristics informed event equations and Monte Carlo random sampling was used to assess the occurrence of events within each model cycle. Incidence of hypoglycemic events, drug discontinuation, costs, and health utilities and disutility values were sourced from the literature.

Results: From a payer perspective, BT-001 plus SoC versus SoC alone was dominant with a gain in quality-adjusted life years (QALYs) of 0.101 and cost savings of $7343 per patient over the lifetime horizon (i.e., more effective and less costly). BT-001 plus SoC was cost-effective at a willingness-to-pay of $100,000 per QALY (incremental net monetary benefit was $17,443). Savings with BT-001 were primarily driven by a reduction in drug acquisition costs. The reduction in hemoglobin A1c with BT-001 was associated with fewer T2D complications.

Conclusions: BT-001 plus SoC was estimated to dominate SoC alone over the lifetime horizon

This manuscript is based on the results of the BT-001 randomized controlled trial, which is detailed in Hsia et al. (Diabetes Care 45(12):2976–2981, 2022).

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from a payer perspective, suggesting that using BT-001 can empower patients to better manage their diabetes with the potential for lifelong advantages.

Keywords: BT-001; Cost-effectiveness analysis; Glycemic control; Prescription digital therapeutic; Type 2 diabetes; A1c

Key Summary Points

Why carry out this study?
BT-001 has been authorized by the US Food and Drug Administration as a prescription digital therapeutic that uses personalized cognitive behavioral therapy to treat patients with type 2 diabetes (T2D).
A randomized clinical trial for BT-001 demonstrated significant and durable hemoglobin A1c reductions in T2D. However, data on the impact of digital therapeutics in T2D on economic outcomes is limited.
It is important to assess both the clinical and economic outcomes of an intervention for decision-making.
What was learned from this study?
BT-001 plus standard of care (SoC) was anticipated to dominate SoC alone over the lifetime horizon from a payer perspective, suggesting that using BT-001 can empower patients to better manage their diabetes, with the potential to reduce long-term complications.
The incremental net monetary benefit of BT-001 plus SoC over SoC alone was $17,443 and considered cost-effective at a willingness-to-pay of $100,000 per quality-adjusted life year.
Savings with BT-001 were primarily driven by a reduction in drug acquisition costs.

INTRODUCTION

Type 2 diabetes (T2D) is a lifelong and chronic disease and is the most expensive chronic condition in the USA, with both significant direct medical costs and indirect impacts on productivity [1]. More than 28 million Americans have been diagnosed with T2D, and an additional eight million have undiagnosed T2D [2]. At least 45% of patients with T2D fail to achieve adequate glycemic control (hemoglobin A1c [HbA1c] < 7%) with the current standard of care (SoC) options resulting in high rates of morbidity and mortality [3]. There is an unmet need for a novel treatment approach as rates of diabetes continue to rise with a significant economic burden.

In-person cognitive behavioral therapy (CBT)-based interventions have been shown to improve glycemic control in patients with diabetes [4–6]. Internet-based CBT demonstrated equivalent efficacy to in-person CBT, suggesting it is a safe and effective alternative for mental health and psychiatric care applications [7]. Similarly, digital therapeutics may utilize CBT to prevent, manage, and treat chronic disease in a manner similar to the in-person CBT methods utilized for the same conditions, with the major advantage of being easily accessible through one's smartphone. Improvement in blood glucose levels was illustrated in various racial/ethnic populations with T2D following the use of a digital therapeutic platform [5, 8]. Digital therapeutics have the potential to improve access as they are inherently scalable and more broadly accessible to patients including those lacking transportation, residing in rural areas, and who need childcare or time off work to attend appointments [7].

BT-001 (AspyreRx^{TM}) is a prescription-only digital therapeutic (PDT) intended to provide CBT to patients 18 years or older with T2D in 3-month treatment cycles. The PDT treats T2D by targeting the behaviors related to achieving glycemic control in patients who are under the care of a physician and can be used adjunctively with pharmacological diabetes treatments [9]. The safety and efficacy of BT-001 with SoC compared to SoC alone were assessed in an

open-label, parallel-group randomized clinical trial (RCT) in 668 patients with T2D. This RCT for BT-001 demonstrated significant and durable HbA1c reductions [8].

It is important to assess both the clinical and economic outcomes of an intervention for decision-making. There is limited evidence on the economic outcomes of digital interventions in T2D. Only one study examined the economic impact of digital behavioral intervention in T2D and suggested that digital interventions may provide substantial cost savings [10]. To fill these knowledge gaps, this study examined the cost-effectiveness of BT-001 plus SoC versus SoC alone in T2D over a lifetime horizon from a healthcare payer perspective.

METHODS

Model Overview

The BT-001 model simulated the T2D pathway using an individual patient-level simulation structured to the specifications of the Institute for Clinical and Economic Review (ICER)'s T2D appraisals of semaglutide and tirzepatide [11, 12]. Patient-level simulations estimate outcomes for individual patients; outcomes are then averaged across a sufficiently large sample. Patient-level simulations have commonly been used in T2D [13], offering an advantage over traditional cohort-level modeling because they can account for heterogeneity in the characteristics of individuals and the progression of different diabetes-related complications. The model was built in Microsoft Excel and the model engine was implemented in Visual Basic for Applications.

Model Structure

The model structure is presented in Fig. 1. Patient-level data for BT-001 plus SoC versus SoC alone was sourced from the BT-001 RCT [14] and was used to assign patient characteristics at baseline. Patient characteristics included demographics (e.g., age, sex, ethnicity), patient behaviors (e.g., smoking status), disease history (e.g., myocardial infarction, stroke, blindness), and other clinical variables (e.g., HbA1c, systolic blood pressure [SBP], body mass index [BMI], low-density lipoprotein [LDL], duration of diabetes). Events were simulated using the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model 2 (OM2) risk equations, which are widely used in diabetes patient-level simulation models [15]. UKPDS OM2 comprises 17 risk equations including seven macrovascular T2D complications (covering congestive heart failure, ischemic heart disease, myocardial infarction, and stroke), six microvascular T2D complications (covering blindness, foot ulcers, amputation, and end-stage renal disease), and four death risk equations [15].

A 3-month model cycle length was used in the first year to capture BT-001-specific costs and clinical inputs, then annual model cycles were used in line with the original risk engine specifications (UKPDS OM2). In each model cycle, patient characteristics informed event equations that predicted the clinical outcomes. The probability of each event was converted to the cycle length and Monte Carlo random sampling was used to assess whether the patient experienced the event or not. Event history was recorded and patient characteristics were updated over time. The clinical experience of a patient was estimated in each cycle, until death was predicted or until the time horizon (lifetime). Outcomes were stored and the next patient was then simulated through the model. After every patient was simulated, results were aggregated as average cost and health outcomes.

Patient Population

The population in the model comprised 610 patients to match the intention-to-treat (ITT) population of the BT-001 RCT. The ITT population included participants who completed onboarding into the assigned treatment and had an HbA1c at the day 90 study time point [14], and was the primary source of demographic and patient history data (Table 1). Variables required for risk estimation that were not collected in the BT-001 RCT were derived

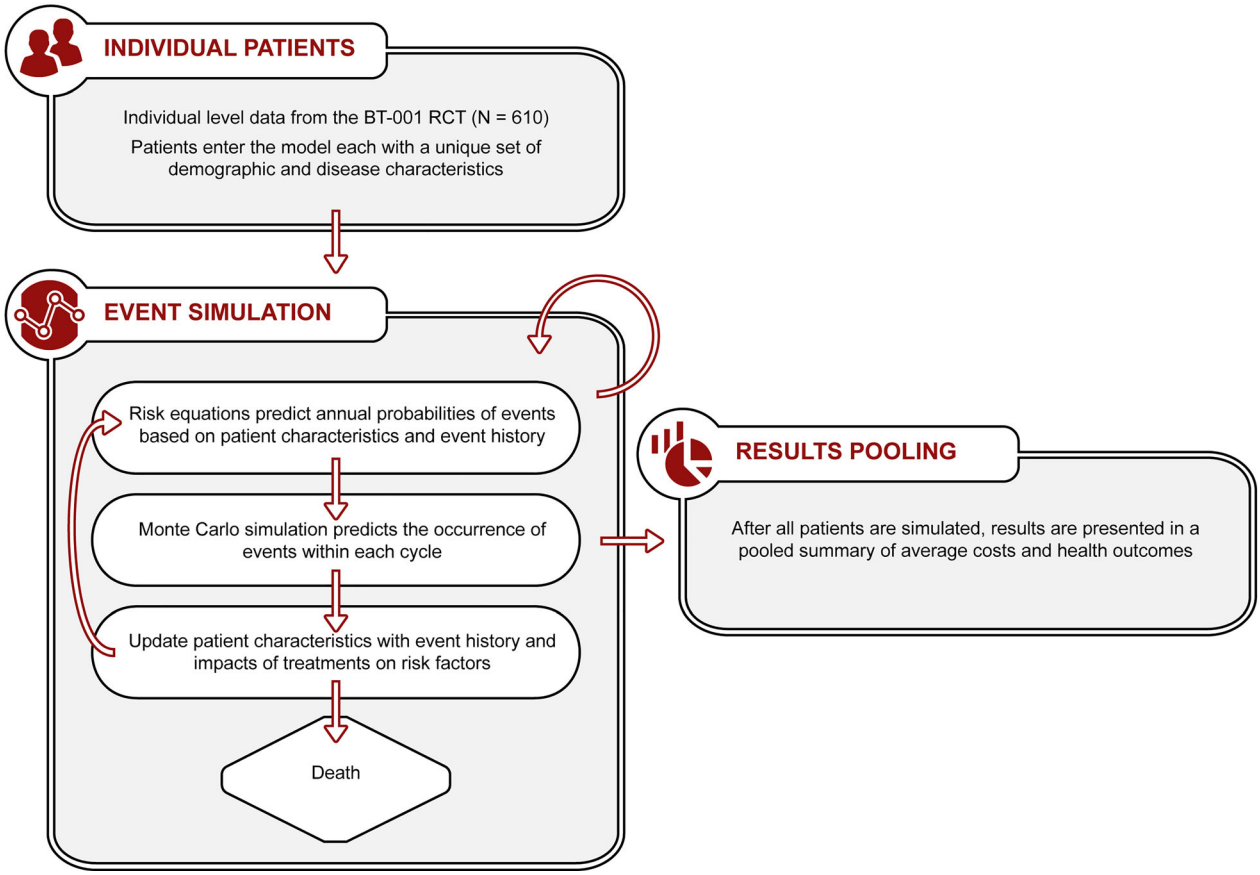

Fig. 1 Patient-level simulation structure. RCT, randomized controlled trial

from National Health and Nutrition Examination Survey (NHANES, 2017–2020) data, filtered to identify patients with T2D and HbA1c between 7% and 11% (n = 593), in line with the trial population [16].

Random sampling was used to assign patient histories of stroke and ischemic heart disease in the model, based on the proportions derived from NHANES. Patient-reported histories of congestive heart disease in NHANES data [16] were assumed to be the same as histories of ischemic heart disease (National Health Survey, 2020) [17]. Patients with albumin-to-creatinine ratio (ACR) of 30–300 mg/g were assumed to have microalbuminuria and patients with ACR > 300 mg/g to have macroalbuminuria [17, 18]. Mean values for continuous variables in NHANES were assigned to patients in the model for hemoglobin, white blood cell count, and creatinine [16]. All patients entering the model were assumed to have no prior history of blindness, foot ulcer(s), or hypoglycemia, similar to trial exclusion criteria.

This study does not directly involve any human participants, human data, and/or human material. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Treatment Strategies

The model evaluated two treatment strategies: BT-001 plus SoC versus SoC alone, aligning with the randomized treatment arms of the BT-001 RCT.

The SoC offered to both groups in the BT-001 RCT included health education on diet, exercise, and weight loss at the start of the trial.

Table 1 Patient demographics and patient history

Parameter	Mean (SE)	Source
Age at diagnosis (years)	47.16 (0.41)	BT-001 RCT [14]
Duration of diabetes (years)	11.00 (0.32)	BT-001 RCT [14]
Weight (kg)	99.54 (0.89)	BT-001 RCT [14]
Hemoglobin (g/dL)	13.66 (0.07)	NHANES 2017–2020 [16]
HbA1c (%)	8.14 (0.04)	BT-001 RCT [14]
HDL (mmol/L)	1.21 (0.01)	BT-001 RCT [14]
Heart rate/pulse	74.26 (0.39)	BT-001 RCT [14]
LDL (mmol/L)	2.38 (0.04)	BT-001 RCT [14]
SBP (mmHg)	126.48 (0.60)	BT-001 RCT [14]
eGFR (ml/min/1.73 m^2)	67.83 (0.43)	NHANES 2017–2020 [16]
White blood cell count	7765.60 (90.65)	NHANES 2017–2020 [16]
PHQ-9 score	2.51 (0.12)	BT-001 RCT [14]
Parameter	**Percent patients (%)**	
Sex (female)	56.72	BT-001 RCT [14]
Education (above college)	17.54	BT-001 RCT [14]
Race categories		
BRAVO		
Black	29.02	BT-001 RCT [14]
Hispanic	0.00	BT-001 RCT [14]
White	60.00	BT-001 RCT [14]
Other	10.98	BT-001 RCT [14]
UKPDS		
Afro-Caribbean	29.02	BT-001 RCT [14]
Asian Indian	4.26	BT-001 RCT [14]
Atrial fibrillation	1.80	BT-001 RCT [14]
Peripheral vascular disease	0.16	BT-001 RCT [14]
Current smoker	0.00	BT-001 RCT [14]
Micro/macro album	41.82	NHANES 2017–2020 [16] and NKF 2022 [18]

Table 1 continued

Patient history		
Parameter	**Percent patients (%)**	
Myocardial infarction	0.16	BT-001 RCT [14]
Stroke	9.11	NHANES 2017–2020 [16]
Congestive heart failure	0.66	BT-001 RCT [14] and NHS, 2020 [17]
Ischemic heart disease	11.97	NHANES 2017–2020 [16]
Angina	0.33	BT-001 RCT [14]
End-stage renal disease	0.33	BT-001 RCT [14]
Revascularization surgery	0.33	BT-001 RCT [14]
Blindness	0.00	ICER, 2019—Assumption [11]
Foot ulcer	0.00	ICER, 2019—Assumption [11]
Amputation	0.33	BT-001 RCT [14]
Neuropathy	2.79	BT-001 RCT [14]
Severe hypoglycemia	0.00	ICER, 2019—Assumption [11]
Symptomatic hypoglycemia	0.00	ICER, 2019—Assumption [11]

BRAVO Building, Relating, Assessing, and Validating Outcomes; *eGFR* estimated glomerular filtration rate; *HbA1c* hemoglobin A1c; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *PHQ-9* Patient Health Questionnaire-9; *RCT* randomized controlled trial; *SBP* systolic blood pressure; *UKPDS* United Kingdom Prospective Diabetes Study

HbA1c and biometric assessments, including blood pressure and weight measurements, were conducted every 3 months at scheduled medical visits, during which medications were adjusted on the basis of the collected values.

SoC was implemented in the model as the composition of oral and injectable treatments received by patients in the RCT. This aligns with the set of treatments to which patients with T2D are usually exposed, including metformin, sulfonylurea, dipeptidyl peptidase 4 (DPP4), glucagon-like peptide 1 (GLP-1), and insulin. The composition of treatments was set to vary by treatment arm over time, in line with the observed distributions in the BT-001 RCT (Supplementary Table 1). In the model, a patient was initiated onto an insulin regimen if their HbA1c exceeded a specific threshold, and could discontinue insulin if their HbA1c level dropped below a specific threshold.

All patients in the model were routed through both intervention and comparator arms, using common random numbers to allow treatments to be compared under "similar experimental conditions" [19]. This ensured that the same patient attributes were sampled across arms, and event risks were equal, ceteris paribus.

Clinical Inputs

Inputs for the BT-001 model were based on modeling precedent set by ICER [11, 12].

Treatment-Related Efficacy

Mean changes in HbA1c, weight, SBP, and Patient Health Questionnaire-9 (PHQ-9) at day 90 and day 180 from the BT-001 RCT were used to define short-term efficacy (Table 2) [14]. Beyond the first year, time-varying risk factors including HbA1c, SBP, LDL, body weight, smoking status, and occurrence of severe

hypoglycemia and symptomatic hypoglycemia were modeled using published equations [20].

Incidence of Hypoglycemia Events

Hypoglycemia events were evaluated in the model after year 1 and sourced from published literature [21]. Among patients not yet receiving insulin, the annual probability of severe and mild or moderate hypoglycemic events was 5% and 33%, respectively [21]. Among patients receiving insulin, the annual probability of severe and mild or moderate hypoglycemic events was 21% and 52%, respectively [21].

Depression

The UKPDS OM2 risk engine focuses on physical domains of health. Recognizing the impact of diabetes management on mental well-being, we have included depression as a considered complication in the simulation. In the first year of the model, PHQ-9 data from the BT-001 RCT were used to determine depression status. Beyond year 1, the annual probability of remaining depressed was 36%, calculated from the 4-month probability of 71% reported in the published literature [22]. The annual probability of becoming depressed was 1.20%, sourced from the published literature [23].

Drug Discontinuation

The annual drug discontinuation rate was 9.10% and the HbA1c threshold to commence insulin was greater than or equal to 8.50%. Estimates for both parameters were sourced from an ICER (2022) report on tirzepatide (EMPA-REG EXTEND trial) [12].

Cost Inputs

The model accounted for direct costs related to treatment, monitoring, adverse events, and resource utilization (Table 3). All costs were adjusted to 2022 US dollars and inflated using the Consumer Price Index [24], where required.

Drug Acquisition Costs

The total cost for BT-001 was estimated for 3 months and varied by course of treatment. It was assumed patients can only be on BT-001 in the first 6 months to match the trial data. Net annual insulin acquisition cost was derived from the Red Book [25] and adjusted using patient weight where necessary. Net annual total SoC costs for each drug class were derived on the basis of the wholesale acquisition cost of each drug within each class (from the Red Book [25]), dosing (sourced from prescribing information for each drug), and frequency of use in patients with T2D (from the BT-001 RCT [14]) (Supplementary Tables 1 and 2).

Table 2 Treatment efficacy of ITT sample from the BT-001 RCT

Change from baseline at 3 months*	BT-001 plus SoC Mean (SD)	SoC Mean (SD)
HbA1c	− 0.27 (1.11)	0.14 (1.23)
SBP (mmHg)	− 3.20 (15.47)	− 0.78 (14.21)
Weight (kg)	− 1.33 (5.43)	− 0.71 (7.28)
PHQ-9	− 0.10 (3.22)	0.41 (3.64)

HbA1c hemoglobin A1c; *ITT* intention-to-treat; *PHQ-9* Patient Health Questionnaire-9; *RCT* randomized controlled trial; *SBP* systolic blood pressure; *SD* standard deviation; *SoC* standard of care.

*6-month efficacy data on changes from baseline were also used to inform model inputs. These data are pending publication elsewhere and thus not presented within this table but are available upon request to the authors

Annual Monitoring Costs

Annual monitoring costs included self-monitoring costs for non-insulin medications and insulin. These costs were sourced from Laiteerapong et al.'s (2018) study that used data from the NHANES 2011–2012 for estimating self-monitoring costs among patients with T2D [21].

Adverse Event Costs

As per the ICER models of semaglutide and tirzepatide [11, 12], complication costs in the year of the event reflected acute care and any subsequent care provided in the first year. Complication costs in the years following the event reflected ongoing maintenance costs. The acute and ongoing annual costs for each adverse event were sourced from the published

Table 3 Cost inputs (2022 USD)

Parameter	Value		Source	
BT-001 Total cost per course (3 months)				
Initial course	$750		Data on file	
Cost of 2nd course	$525		Assumes 70% initiate second course	
Insulin acquisition cost				
Cost per unit	$0.27		Red Book, 2022 [25]	
Net annual SoC drug costs (excluding insulin)	**Baseline**	**Day 90**	**Day 180**	
BT-001 + SoC				
DPP4	$746	$735	$660	Derived
GLP-1	$1144	$1212	$1525	Derived
Meglitinides	$12	$12	$12	Derived
Metformin	$27	$27	$27	Derived
SGLT2	$1048	$1097	$1219	Derived
SU	$46	$46	$46	Derived
SoC				
DPP4	$520	$495	$438	Derived
GLP-1	$1695	$1962	$2091	Derived
Meglitinides	$11	$19	$19	Derived
Metformin	$27	$27	$27	Derived
SGLT2	$1199	$1297	$1406	Derived
SU	$59	$60	$60	Derived
Annual monitoring costs				
Self-monitoring costs: non-insulin	$94			Laiteerapong [21]
Self-monitoring costs: insulin	$289			Laiteerapong [21]
Adverse events				
One-off cost per event				
Congestive heart failure	$36,142			Yang [27]
Ischemic heart disease	$27,860			Ward [26]
Myocardial infarction	$52,415			Yang [27]
Stroke	$27,545			Yang [27]
Blindness	$15,052			Yang [27]

Table 3 continued

Net annual SoC drug costs (excluding insulin)	Baseline	Day 90	Day 180	
Foot ulcer	$2794			Ward [26]
Amputation	$11,767			Ward [26]
End-stage renal disease	$109,149			Yang [27]
Ongoing annual costs				
Congestive heart failure	$8180			Yang [27]
Ischemic heart disease	$2478			Ward [26]
Myocardial infarction	$9929			Yang [27]
Stroke	$5478			Yang [27]
Blindness	$2754			Yang [27]
Foot ulcer	$0			ICER [11]
Amputation	$0			ICER [11]
End-stage renal disease	$114,651			Yang [27]
Other health conditions cost per event				
Depression	$6375			Egede [28]
Resource utilization and costs				
Outpatient visit: non-insulin	100.00%			Assumption
Outpatient visit: insulin	100.00%			Assumption
Hypoglycemia episode requiring hospitalization	0.90%			Laiteerapong [21]
Hypoglycemia episode requiring ED visit	2.60%			Laiteerapong [21]
Hypoglycemia episode requiring glucagon injection	96.50%			Laiteerapong [21]
Resource utilization costs				
Outpatient visit: non-insulin	$602			Laiteerapong [21]
Outpatient visit: insulin	$659			Laiteerapong [21]
Hypoglycemia episode requiring hospitalization	$21,446			Ward [26]
Hypoglycemia episode requiring ED visit	$1706			Ward [26]
Hypoglycemia episode requiring glucagon injection	$229			Ward [26]

DPP4 dipeptidyl peptidase 4; *ED* emergency department; *GLP-1* glucagon-like peptide 1; *SGLT2* sodium-glucose cotransporter 2; *SoC* standard of care; *SU* sulfonylurea; *USD* United States dollars

literature [12, 26, 27]. Ward et al. (2014) used direct data analysis and a micro-costing approach to estimate the costs for an event leading to either a hospital admission or outpatient care and the post-acute care associated with managing macrovascular and microvascular complications, hypoglycemia episodes, and infections [26]. Data were obtained from multiple sources, including national physician and laboratory fee schedules, inpatient and emergency department databases, government reports, and literature [26]. Yang et al. (2020) estimated complication cost both in years of the first occurrence and subsequent years using longitudinal panel data from one of the largest claims databases in the USA for privately insured patients with T1D and T2D with 1 to 10 years of follow-up time [27].

Other Health Conditions

Depression-related costs were also considered in the model and were sourced from Egede et al.'s (2016) study that used data from the 2004–2011 Medical Expenditure Panel Survey (MEPS) to compute nationally representative estimates in adults with diabetes and comorbid depression [28].

Resource Utilization and Costs

Costs for resource utilization included annual outpatient visits (insulin and non-insulin) as well as hypoglycemia episodes requiring hospitalization, emergency department visit, or glucagon injection. Annual outpatient visits were assumed to be required in both arms and related costs were sourced from Laiteerapong et al. (2018) [21]. Estimates on the frequency of hypoglycemia episodes were sourced from Laiteerapong et al. (2018) [21] and related costs were sourced from Ward et al. (2014) [26].

Health Utilities

Utility values are used to represent the quality of life for patients in a specific health state, often ranging between 0 (death) and 1 (perfect health) [29, 30]. Utility values sourced from the published literature were consistent with those used in the ICER reviews (Table 4) [11, 12]. Baseline T2D utility was sourced from Shao et al.'s (2019) study that utilized data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial for generating utilities [31]. The ACCORD trial was one of the largest multicenter trials conducted in patients with T2D from the USA (n = 10,251).

Disutility values were applied additively for patient demographics, injection, and complications. The annual disutility of injection was sourced from Boye et al. (2011), a study on patients with T2D in Scotland that used a standard gamble approach to assess the utility of hypothetical health states and their current health state [32]. Disutility for patient demographics and macrovascular/microvascular complications was sourced from Shao et al. (2019) [31]. Disutility for microvascular complications including foot ulcer and amputation was sourced from Sullivan et al.'s (2016) study that mapped the European Quality of Life 5 Dimensions 3 Level Version (EQ-5D-3L) questionnaire responses from short-form 12 health survey responses in MEPS (2000–2011) data [33].

Model Outcomes

Model results included the occurrence of macrovascular and microvascular complications, severe hypoglycemia, and depression over a lifetime horizon for each treatment arm. Total costs, life years (LYs), and quality-adjusted life years (QALYs) were calculated to support the estimation of cost-effectiveness. Quality of life was modeled with QALYs using projected patient survival weighted by additive disutility values for each diabetes-related complication experienced in each model cycle. The willingness-to-pay threshold for incremental net monetary benefit (INMB) calculations was assumed to be $100,000 per QALY. Cost and health outcomes were discounted annually by 3% [34].

Sensitivity Analyses

In the base case of the model, the point estimate of each input was used to generate results. To

Table 4 Health utility and disutility values

Parameter	Estimate	Source
Baseline T2D utility	0.800	Shao [31]
Demographic disutility values		
Age at diagnosis (per year ≥ 52)	− 0.002	Shao [31]
Female	− 0.043	Shao [31]
Race (Ref = black)		Shao [31]
Hispanic	− 0.045	Shao [31]
Other	− 0.010	Shao, 2019 [31]
White	− 0.019	Shao [31]
Current smoker	− 0.054	Shao [31]
BMI (per unit ≥ 32 kg/m^2)	− 0.007	Shao [31]
Diabetes duration (per year)	− 0.005	Shao [31]
Annual disutility for injection	− 0.054	Boye [32]
Macrovascular complications (event)		
Congestive heart failure	− 0.089	Shao [31]
Ischemic heart disease	–	Assumption
Myocardial infarction	− 0.042	Shao [31]
Stroke	− 0.204	Shao [31]
Angina	− 0.010	Shao [31]
Microvascular complications (event)		
Blindness	–	Assumption
Foot ulcer	− 0.024	Sullivan [33]
Amputation	− 0.051	Sullivan [33]
Renal disease	–	Assumption
Revascularization	− 0.038	Shao [31]
Neuropathy	–	Assumption
Hypoglycemic event	− 0.036	Shao [31]
Depression	− 0.380	Wexler [35]
Macrovascular complications (history)		
Congestive heart failure	− 0.041	Shao [31]
Ischemic heart disease	− 0.016	Shao [31]
Myocardial infarction	− 0.011	Shao [31]
Stroke	− 0.101	Shao [31]
Angina	− 0.032	Shao [31]
Microvascular complications (history)		
Blindness	− 0.057	Shao [31]
Foot ulcer	–	Assumption
Amputation	–	Assumption
Renal disease	− 0.024	Shao [31]
Revascularization	− 0.016	Shao [31]
Neuropathy	− 0.066	Shao [31]
Hypoglycemia history	− 0.033	Shao [31]

BMI body mass index; *T2D* type 2 diabetes

account for the uncertainty around model parameters, and to test the robustness of the model, both one-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were conducted. The bounds for DSA were defined using 95% confidence intervals. When there was no uncertainty information for a given parameter, the standard error was assumed to be 10% of the mean estimate and used to estimate lower and upper bounds. In PSA, parameters were represented as distributions around the point estimate and the set of inputs was drawn by random sampling from each distribution. Beta distributions were used for inputs bounded by 0 and 1; gamma distributions were used for costs to account for their common skewness and to ensure non-negativity; and normal distributions were used for efficacy changes from baseline. Results were simulated 200 times per patient, after which cost-effectiveness outcomes had stabilized, resulting in 122,000 effective patients.

Scenario Analyses

In the base case of the model, a lifetime time horizon was assumed (which follows patients from the treatment initiation until age 100 or death); a 3% annual discount rate for costs and health outcomes was applied [34]; patient HbA1c after 1 year was calculated using the Building, Relating, Assessing, and Validating Outcomes (BRAVO) HbA1c time-varying equation [20]; the UKPDS OM2 risk equations were used for complication risks [15]; a healthcare payer perspective was assumed; and depression was modeled over the short term according to PHQ-9 data from the BT-001 RCT and over the long term using published probabilities [22, 23].

Six sets of scenarios were examined. Parameters varied for scenario analysis included (i) a different time horizon (1, 2, 5, 10, and 20 years); (ii) different discounting for costs and benefits (0% and 6%); (iii) considering HbA1c constant after 1 year; (iv) use of BRAVO equations for all complication risks; (v) modified societal perspective (productivity saving per incremental QALY of $5842) [12]; and (vi) exclusion of depression.

RESULTS

Base Case Analysis

Cost-effectiveness Outcomes

Over a lifetime horizon, BT-001 plus SoC was superior to SoC alone in terms of LYs and QALYs per patient (Table 5). Through its impact on HbA1c, BT-001 plus SoC provided 0.034 more LYs than SoC alone, and offered improvements in quality of life with an additional 0.101 QALYs. BT-001 plus SoC versus SoC alone resulted in a cost savings of $7343. At a willingness-to-pay of $100,000 per QALY, BT-001 plus SoC is considered cost-effective over SoC alone with an INMB of $17,443. At other commonly applied thresholds of $50,000 and $150,000 per QALY, the base case inputs yielded INMBs of $12,393 and $22,493, respectively.

Table 5 Base case cost-effectiveness outcomes (discounted, 2022 costs)

Parameter	SoC	BT-001 plus SoC	Incremental
Life years	15.455	15.489	0.034
Quality-adjusted life years	6.730	6.831	0.101
Cost	$258,491	$251,148	− $7343
Incremental cost-effectiveness ratio	–	–	Dominant
Incremental net monetary benefit[a]	–	–	$17,433

SoC standard of care

[a]The willingness-to-pay threshold for incremental net monetary benefit was assumed to be $100,000 per QALY

Total Costs

The costs were lower for BT-001 plus SoC ($251,148) versus SoC alone ($258,491) over the lifetime horizon (Table 6). Savings with BT-001 were primarily driven by a reduction in drug acquisition costs ($6230) followed by adverse event costs ($438).

Other Outcomes and Adverse Events

A greater proportion of patients experienced better outcomes with BT-001 plus SoC (Table 7). Incremental increases in good HbA1c control (< 8%) and SBP control (≤ 120 mm g) were 12.95% and 9.02%, respectively. The reduction in HbA1c for patients treated with BT-001 plus SoC was associated with fewer T2D macrovascular and microvascular complications (Table 8).

Sensitivity Analysis

DSA

Changes in efficacy (HbA1c and SBP) at 6 months were a key driver of cost-effectiveness (Fig. 2). The change in SoC treatment composition in either arm at the exit visit (day 180+)

Table 6 Base case total costs per patient (discounted, 2022 costs)

	SoC	BT-001 plus SoC	Incremental
Total acquisition costs	$84,291	$78,061	− $6230
BT-001 costs	$0	$1262	$1262
SoC treatment (non-insulin)	$26,362	$22,734	− $3627
SoC treatment (insulin)	$57,930	$54,065	− $3864
Self-monitoring costs	$4792	$4586	− $206
Non-insulin	$743	$744	$1
Insulin	$4049	$3842	− $207
Total adverse event costs	$154,922	$154,484	− $438
Macrovascular complications	$52,465	$51,487	− $977
Microvascular complications*	$102,457	$102,996	$539
Depression costs	$1713	$1676	− $36
Other resource use	$12,772	$12,340	− $432
Outpatient visit: non-insulin	$3956	$3960	$4
Outpatient visit: insulin	$7672	$7280	− $392
Hypoglycemia	$1144	$1100	− $45
Total costs	$258,491	$251,148	− $7343

SoC standard of care; *UKPDS OM2* United Kingdom Prospective Diabetes Study Outcomes Model 2
*Microvascular complication costs increase as a result of the UKPDS OM2 predictions for end-stage renal disease, which were driven by the extension in survival time

was also shown in DSA to be influential on results, as drug acquisition costs were impacted.

Table 7 Base case other outcomes

Outcome at 1 year	SoC %	BT-001 plus SoC %	Incremental %
Patients with good HbA1c control (< 8%)	54.75	67.70	12.95
Patients with poor HbA1c control (> 9%)	16.23	12.79	− 3.44
Patients with good SBP control (≤ 120 mmHg)	41.64	50.66	9.02

HbA1c hemoglobin A1c; *SBP* systolic blood pressure; *SoC* standard of care

BT-001 remained dominant (cost-saving and more effective) in all cases.

PSA

The average results generated in PSA aligned with the deterministic base case (Fig. 3). On average, BT-001 use was associated with incremental QALYs of 0.102 and savings of $7192. At the a priori willingness-to-pay threshold of $100,000 per QALY, BT-001 was cost-effective in 100% of iterations, and this held true at a $50,000 per QALY threshold. BT-001 was cost-saving in 98.0% of iterations. The INMB was stabilized beyond 150 iterations (Supplementary Fig. 1).

Scenario Analyses

At shorter time horizons of 1, 2, and 5 years, cost-effectiveness was less favorable compared with a longer time horizon (Fig. 4). The most favorable scenario was 0% discounting for costs and benefits, followed by assuming constant HbA1c after 1 year of follow-up, and then BRAVO risk equations.

Table 8 Adverse events and costs

	Costs			Event numbers		
	SoC	BT-001 plus SoC	Incremental	SoC %	BT-001 plus SoC %	Incremental %
Total adverse event costs	$154,922	$154,484	− $438			
Macrovascular complications	$52,465	$51,487	− $977			
Congestive heart failure	$17,212	$16,767	− $445	27.13	26.43	− 0.70
Ischemic heart disease	$8711	$8661	− $50	13.50	13.28	− 0.22
Myocardial infarction	$13,413	$13,181	− $232	17.15	16.85	− 0.30
Stroke	$13,129	$12,879	− $250	16.37	15.86	− 0.51
Microvascular complications	$102,457	$102,996	$539			
Blindness	$1071	$1046	− $25	3.83	3.73	− 0.10
Foot ulcer	$58	$56	− $2	2.90	2.81	− 0.09
Amputation	$458	$443	− $15	4.84	4.70	− 0.14
End-stage renal disease*	$100,870	$101,451	$581	16.17	16.26	0.09
Other						
Severe hypoglycemia	$1144	$1100	− $45	86.18	85.07	− 1.11
Depression*	$1713	$1676	− $36	25.34	25.40	0.06

ESRD end-stage renal disease; *SoC* standard of care
*Increases in ESRD and depression rates are driven solely by the extension in survival time

DISCUSSION

Through its impact on HbA1c and other variables, BT-001 was associated with greater LYs, QALYs, and lower costs over a lifetime horizon. BT-001 plus SoC was shown to be more effective and less costly than SoC alone. Savings with BT-001 were primarily driven by a reduction in drug acquisition costs of SoC (insulin and non-insulin) treatments. While other cost categories were significant contributors, the higher impact of changes in acquisition costs is largely due to the inherent expensiveness of certain T2D medications, which were mitigated by the implementation of BT-001. BT-001 provided better HbA1c and SBP control, delaying the escalation to insulin. T2D complications were also reduced leading to lower costs associated with adverse events.

The cost-effectiveness of prescription digital therapy in T2D has been examined in a limited number of studies [10]. A decision analytic model from a US commercial payer perspective was used to examine the economic impact of digital behavioral therapy in T2D and hypertension [10]. Over a 3-year time horizon, the average health resource utilization savings ranged from $97 to $145 per patient per month. Using a willingness-to-pay threshold of $100,000/QALY, digital therapy in T2D was estimated to be cost-effective at total 3-year program costs of $8348. These estimates are in line with our findings with lifetime cost savings of $7343 following the usage of BT-001. Both,

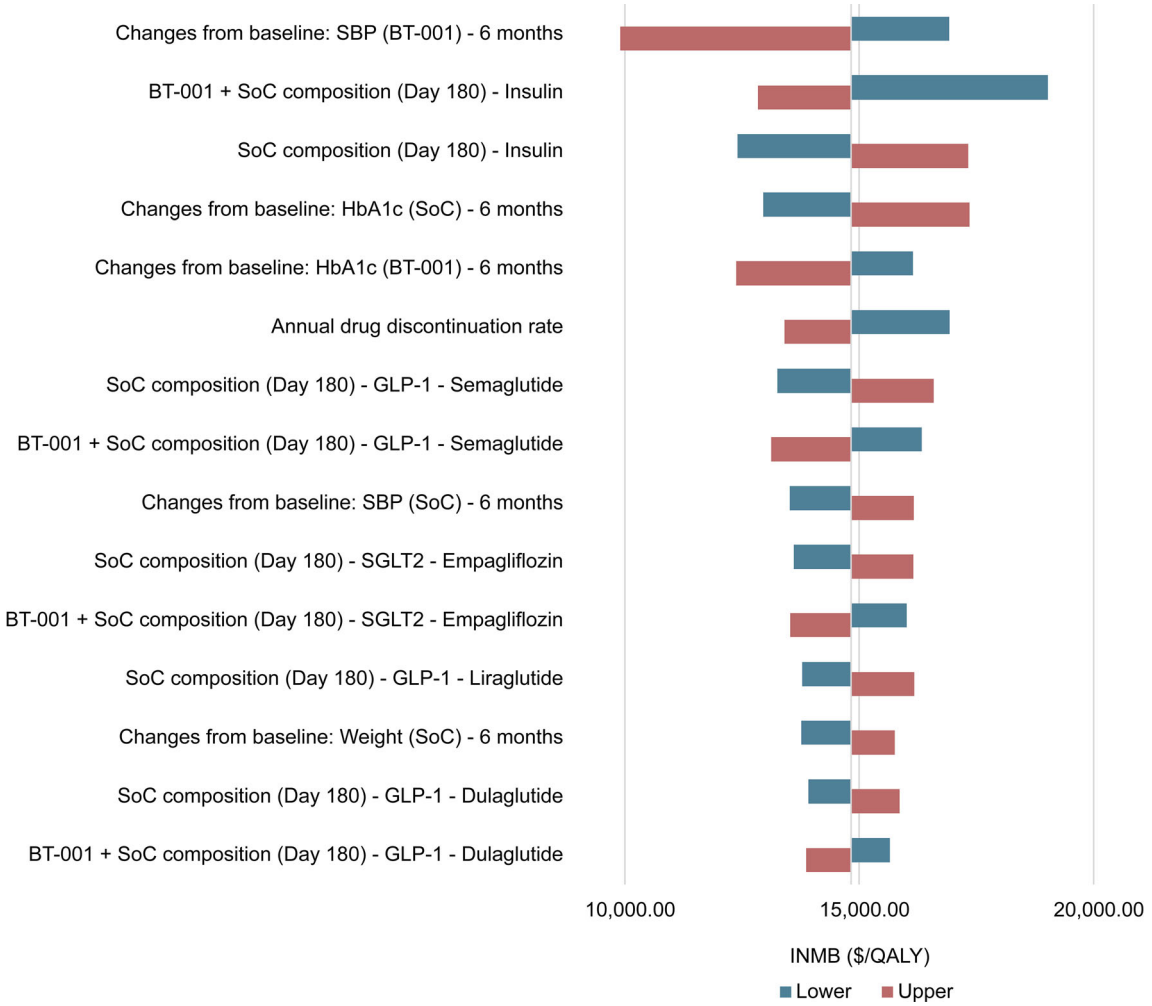

Fig. 2 Deterministic sensitivity analysis tornado plot. *GLP-1* glucagon-like peptide 1; *HbA1c* hemoglobin A1c; *INMB* incremental net monetary benefit; *QALY* quality-adjusted life years; *SBP* systolic blood pressure; *SGLT2* sodium-glucose cotransporter 2; *SoC* standard of care. Note: Deterministic sensitivity analysis was performed using one iteration per patient because of its computational intensity, and so results provide an indication of directionality, rather than a full assessment

the study and our findings, describe the potential reduction in medication costs to be the primary driver in cost savings [10].

Changes in efficacy at 6 months and changes in treatment composition at the exit visit were also key drivers of cost-effectiveness in this model. At 1 year, a greater proportion of patients experienced better SBP outcomes with BT-001 (50.7% vs 41.6%), an important outcome for payers. Furthermore, BT-001 remained dominant in several sensitivity analyses. At shorter time horizons of 1, 2, and 5 years, there was less opportunity for the lifetime advantages of BT-001 to occur and treatment was less cost-effective.

The model included all treatment costs associated with each drug regimen, including acquisition costs for SoC, cyclic costs of BT-001, monitoring costs, resource use costs, and all costs associated with diabetes-related complications experienced in each model cycle. The increases in depression and end-stage renal disease (ESRD; microvascular complication) rates for the BT-001 plus SoC arm were driven solely by the extension in survival time. The

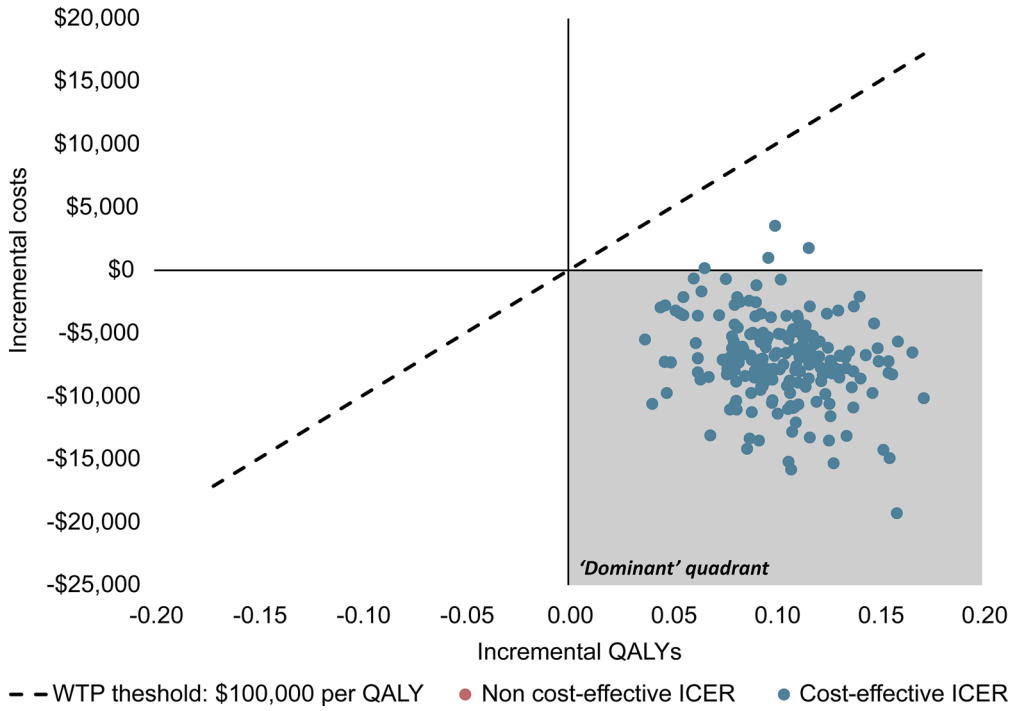

Fig. 3 Incremental cost-effectiveness plane. *ICER* incremental cost-effectiveness ratio; *QALY* quality-adjusted life years; *WTP* willingness-to-pay

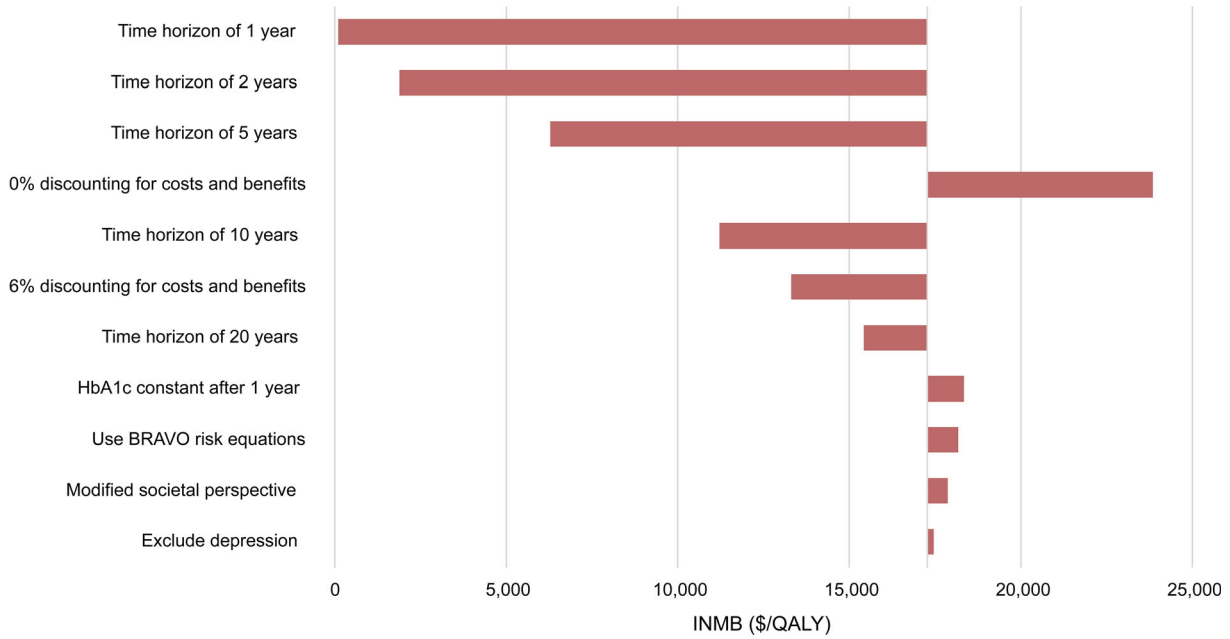

Fig. 4 Scenario analyses tornado plot. *BRAVO* Building, Relating, Assessing, and Validating Outcomes; *HbA1c* hemoglobin A1c; *INMB* incremental net monetary benefit; *QALY* quality-adjusted life years. Note: a willingness-to-pay threshold of $100,000 per QALY was assumed

associated costs only increased for ESRD by $581.

This cost-effectiveness analysis follows the modeling precedent established by ICER [11, 12]. Digital therapeutics using behavioral interventions have the potential to improve access owing to their inherent scalability and reach beyond physical location and scheduling constraints. App-based healthcare can empower patients to develop healthy behaviors leading to better adherence and lower costs. A recent study examined the impact of a digital Diabetes Prevention Program among 2027 adult participants and demonstrated a reduction in all-cause health care spending of USD 1169 per participant owing to fewer hospital admissions and shorter lengths of stay [36]. App-based healthcare interventions have demonstrated cost-effectiveness in T2D and other therapeutic areas.

At the time of writing, BT-001 has not yet been studied beyond 180 days. The instructions for use indicate that a second 90-day treatment could be prescribed and is likely to offer further benefit to the patient. It should be acknowledged that if further courses are administered in clinical practice beyond 180 days, additional acquisition costs for BT-001 would be incurred. As BT-001 promotes long-lasting changes in the underlying core beliefs related to diabetes management behaviors, it is plausible that further treatment offers further benefits to the patient, which could offset this additional cost.

The results from this study should be interpreted carefully with the following limitations in mind. First, only short-term data was available from the BT-001 RCT and may have resulted in under- or overestimation of long-term clinical and economic outcomes. Second, clinical data from the BT-001 RCT may limit the application of these findings to real-world clinical practice. Patients in the BT-001 RCT were well treated (e.g., baseline SBP was near normal, very high use of background therapy) and the SoC treatment may have underestimated effect sizes by introducing a degree of glycemic equipoise not likely observed in the real world. However, the BT-001 RCT had many real-world elements. Most notably the ability for medications to be adjusted from day 1, open-label draws of HbA1c, and no compensation was provided for use of cognitive behavioral therapy (CBT) features. On balance, the use of randomized controlled evidence reduces the potential for selection bias (differences in confounding factors at baseline) associated with real-world evidence. A third limitation is that medical history was self-reported, which may lead to underestimation of the prevalence of baseline comorbidities. The model had a reliance on certain assumptions; however, sensitivity analyses were conducted to overcome this limitation and test uncertainty with specific parameters. Finally, the complexity of T2D renders it challenging to make reliable predictions, although the model considered patient characteristics, comorbidities, and risk equations to account for this heterogeneity.

CONCLUSIONS

This model found that BT-001 plus SoC dominated over SoC alone over the lifetime horizon from a payer perspective, suggesting that BT-001 can empower patients to better manage their diabetes, with the potential for lifelong advantages.

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Data Availability. Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Niall J. Davison and Sarah Medland were contracted consultants of Maple Health Group, who were paid for work related to the model and manuscript by the study sponsor (Better Therapeutics). Sarah Medland's current affiliation is York Health Economics Consortium, United Kingdom. Nicole L. Guthrie and Mark A. Berman were employees of Better Therapeutics at the time of the study and received compensation in the form of equity units and stock options. Paul Lupinacci was a contracted consultant of the study sponsor (Better Therapeutics) and was paid for work related to the manuscript. Robert J. Nordyke has no conflicts of interest to declare.

Ethical Approval. This study does not directly involve any human participants, human data, and/or human material. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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