Quantifying Preferences for Urea Cycle Disorder Treatments Using a Discrete-Choice Experiment

Josiah Edelblut[1], Jeffrey R. Skaar[1], John Hilton[2], Matthew Seibt[2], Kyle Martin[1], Nandini Hadker[1], Adrian Quartel[2], Robert D. Steiner[3]

[1]Trinity Life Sciences, Waltham, MA, USA; [2]Acer Therapeutics, Newton, MA, USA; [3]Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Background

- Urea cycle disorders (UCDs) are rare metabolic disorders that impact approximately 1,100 patients in the United States (US) [1,2]

- In patients with UCDs, the inability to convert toxic ammonia to urea for excretion results from a missing or dysfunctional protein in the urea cycle[3]

- Elevated levels of ammonia in patients with UCDs can lead to hyperammonemic crises (HACs), central nervous system toxicity, brain damage, and death[1,4-6]

- Nitrogen-binding medications, such as sodium phenylbutyrate or glycerol phenylbutyrate, can be efficacious in the treatment of UCDs if patients are adherent to their prescribed treatment[1,7]

- However, 25% of HACs in patients with UCDs may be precipitated by a lack of adherence to medications and/or diet, and existing nitrogen-binding medications may be associated with attributes that negatively impact adherence[8]

Objective

- This study sought to quantify the attributes of nitrogen-binding medications for UCDs that may influence overall prescription and patient adherence using a discrete choice experiment (DCE)

Methods

- This study used a web-based, quantitative survey study design with DCE methodology to capture the perspectives of healthcare providers (HCPs; board-certified physicians and dieticians) for patients with UCDs

  - US-based HCP respondents were eligible to participate if they had been in medical practice 3 to 35 years; spent at least 50% of their time in direct patient care; managed/treated at least 3 unique patients with UCDs in the last 5 years, with at least 1 patient prescribed chronic pharmaceutical management; had primary treatment selection decision-making authority or provided guidance and influenced decisions around treatment selection; and have used currently-approved nitrogen-binding medications to treat patients with UCDs (i.e., sodium phenylbutyrate or glycerol phenylbutyrate)

- A DCE with an orthogonal design was developed to assess pre-defined treatment attributes and levels of each attribute

  - Attributes included: route of administration, taste/odor, preparation instructions, packaging, measurement (pre-measured vs not pre-measured medication), and weight use restrictions [treatment indicated for patients over a certain weight (>10kg, >20kg) or is indicated for patients of all weights]

  - Respondents were asked to assume that all hypothetical treatment profile sets had a similar efficacy, mechanism of action, insurance coverage, out of pocket costs for patients, and similar rates and types of adverse events in randomized clinical trials

- Respondents were presented with a series of hypothetical treatment profile sets that described treatment attributes and were then asked to select the profile they preferred overall and for patient adherence/compliance from 16 choice sets, with 3 hypothetical product profiles presented in each choice set

- All data were blinded and de-identified, and the study received exemption from Institutional Review Board (IRB) oversight from Advarra, an independent IRB (Advarra, Columbia, MD)

Results

	Dietitians (n=26)	Physicians (n=25)	All HCPs (n=51)
Gender – % (n)			
Male	12% (3)	76% (19)	43% (22)
Female	77% (20)	24% (6)	51% (26)
Prefer not to answer	12% (3)	0% (0)	6% (3)
Age – % (n)			
30- 39	15% (4)	12% (3)	14% (7)
40-49	31% (8)	36% (9)	33% (17)
50-59	27% (7)	12% (3)	20% (10)
60-69	12% (3)	40% (10)	25% (13)
70+	0% (0)	0% (0)	0% (0)
Prefer not to answer	15% (4)	0% (0)	8% (4)
Practice location – % (n)			
Urban	50% (13)	52% (13)	51% (26)
Suburban	42% (11)	44% (11)	43% (22)
Rural	8% (2)	4% (1)	6% (3)
Insurance makeup, practice level – Mean (SD)			
Commercial/ employer-based	45.0% (25.2%)	61.7% (21.6%)	53.2% (24.8%)
Government	52.3% (24.9%)	37.5% (21.7%)	24.4% (24.4%)
Other	2.7% (5.8)	0.8% (1.9%)	1.8% (4.4%)
Primary Practice setting – % (n)			
Academic / teaching hospital	50% (13)	40% (10)	45% (23)
Center of Excellence	0% (0)	4% (1)	2% (1)
Office-based practice / outpatient clinic	35% (9)	52% (13)	43% (22)
Community Hospital	15% (4)	4% (1)	10% (5)
Time Providing Direct Patient Care - Mean (SD)	80% (13.7)	90% (11.0)	85% (13.2)
Management of UCD patients [number of patients - Mean (SD)]			
Acute management	11.2 (11.9)	8.4 (12.3)	9.8 (12.1)
Chronic management	20.9 (20.7)	13.1 (13.4)	17.1 (17.8)

Table 1. Health Care Provider Demographics and Practice Setting Characteristics. *HCP = Health Care Provider, MDs= Doctor of Medicine, NPs= Nurse Practitioners, PAs= Physician Assistants*

Attribute	Level 1	Level 2	Level 3	Level 4
1. Taste and Odor	Taste- and odor-masked (neutral taste/smell)	Not taste- or odor-masked (strong odor and taste)	Product stored in a plastic bottle	
2. Packaging	Product contained in pocket-sized single use foil sachets, packaged as a monthly kit with 30-day supply (90 doses)	Product stored in a kit containing-multi-use glass 25mL bottle		
3. Measurement	Patient not required to measure dose	Patient measures appropriate dose		
4. Preparation Instructions	Patients mix with water & drink or mix with pH neutral food	Patient takes product from container using a single use, discardable syringe via connector cap (Patients must use ~3 syringes per day)	Patient mixes contents with food or water (may need to consume multiple cups of water) using a reusable measuring spoon (3.2g or 9.1g scoop)	Patient takes contents with water
5. Route of Administration	Powder to suspend in water and drink. Product can be administered via gastronomy tube	Oral liquid to squirt into mouth. Product can be administered via gastronomy tube	Tablet (Patients takes approximately one tablet per kilogram body weight per day (min. 20 & max. 40 tablets/day)). Product can **NOT** be administered via gastronomy tube (A)	
6. Weight Requirement*	Indicated for patients weighing 10kg or more	Indicated for patients of all weights	Not recommended for patients weighing less than 20 kg	

Figure 1. Discrete Choice Experiment Grid. The attributes and attribute levels depicted in the grid were shown to respondents in the DCE to assess overall preference for treatment and preference for adherence and compliance. A = Attribute 4, Level 2 not shown with Attribute 5, Level 3 due to incompatibility (i.e., syringe and tablets); * Weight requirement describes restrictions for product use based on patient weight
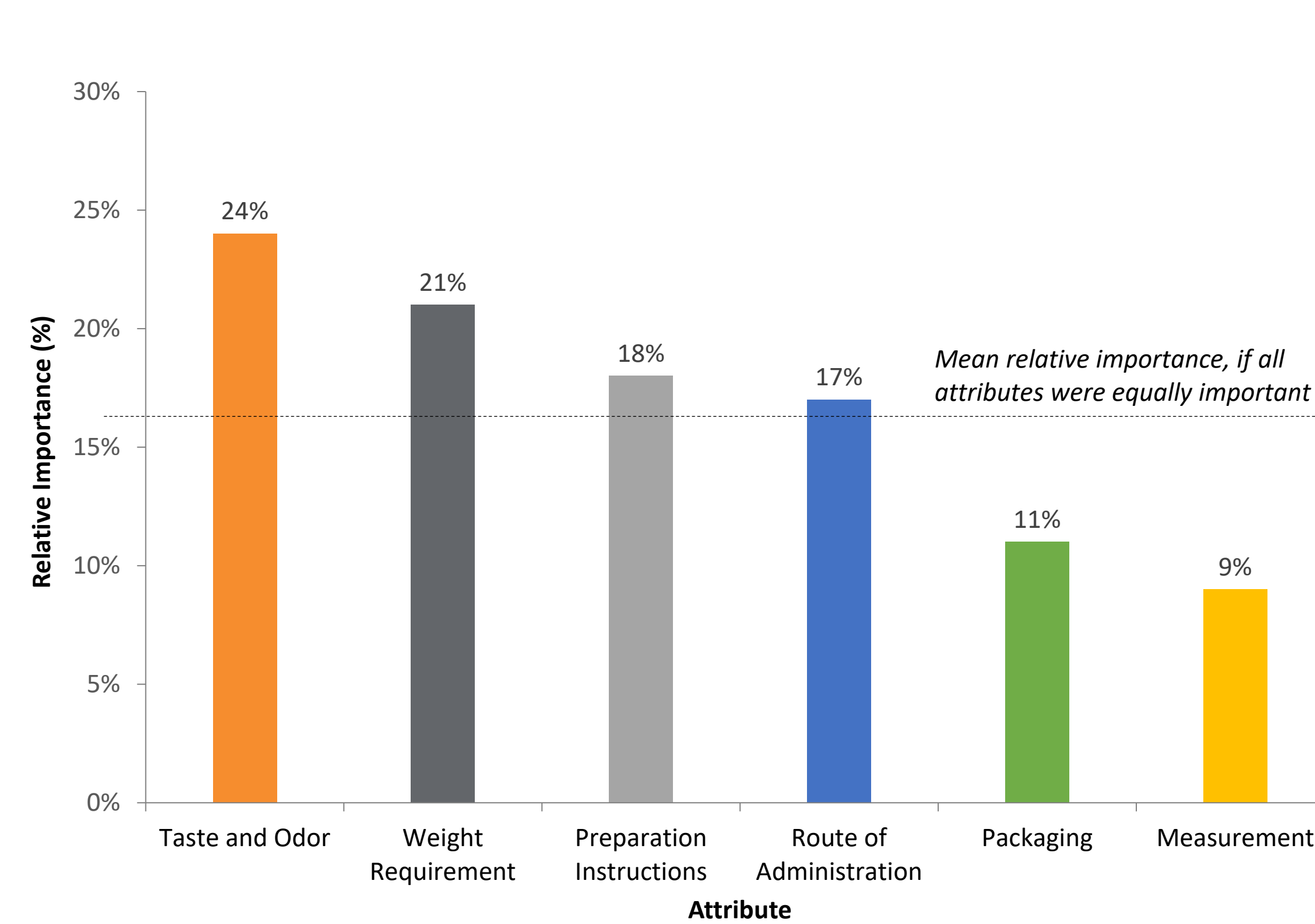

Figure 2. Drivers of Product Overall Preference. The bar graph shows the results from the DCE for overall preference by attribute. The dotted line represents the level anticipated if all attributes were of equal importance (i.e., 100 divided by the number of attributes).

Figure 3. Drivers of Product Adherence and Compliance. The bar graph shows the results from the DCE for adherence and compliance by attribute. The dotted line represents the level anticipated if all attributes were of equal importance (i.e., 100 divided by the number of attributes).
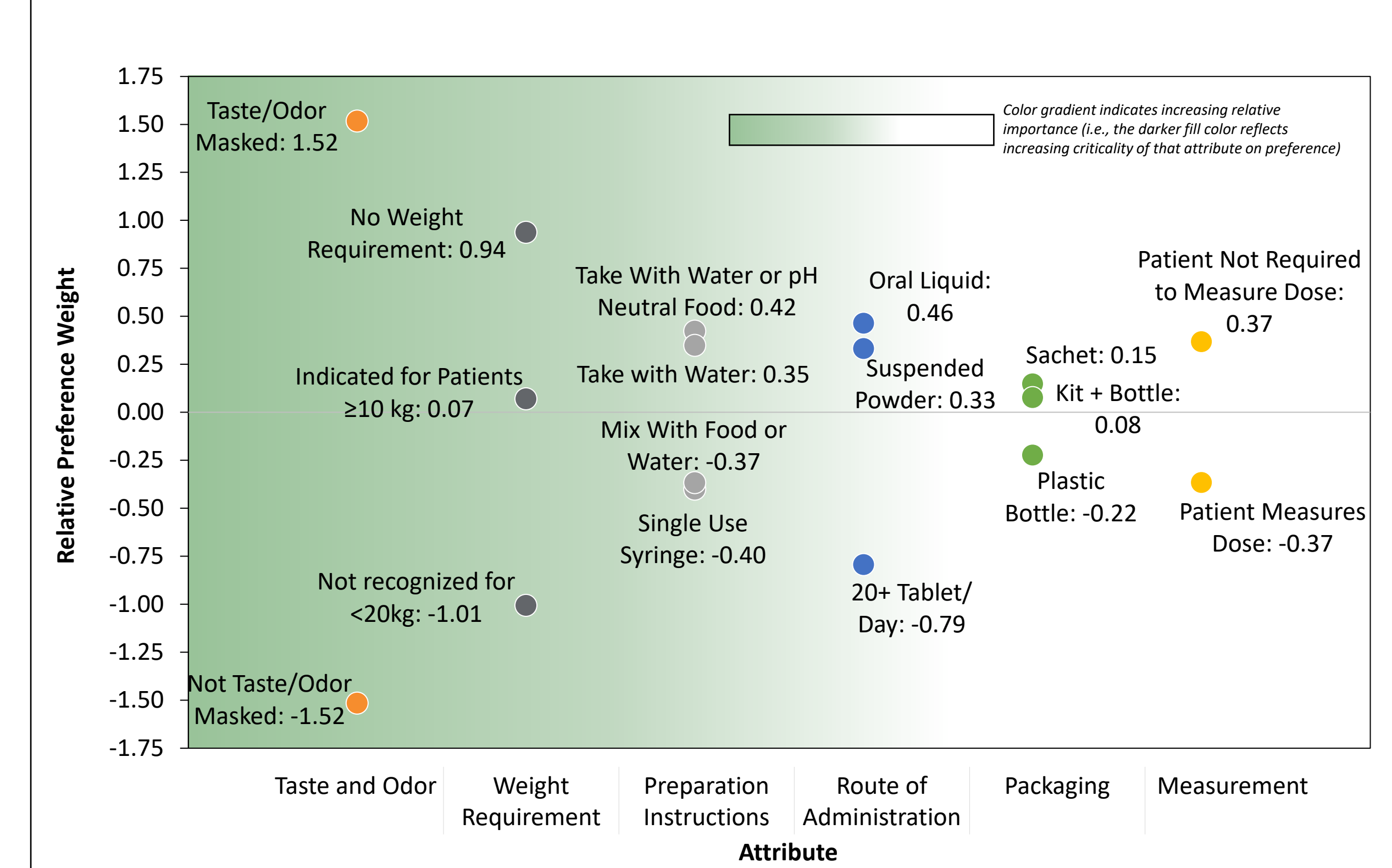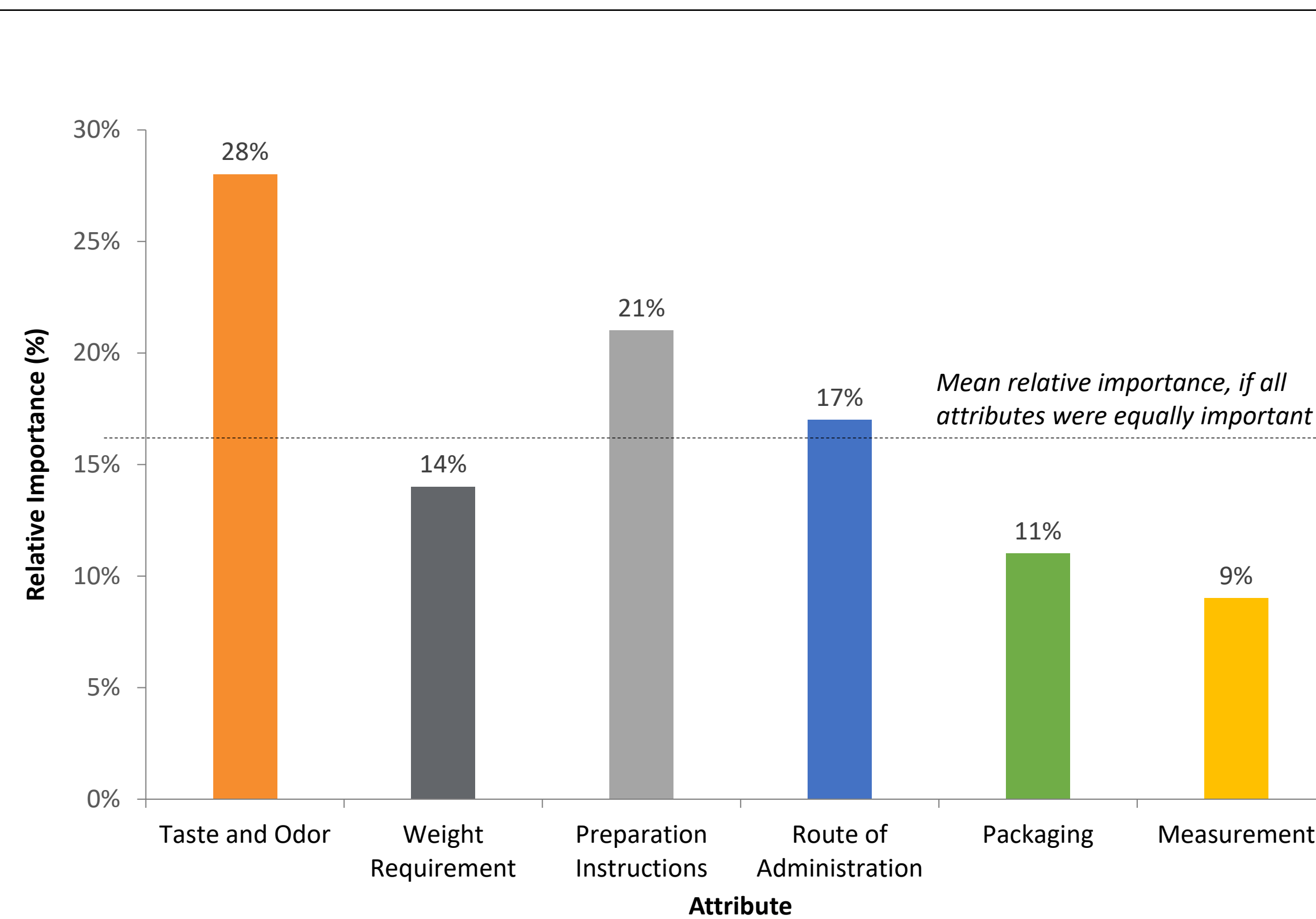

Figure 4. Mean Relative Preference Weights for Overall Treatment Preference. The chart shows the results from the DCE for levels within each attribute for overall preference. Attributes are found on along the x-axis, relative preference weights are on the y-axis, and colored dots show relative preference weights for specific attribute levels. The green gradient background reflects the overall importance of the attributes, with attributes ordered from most important to least important, left to right
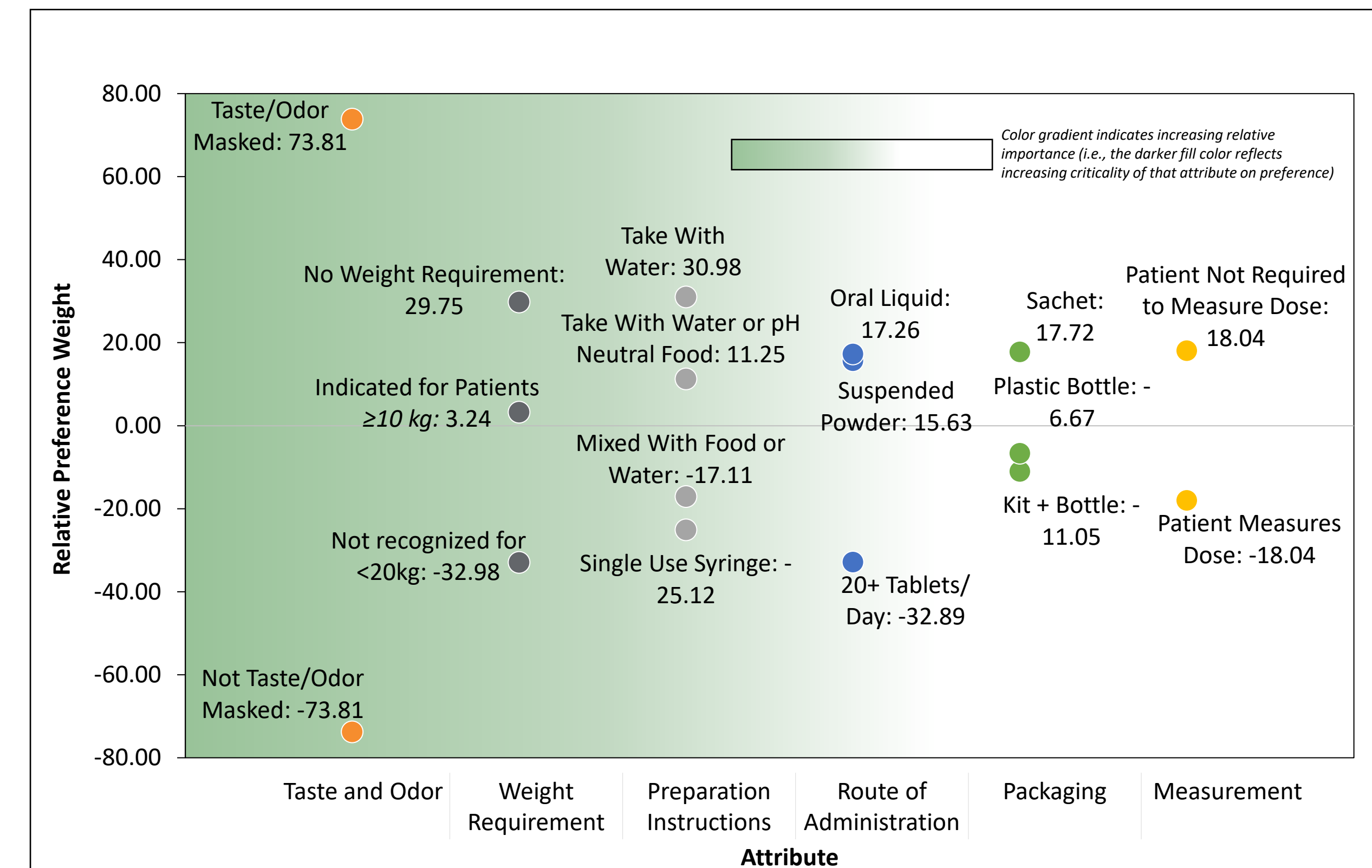

Figure 5. Mean Relative Preference Weights for Treatment Adherence and Compliance. The chart shows the results from the DCE for levels within each attribute for treatment adherence and compliance. Attributes are found on along the x-axis, relative preference weights are on the y-axis, and colored dots show relative preference weights for specific attribute levels. The green gradient background reflects the overall importance of the attributes, with attributes ordered from most important to least important, left to right

Limitations

- The results of this study may not be generalizable due to the small sample size associated with a rare genetic disease and the use of convenience sampling to recruit respondents

- The online survey methodology also relies upon self-reported data from health care providers

- Responses relating to patient adherence, treatment experience, and perceptions of UCD treatment were subject to recall bias

- The DCE required health care providers to consider the use of hypothetical products, and these profiles cannot fully reflect real-word products

- The study limited its examination to nitrogen-binding medications for UCDs, so preferences for non-pharmacologic treatments, such as low-protein diet and amino acid supplementation were not explicitly examined

Conclusions

- Taste/odor was the most important attribute when overall preference for both prescribing and for patient adherence and compliance was ascertained

  - Preparation instructions and route of administration were also considered important attributes for both prescribing and for patient adherence and compliance

- Among the levels of the taste/odor attribute, taste/odor masking was preferred for both overall preference for prescribing and patient adherence and compliance

- Masking taste/odor and Preparation Instructions were considered the two most important product attributes for optimizing nitrogen-binding medications for UCD treatment to facilitate and encourage increased patient adherence

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