Development and evaluation of Gaucher disease-specific patient-reported outcome measurement in Japan

Midori Ono,[1] **Shinichi Noto**,[2] **Aya Narita**,[3] **Yuta Koto**,[4] **Masafumi Okada**,[5] **Rieko Sagara**,[1] **Norio Sakai**[6]

[1]Japan Medical Office, Takeda Pharmaceutical Company Limited, Tokyo, Japan; [2]Niigata Univ. of Health and Welfare, Niigata, Japan;
[3]Division of Child Neurology, Institute of Neurological Science, Tottori University Faculty of Medicine, Tottori, Japan;
[4]School of Nursing, Faculty of Health Science, Osaka Aoyama University, Osaka, Japan; [5]IQVIA Solutions Japan K.K. Real World Evidence Solutions, HEOR, Tokyo, Japan;
[6]Child Healthcare and Genetic Science Laboratory, Division of Health Sciences, Osaka University Graduate School of Medicine, Osaka, Japan

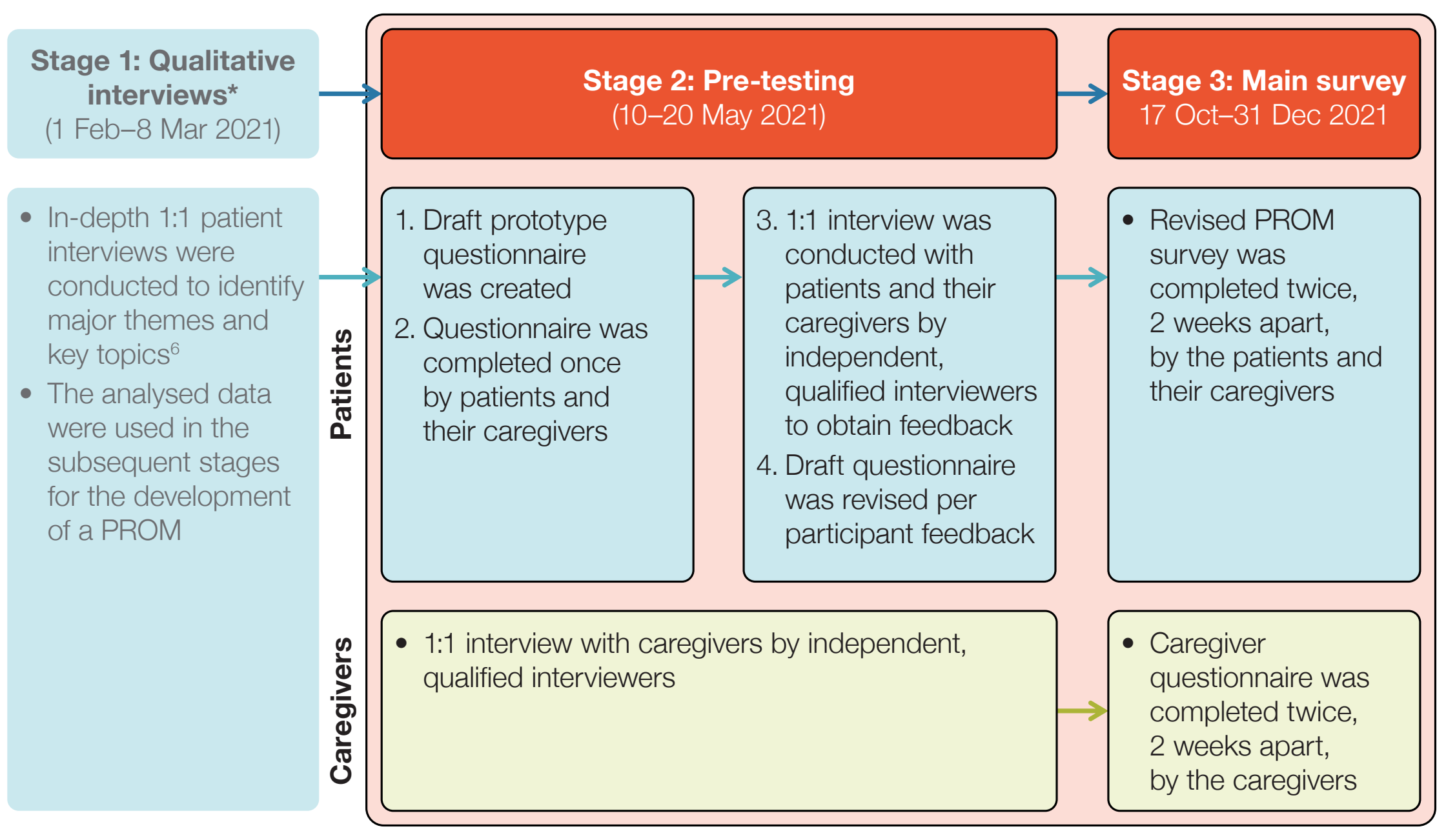
BACKGROUND

- Gaucher disease (GD) is a rare autosomal recessive lysosomal storage disorder categorised into 3 phenotypes: type 1 (non-neuronopathic GD) and types 2 and 3 (neuronopathic GD [nGD]).[1]
- The composition of these phenotypes differs by ethnicity; most Japanese patients have nGD, whereas most non-Japanese patients have type 1 GD.[2,3]
- Although a patient-reported outcome measure (PROM) for type 1 GD has been developed previously,[4] this is not applicable for nGD.
- Therefore, there is currently no PROM that covers all GD types.
- Following a qualitative analysis of interviews with Japanese patients with nGD,[5] we report here the subsequent development and evaluation of the combined type 1 GD questionnaire[4] and the nGD-specific items.
- We also assessed the burden of caregivers of patients with GD in Japan using previously validated caregiver questionnaires.

METHODS

- This was a cross-sectional observational study conducted in Japan comprising 3 stages (UMIN000042872).
  - Here we report the results of Stages 2 and 3.

Figure 1. Study flow



Stage 1: Qualitative interviews*
(1 Feb–8 Mar 2021)

- In-depth 1:1 patient interviews were conducted to identify major themes and key topics[6]
- The analysed data were used in the subsequent stages for the development of a PROM

Stage 2: Pre-testing
(10–20 May 2021)

Stage 3: Main survey
17 Oct–31 Dec 2021

Patients

1. Draft prototype questionnaire was created
2. Questionnaire was completed once by patients and their caregivers
3. 1:1 interview was conducted with patients and their caregivers by independent, qualified interviewers to obtain feedback
4. Draft questionnaire was revised per participant feedback

- Revised PROM survey was completed twice, 2 weeks apart, by the patients and their caregivers

Caregivers

- 1:1 interview with caregivers by independent, qualified interviewers
- Caregiver questionnaire was completed twice, 2 weeks apart, by the caregivers

Abbreviation: PROM, patient-reported outcome measure.
*The results of this stage are reported at Poster #PCR10.

Study population

Patients

- Included patients with a confirmed type 1, 2 or 3 GD diagnosis receiving treatment.
  - For patients aged <16 years, a proxy participated on their behalf.
- Excluded undiagnosed patients and participants not fluent in Japanese.

Caregivers

- Giving care, on a daily basis, to patients with GD (any type) receiving treatment.
- Excluded persons with cognitive disabilities and/or lacking fluency in Japanese.

Questionnaires

PROM questionnaire

- Parts 1 and 2 (previously published[4] and translated into Japanese).
  - Part 1: 15 items, 0–10-point scale (impact of GD in the past month).
  - Part 2: 9 items, 0–10-point scale (condition of GD in the past week).
- **Part 3:** 15 items (pre-test)/16 items* (main survey), 0–10-point scale (newly developed for nGD).

Caregiver Impact Questionnaire (CIQ)[6]

- Social functioning (7 items), Impact on daily activities (5 items), Emotional/psychological functioning (10 items), Physical functioning (6 items) and Financial impact (2 items).
- Maximum (highest burden) total score of 120 points.

Zarit Caregiver Burden Interview (ZBI)[7]

- Relationship (6 items), Emotional well-being (7 items), Social and family life (4 items), Finances (1 item), Loss of control over one's life (4 items).
- Maximum (highest burden) total score of 88 points.

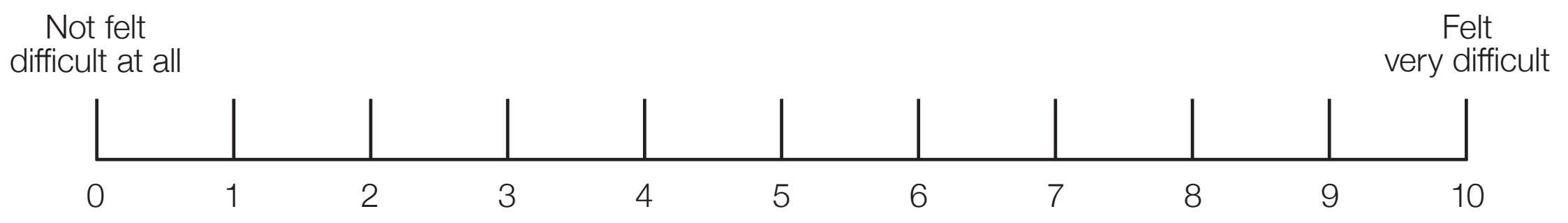
*Based on participant feedback in the pre-test, 1 item of the questionnaire was divided into 2 items for the main survey.

Figure 2. Snapshot of PROM questionnaire Part 3

Part 3 items

- Hearing impairment
- Visual impairment
- Difficulty swallowing
- Difficulty speaking
- Involuntary movement of extremities
- Epileptic seizures
- Body aches
- Anxiety about symptoms
- Memory loss
- Difficulty with exercise and work
- Anxiety about continuing treatment
- Anxiety about going out
- Tiredness from hospital visit or treatment
- Dissatisfaction about government service
- Lack of social support
- Information exchange in patient association

Example:
10. Over the past week, did you find it difficult to exercise, study, or work compared to your friends at the same age?



Statistical analyses

Overview and validation of the PROM

1. Inter-item correlation coefficients.
2. Content consistency evaluated by Cronbach's alpha using completed answers.
3. Test-retest reliability evaluated by Cohen's kappa, using 2 rounds of questionnaires in the main survey (2-week interval).

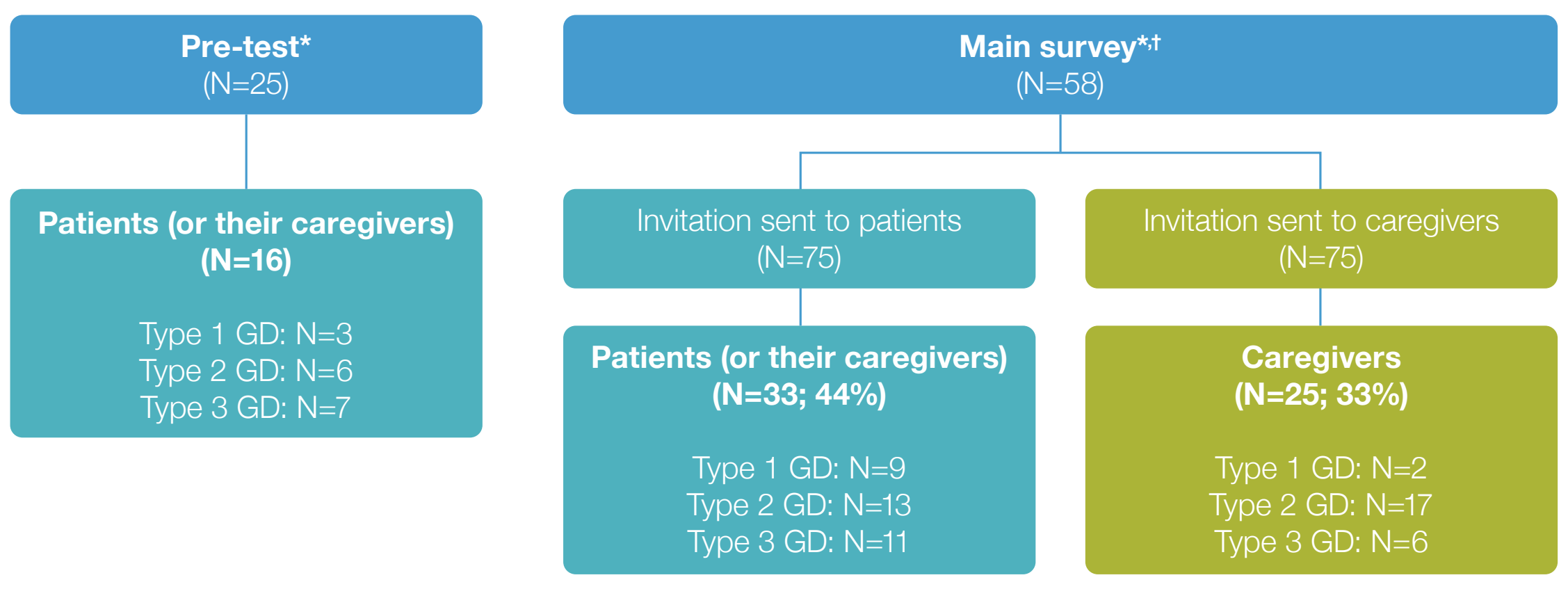
Survey results

- Relationship between disease duration and caregiver burden.

RESULTS

Patient disposition

Figure 3. Patient and caregiver disposition



Pre-test*
(N=25)

Patients (or their caregivers)
(N=16)
Type 1 GD: N=3
Type 2 GD: N=6
Type 3 GD: N=7

Main survey*,†
(N=58)

Invitation sent to patients
(N=75)

Patients (or their caregivers)
(N=33; 44%)
Type 1 GD: N=9
Type 2 GD: N=13
Type 3 GD: N=11

Invitation sent to caregivers
(N=75)

Caregivers
(N=25; 33%)
Type 1 GD: N=2
Type 2 GD: N=17
Type 3 GD: N=6

Abbreviation: GD, Gaucher disease.
*Recruited from patient association group.
†Recruited from specialist referral.

Patient characteristics

Characteristics	Pre-test Type 1 (N=3)	Type 2 (N=6)	Type 3 (N=7)	Overall (N=16)	Main survey Type 1 (N=9)	Type 2 (N=13)	Type 3 (N=11)	Overall (N=33)
Sex, female, n (%)	2 (66.7)	4 (66.7)	3 (42.9)	9 (56.3)	7 (77.8)	5 (38.5)	5 (45.5)	17 (51.5)
Age at diagnosis, years	4.3 (1.5)	1.0 (0.5)	6.6 (6.6)	4.1 (5.0)	23.4 (16.9)	0.6 (0.7)	8.1 (7.5)	9.3 (13.3)
Current age, years	46.3 (3.5)	9.0 (7.9)	28.4 (18.1)	24.5 (18.8)	58.6 (18.5)	10.0 (8.2)	37.1 (16.9)	32.3 (24.6)
Duration of GD, years	42.0 (2.0)	8.1 (7.9)	21.9 (13.2)	20.5 (15.7)	56.6 (27.0)	9.6 (8.1)	34.6 (17.9)	25.5 (23.2)
Respondent, n (%)								
Self	3 (100)	0 (0)	4 (57.1)	7 (43.8)	9 (100)	0 (0)	8 (72.7)	17 (51.5)
Caregiver	0 (0)	6 (100)	3 (42.9)	9 (56.3)	0 (0)	13 (100)	3 (27.3)	16 (48.5)

Abbreviations: GD, Gaucher disease; SD, standard deviation.
Data are shown as mean (SD) unless otherwise indicated. Note: Data were not collected for 1 patient with type 3 GD.

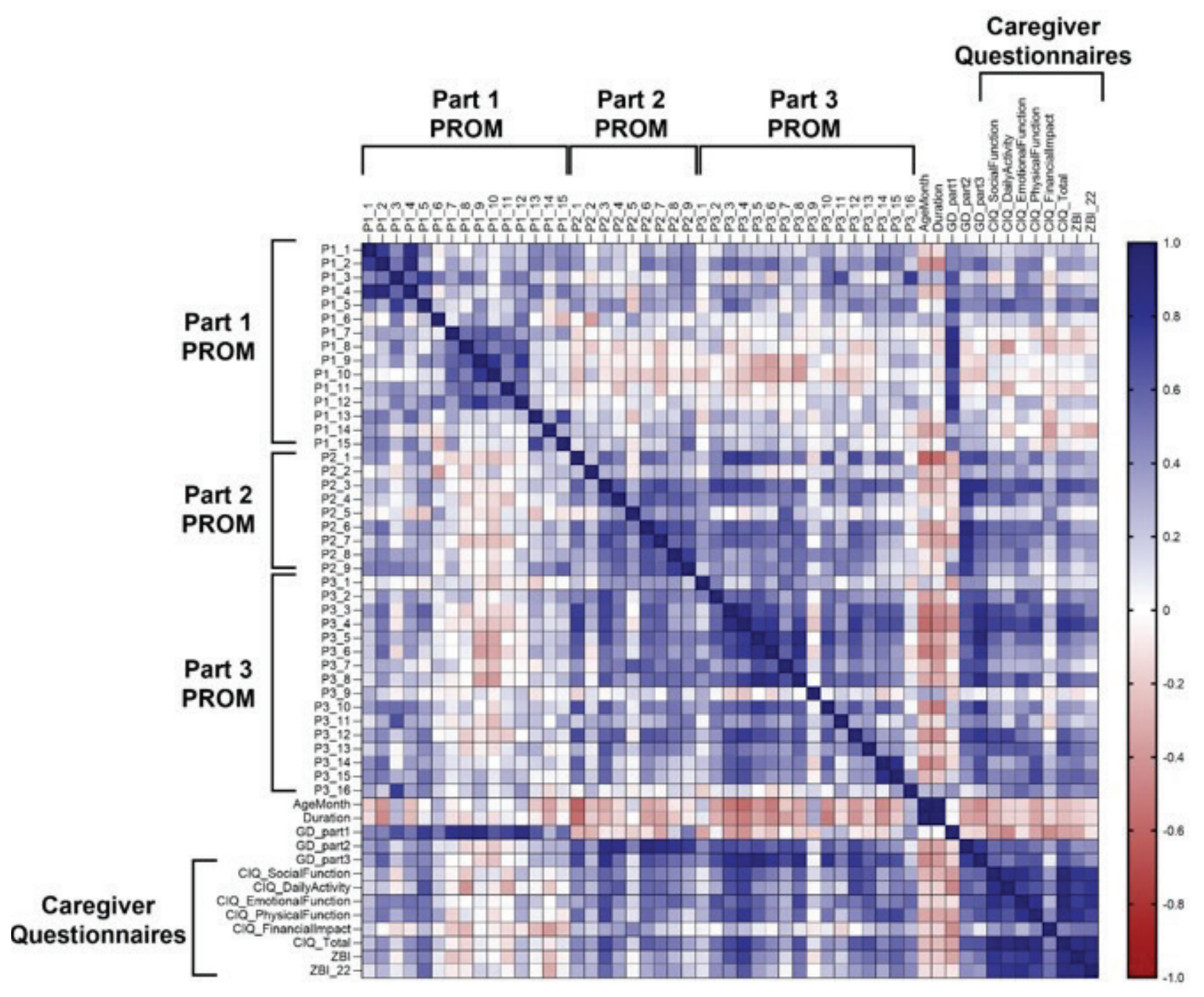
- In the main survey, mean patient ages for each GD type suggest that patients with type 1 GD were mostly adults, whereas patients with type 2 GD were children.
- For type 2 GD, all survey respondents were caregivers; for type 3 GD, ~50% of respondents were caregivers.
- Disease duration was longest for type 1 GD and shortest for type 2 GD.

Overview and validation of the PROM

1. Inter-item correlation of PROM

- Positive correlation was observed between Part 2 and 3 items.
- Each item in Parts 2 and 3 highly correlated with Part 2 and 3 total scores but did not correlate with Part 1 total score.
- Each item in Parts 2 and 3 negatively correlated with patient age and disease duration.

Figure 4. Inter-item correlations of PROM in the main analysis (overall population)



Abbreviations: CIQ, Caregiver Impact Questionnaire; GD, Gaucher disease; P, Part; PROM, patient-reported outcome measure; ZBI, Zarit Caregiver Burden Interview.
Note: The magnitude of the correlation coefficients is indicated by the colour. A positive correlation is indicated in blue, a negative correlation is indicated in red.

2. Content consistency

- Cronbach's alpha coefficient for the overall PROM and for each part was high (≥0.9), indicating good internal content consistency (Supplementary Table S1).

3. Test-retest reliability

- Most Part 2 and 3 items had high reliability.
- Patterns of test-retest reliability varied between GD types (Supplementary Table S2).

PROM scores

	Pre-test Type 1 (N=3)	Type 2 (N=6)	Type 3 (N=7)	Overall (N=16)	Main survey Type 1 (N=9)	Type 2 (N=13)	Type 3 (N=11)	Overall (N=33)
Part 1								
Mean (SD)	NA	27.5 (10.6)	38.8 (27.2)	35.0 (22.4)	42.1 (31.5)	13.8 (12.4)	65.0 (21.3)	45.0 (30.3)
Not collected, n (%)	3 (100)	4 (66.7)	3 (42.9)	10 (62.5)	3 (33.3)	11 (84.6)	7 (63.6)	21 (63.6)
Part 2								
Mean (SD)	17.0 (8.2)	45.8 (24.1)	16.2 (15.7)	25.5 (21.4)	17.0 (8.5)	38.7 (21.5)	26.5 (20.6)	29.1 (20.3)
Not collected, n (%)	0 (0)	2 (33.3)	1 (14.3)	3 (18.8)	1 (11.1)	0 (0)	0 (0)	1 (3.0)
Part 3								
Mean (SD)	NA	79.0 (41.4)	25.7 (12.7)	52.3 (40.0)	24.2 (16.5)	79.7 (42.5)	52.1 (30.2)	57.9 (39.6)
Not collected, n (%)	3 (100)	3 (50.0)	4 (57.1)	10 (62.5)	3 (33.3)	1 (7.7)	1 (9.1)	5 (15.2)

Abbreviations: NA, not applicable; SD, standard deviation.

- A greater proportion of patients were able to complete Part 3 in the main survey than in the pre-test.
- The proportion of patients with nGD who were able to complete Part 1 was low.
- The burden of type 2 GD may have been underestimated in Part 1 compared with that in Parts 2 and 3.
- High Part 2 and 3 scores in patients with type 2 GD indicated high burden in this patient population.

Caregiver characteristics

Characteristics	Type 1 (N=2)	Type 2 (N=17)	Type 3 (N=6)	Overall (N=25)
Sex, female, n (%)	2 (100)	15 (88.2)	6 (100)	23 (92.0)
Age, years, mean (SD)	72.0 (21.2)	39.9 (6.48)	53.3 (15.3)	45.7 (13.8)

Abbreviation: SD, standard deviation.

- Most caregivers were female.
- Caregivers of patients with type 1 GD were older than caregivers of patients with types 2 and 3 GD.

Caregiver CIQ and ZBI scores

Scores	Type 1 (N=2)	Type 2 (N=17)	Type 3 (N=6)	Overall (N=25)
CIQ, mean (SD)				
Social functioning	1.5 (2.2)	9.9 (7.8)	7.7 (5.7)	8.7 (7.3)
Impact on daily activities	0 (0)	6.1 (5.2)	5.8 (6.5)	5.5 (5.5)
Emotional/psychological functioning	2.5 (2.1)	13.8 (10.5)	13.8 (6.6)	12.9 (9.6)
Physical functioning	0 (0)	6.9 (4.7)	4.5 (3.7)	5.8 (4.7)
Financial impact	0 (0)	1.4 (2.2)	0.7 (0.8)	1.1 (1.9)
Total	4.0 (4.2)	37.9 (27.5)	32.5 (19.6)	33.9 (25.9)
ZBI, mean (SD)				
Total	5.0 (1.4)	23.4 (16.9)	17.8 (14.7)	20.6 (16.3)

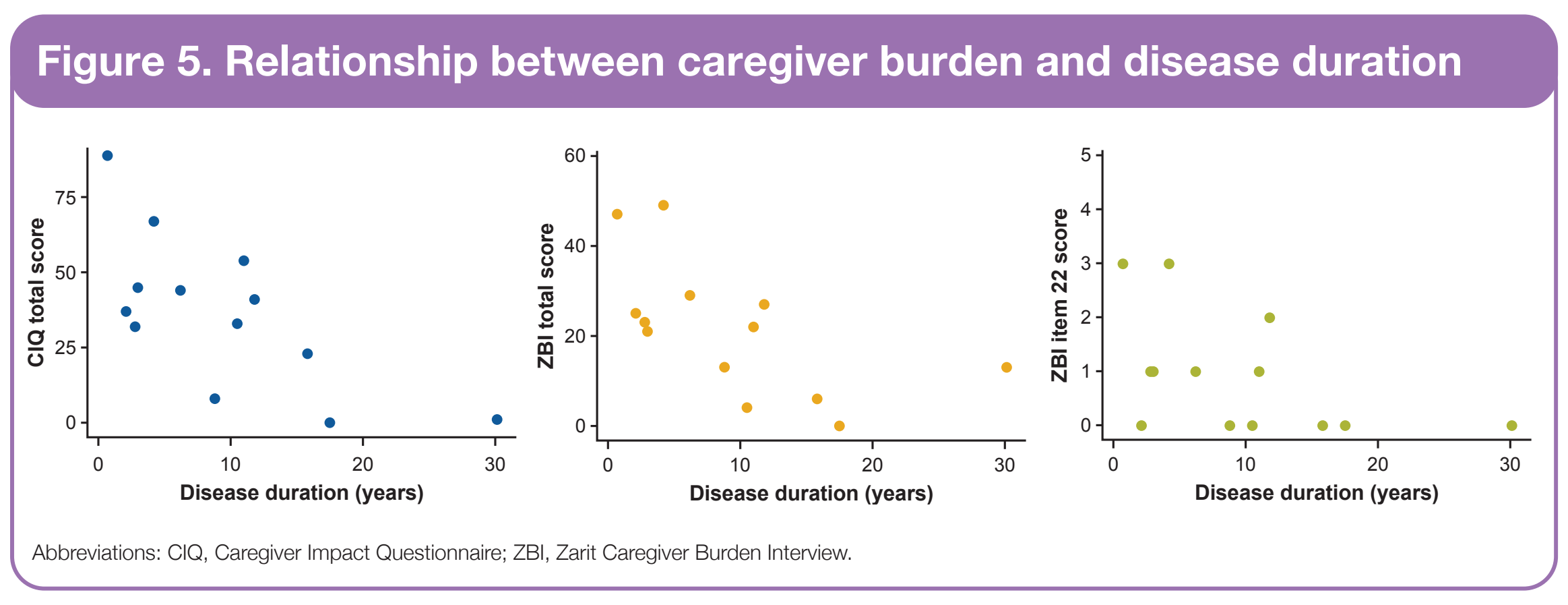
Abbreviations: CIQ, Caregiver Impact Questionnaire; SD, standard deviation; ZBI, Zarit Caregiver Burden Interview.

- Total CIQ score, each CIQ subscore and total ZBI score tended to be higher in caregivers of patients with type 2 GD than in caregivers of patients with types 1 and 3 GD.

Relationship between caregiver burden and disease duration

- The relationship between caregiver burden and disease duration was assessed in caregivers of patients with type 2 GD (N=17).
  - The number of caregivers of patients with type 1 GD (N=2) and type 3 GD (N=6) was insufficient for the analysis.
- CIQ total score, ZBI total score and item 22 of ZBI ("Overall, how burdened do you feel in caring for your relative?") were all negatively correlated with disease duration.

Figure 5. Relationship between caregiver burden and disease duration



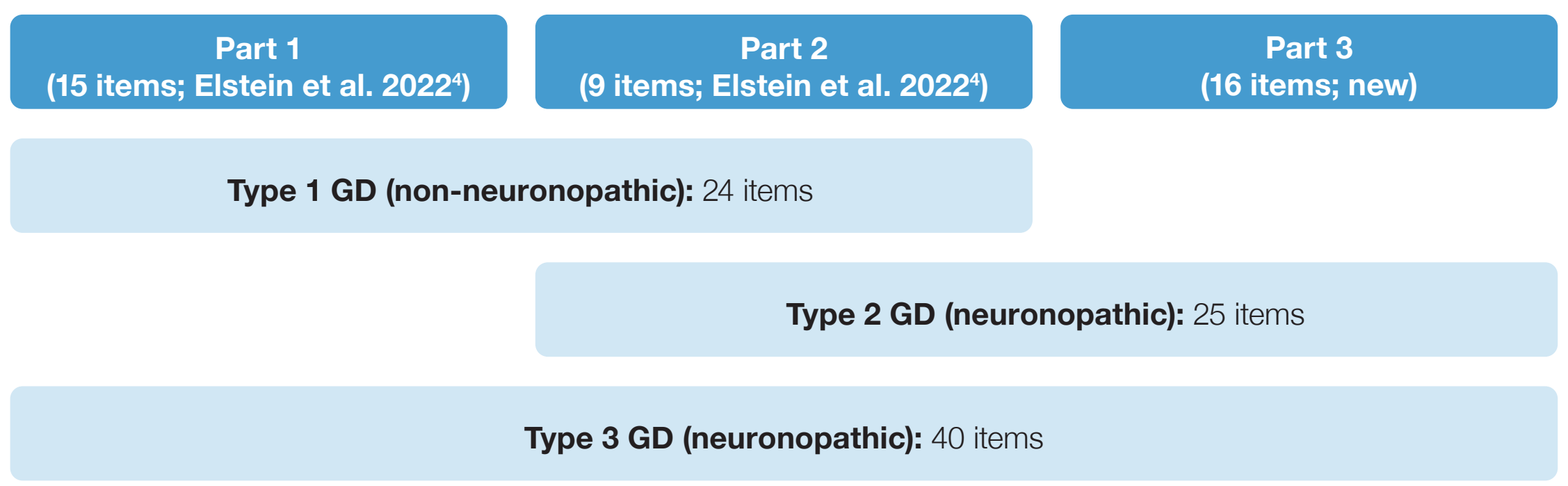
Abbreviations: CIQ, Caregiver Impact Questionnaire; ZBI, Zarit Caregiver Burden Interview.

DISCUSSION

Recommendation for GD type-specific PROM items

- The PROM, combining the newly developed Part 3 with pre-existing Parts 1 and 2, can be tailored for each GD type.
- However, a minimal important change in score (or subscores for each part) must be established before the PROM can be used in clinical practice.

Figure 6. Recommendation for GD type-specific PROM items



Part 1
(15 items; Elstein et al. 2022[4])

Part 2
(9 items; Elstein et al. 2022[4])

Part 3
(16 items; new)

Type 1 GD (non-neuronopathic): 24 items

Type 2 GD (neuronopathic): 25 items

Type 3 GD (neuronopathic): 40 items

Abbreviation: GD, Gaucher disease.

CONCLUSIONS

GD-specific PROM development

- In this study, a GD-specific PROM for all 3 GD phenotypes was developed and evaluated in Japanese patients with GD.
  - The new PROM is composed of 3 parts; the newly developed Part 3, which had high reliability in our study, evaluates the burden of nGD.
  - Parts 1 and 2 were previously established for non-nGD; with the addition of the nGD-specific Part 3, the new PROM can be used for all patients with GD.

GD-specific burden evaluation

Patients

- The PROM results indicated that patients with type 2 GD had the highest burden among all GD types.
- The burden scores negatively correlated with patient age and disease duration.

Caregivers

- Among all GD types, caregiver burden, assessed by CIQ and ZBI, was highest in caregivers of patients with type 2 GD.
- The burden of the caregiver decreased with increased duration of disease.

We expect the PROM to be used in the future to assess the burden of GD, which could improve understanding of the progression and management of the disease.

ACKNOWLEDGEMENTS

The authors would like to thank all patients and their caregivers for their participation, Yayoi Hoshi (IQVIA Solutions Japan K.K.) for overseeing the execution of the study, and Sayaka Takabuchi (graduate student at Osaka University) for their contributions to the study operations. This study was funded by Takeda Pharmaceutical Company Limited. Medical writing assistance was provided by Hana Nomura, BPharm (Hons), of ProScribe – Envision Pharma Group, and was funded by Takeda Pharmaceutical Company Limited.

DISCLOSURES

M. Ono and R. Sagara are employees of Takeda Pharmaceutical Company Limited (hereafter, Takeda). M. Ono is a stockholder of Takeda. S. Noto has served as a consultant for Takeda. A. Narita, Y. Koto and N. Sakai have received research funding from and have served as consultants and on speakers' bureaus for Takeda. M. Okada is a former employee of IQVIA Solutions Japan K.K.

REFERENCES

1. Stirnemann J, et al. *Int J Mol Sci* 2017;18:441.
2. Koto Y, et al. *Mol Genet Metab* 2021;133:277-88.
3. Zimran A, et al. *Am J Hematol* 2018;93:205-12.
4. Elstein D, et al. *Orphanet J Rare Dis* 2022;17:9.
5. Koto Y, et al. *Orphanet J Rare Dis* 2022;17:280.
6. Harrington M, et al. *J Patient Rep Outcomes* 2019;3:44.
7. Al-Rawashdeh SY, et al. *J Cardiovasc Nurs* 2016;31:E21-E28.

Presented at the ISPOR Europe 2022 Conference, 6–9 November 2022; Vienna, Austria and Virtual