Supplementary Materials

Exposure of Phenylacetic Acid and Phenylacetylglutamine Across Different Subpopulations and Correlation With Adverse Events

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Xiaofeng Wang¹,⁎; Jack Tseng¹; Carmen Mak¹,⁎; Nagaraju Poo¹,⁎; Regis A. Vilchez¹

¹Mallinckrodt Pharmaceuticals, Bedminster, NJ, USA; *Affiliation at the time that the research was conducted.

Corresponding Author: Dr Regis A. Vilchez, Mallinckrodt Pharmaceuticals, email:
regis.vilchez@mnk.com

Online Resource 1

Supplementary Table S1. Institutional review boards granting study protocol approval.

| Study   | Name and address of ethics committee                                      |
|---------|-------------------------------------------------------------------------|
| HE201   | Sharp Institutional Review Board                                         |
|         | 8695 Spectrum Center Blvd.                                               |
|         | San Diego, CA 92123                                                     |
| HV201   | Independent Ethics Committee of the Foundation                           |
|         | “Evaluation of the Ethics of Biomedical Research”                       |
|         | P.O. Box 1004, 9400 BA                                                   |
|         | Assen, The Netherlands                                                   |
| MNK61051112 | IntegReview IRB                                      |
|         | 3815 S. Capital of Texas Highway                                         |
|         | Suite 320                                                               |
|         | Austin, TX 78704                                                        |
| MNK61051111 | Salus IRB                                                  |
|         | 2111 W. Braker Lane                                                     |
|         | Suite 100                                                               |
|         | Austin, TX 78758                                                        |
| MNK61051111 | IntegReview IRB                                      |
|         | 3815 S. Capital of Texas Highway                                         |
|         | Suite 320                                                               |
|         | Austin, TX 78704                                                        |
| HE209   | Albert Einstein Healthcare Network Institutional Review Board            |
|         | 5501 Old York Road, Korman Building, Suite 100                           |
| Study | Name and address of ethics committee |
|-------|--------------------------------------|
| HE209 | Aspire IRB                             |
|       | 11491 Woodside Avenue                 |
|       | Santee, California 92071 United States|
| HE209 | Baylor Scott and White Research Institute |
|       | 3310 Live Oak, Suite 501              |
|       | Dallas, Texas 75204 United States     |
| HE209 | Beth Israel Deaconess Medical Center Committee on Clinical Investigations |
|       | 330 Brookline Ave., Dana 9            |
|       | Boston, Massachusetts 02215 United States |
| HE209 | Biomedical EC of the SBHI Scientific Research Institute of Emergency Care named after N.V. Scifosovsky of HD of Moscow 3, Bolshaya Sukharevskaya Square Moscow, Russia 129090 |
| HE209 | Biomedical Research Alliance of New York |
|       | 1981 Marcus Avenue, Suite 210         |
|       | Lake Success, New York 11042 United States |
| HE209 | CEC/LEC - Fakultni nemocnice Brno, Multicentricka eticka komise Jihlavská 20 |
|       | Brno, Czech Republic 625 00           |
| HE209 | Cedars-Sinai Medical Center Institutional Review Board |
|       | 6500 Wilshire Boulevard, Suite 1800   |
|       | Los Angeles, California 90036 United States |
| HE209 | CEIC Hospital Universitari Vall d'Hebron |
|       | Passeig Vall d'Hebron, 119-129 Barcelona, Barcelona, Spain 08035 |
| HE209 | Chesapeake Institutional Review Board |
|       | 6940 Columbia Gateway Dr., Suite 110  |
|       | Columbia, Maryland 21046 United States |
| HE209 | Columbia University Medical Center Institutional Review Board |
|       | 154 Haven Ave, 1st Floor              |
|       | New York, NY 10032 United States      |
| HE209 | Comitato Etico Area Vasta Centro Azienda Ospedaliera Universitaria Careggi |
|       | Largo Brambilla 3                     |
|       | Firenze, Firenze, Italy 50134         |
| HE209 | Comitato Etico Indipendente IRCCS - Istituto Clinico Humanitas Via Manzoni, 56 |
|       | Rozzano, Milano, Italy 20089          |
| HE209 | Comitato Etico IRCCS Casa Sollievo della Sofferenza IRCCS Casa Sollievo della Sofferenza |
|       | Viale Cappuccini 1                     |
|       | San Giovanni Rotondo, Foggia, Italy 71013 |
| HE209 | Comitato Etico Milano Area B Fondazione IRCCS Ca Granda |
| Study | Name and address of ethics committee |
|-------|-------------------------------------|
|       | Ospedale Maggiore Policlinico Via Francesco S forza, 35 Milano, Milano, Italy 20122 |
| HE209 | Comitato Etico Palermo 1 Via del Vespro 129 Palermo, Italy 90127 |
| HE209 | Comité de Protection des Personnes Sud Ouest et Outre Mer III/Hopital Pellegrin Service de Pharmacologie Clinique Bat 1A Place Amélie Raba-Léon Bordeaux Cedex, France 33076 |
| HE209 | Committee on Human Research 3333 California Street, Suite 315 San Francisco, California 94118 United States |
| HE209 | Dallas VA Institutional Review Board 4500 South Lancaster Road Dallas, Texas 75216 United States |
| HE209 | De videnskabsetiske Komitéer for Region Midtjylland Skottenborg 26 Viborg, Denmark 8800 |
| HE209 | De videnskabsetiske Komitéer for Region Hovedstaden Kongens Vaenge 2 Hillerod, Denmark 2100 |
| HE209 | Emory University Institutional Review Board (IRB) 1599 Clifton Road, 5th Floor Atlanta, Georgia 30322 United States |
| HE209 | Ethics Committee at LLC Medical Company "Hepatolog" 36A, Serdobskaya str. Samara, Russia 443063 |
| HE209 | Ethics Committee for Multicenter Trials 5, “Sveta Nedelya” Square Sofia, Bulgaria 1000 |
| HE209 | Ethik-Kommission der Medizinischen Fakultät Heidelberg Alte Glockengiesserei 11/1 Heidelberg, Germany 69115 |
| HE209 | Ethikkommission der Medizinischen Universität Graz, LKH-Universitätsklinikum Auenbruggerplatz 2 Graz, Austria 8037 |
| HE209 | Ethikkommission der Medizinischen Universität Wien Borschkegasse 8b/E06 Vienna, Austria 1090 |
| HE209 | Ethikkommission der Stadt Wien Thomas-Klestil-Platz 8/2 Vienna, Austria 1030 |
| HE209 | Ethisch Comité Universitair Ziekenhuis Gent, De Pintelaan 185 - 1K4 |
| Study | Name and address of ethics committee |
|-------|-------------------------------------|
| HE209 | Gent, Belgium 9000                  |
| HE209 | Georgetown University Institutional Review Board  
SW 104 Med-Dent Building  
3900 Reservoir Rd  
Washington, District of Columbia 20057 United States |
| HE209 | Health Sciences Institutional Review Board  
University of Missouri  
905 Hitt Street  
190 Galena Hall  
Columbia, Missouri 65211 United States |
| HE209 | Human Research Protection Program,  
University of Minnesota  
420 Delaware Street SE  
Mayo Mail Code 820  
Minneapolis, Minnesota 55455 United States |
| HE209 | Icahn School of Medicine at Mount Sinai Program for the  
Protection of Human Subjects  
One Gustave L. Levy Place, Box 1081  
New York, New York 10029 United States |
| HE209 | Institutional Review Board Administration  
2921 Stockton Boulevard  
Suite 1400, Room 1429  
Sacramento, California 95817 United States |
| HE209 | Institutional Review Board,  
University of Mississippi Medical Center  
2500 North State Street  
U020 Verner S. Holmes Learning Resource Center  
Jackson, Mississippi 39216 United States |
| HE209 | Johns Hopkins Institutional Review Board  
1620 McElderry Street  
Reed Hall-B130  
Baltimore, Maryland 21205-1991 United States |
| HE209 | Local Ethic Committee  
Tel Aviv Sourasky Medical Center  
6 Weizmann St.  
Tel Aviv, Israel 6423907 |
| HE209 | Local Ethic Committee  
The Lady Davis Carmel MC Ethics Committee  
7 Michal St.  
Haifa, Israel 3436212 |
| HE209 | Local Ethic Committee  
Rabin Medical Center  
39 Jabotinsky str.  
Petah Tikva, Israel 4941492 |
| HE209 | Local Ethic Committee |
| Study | Name and address of ethics committee |
|-------|-------------------------------------|
| HE209 | Local Ethic Committee  
Rambam Medical Center  
8 Haaliyya St., POB 9602  
Bat Galim, Haifa, Israel 3109601 |
| HE209 | Local Ethics Committee  
Hadassah Ein Karem Medical Center  
POB 12000  
Jerusalem, Israel 9112001 |
| HE209 | Local Ethics Committee  
Sheba Medical Center  
Tel Hashomer  
Ramat Gan, Israel 5262000 |
| HE209 | Mayo Clinic Institutional Review Board  
200 First Street S.W.  
Rochester, Minnesota 5905 United States |
| HE209 | McGuire Institutional Review Board McGuire DVAMC  
1201 Broad Rock Boulevard, Room 3C-126  
Richmond, Virginia 23249 United States |
| HE209 | MCW/FH Institutional Review Board  
8701 Watertown Plank Road  
Milwaukee, Wisconsin 53226 United States |
| HE209 | Medical Research Council Ethics Committee for Clinical Pharmacology  
Arany J. u. 6-8  
Budapest, Hungary 1051 |
| HE209 | Medisch-ethische toetsingscommissie azM/UM  
Oxfordlaan 70 Room 4.R1.033  
BioPartner Center Maastricht, niveau 1  
Maastricht, The Netherlands 6229 EV |
| HE209 | New York University School of Medicine - Institutional Review Board  
One Park Ave, 6th Floor  
New York, New York 10016 United States |
| HE209 | NorthShore University Health System Institutional Review Board  
NorthShore University Health System  
2650 Ridge Ave  
Evanston, Illinois 60201 United States |
| HE209 | Northwestern University - Institutional Review Board  
750 N. Lake Shore Drive  
Rubloff Hall - 7th Floor  
Chicago, Illinois 60611 United States |
| HE209 | Ochsner Clinic Foundation Institutional Review Board  
1514 Jefferson Highway  
New Orleans, Louisiana 70121 United States |
| HE209 | Office of Human Research, |
| Study | Name and address of ethics committee |
|-------|-------------------------------------|
|       | Thomas Jefferson University        |
|       | 1015 Chestnut Street, Suite 1100   |
|       | Philadelphia, Pennsylvania 19107 United States |
| HE209 | Office of Research Integrity       |
|       | MUSC Institutional Review Board for Human Research (IRB) |
|       | 19 Hagood Avenue, Suite 601 MSC 857 |
|       | Charleston, South Carolina 29407 United States |
| HE209 | Oregon Health & Science University (OHSU IRB) |
|       | 3181 SW Sam Jackson Park Road Mail Code: L-471 |
|       | Portland, Oregon 97239 United States |
| HE209 | Partners Human Research Committee Human Research Office |
|       | 116 Huntington Ave, Suite 1002      |
|       | Boston, Massachusetts 02116 United States |
| HE209 | Piedmont Healthcare Institutional Review Board |
|       | 1968 Peachtree Road NW             |
|       | Atlanta, Georgia 30309 United States |
| HE209 | Research Ethics Committee of the University of Tartu |
|       | Lossi 3-318                       |
|       | Tartu, Estonia 51003              |
| HE209 | Royal Adelaide Hospital Research Ethics Committee |
|       | Royal Adelaide Hospital, North Terrace |
|       | Adelaide, SA, Australia 5000      |
| HE209 | Rush University Institutional Review Board |
|       | 1653 West Congress Parkway         |
|       | Chicago Illinois 60612 United States |
| HE209 | Sharp Healthcare Institutional Review Board |
|       | 8695 Spectrum Center Boulevard      |
|       | San Diego, California 92123 United States |
| HE209 | Southern Health and Disability Ethics Committee |
|       | C/- Ministry of Health, Ethics Department, Freyberg Building |
|       | 20 Aitken Street                  |
|       | Wellington, New Zealand 6011      |
| HE209 | The Institutional Review Board at the University of Arkansas for Medical Sciences |
|       | 4301 W. Markham Street            |
|       | Little Rock, Arizona 72205 United States |
| HE209 | The Methodist Hospital Research Institute |
|       | Institutional Review Board         |
|       | 6670 Bertner                      |
|       | Houston, Texas 77030 United States |
| HE209 | The University of Chicago Institutional Review Board (IRB) |
|       | 5751 South Woodlawn Avenue         |
|       | McGiffert Hall, 2nd Floor          |
|       | Chicago, Illinois 60637 United States |
| HE209 | Tulane University Human Research Protection Program |
| Study | Name and address of ethics committee |
|-------|-------------------------------------|
|       | 1440 Canal Street, Suite 1705       |
|       | New Orleans, Louisiana 70112 United States |
| HE209 | University of Alberta, Health Research Ethics Board |
|       | 308 Campus Tower                     |
|       | 8625-112 St                          |
|       | Edmonton, Alberta T6G 1K8 Canada     |
| HE209 | University of Iowa Human Subjects Office/IRB |
|       | Hardin Library for the Health Sciences, Office 105 |
|       | 600 Newton Rd.                       |
|       | Iowa City, Iowa 52242 United States  |
| HE209 | University of Maryland School of Medicine |
|       | Human Research Protection Office (HRPO) |
|       | 800 W. Baltimore St., Suite 100     |
|       | Baltimore, Maryland 21201 United States |
| HE209 | University of Miami Human Subjects Research Office |
|       | 1400 N.W. 10th Avenue, Suite 1200 A |
|       | Miami, Florida 33136 United States  |
| HE209 | University of Pennsylvania - Office of Research Administration |
|       | 3624 Market St, Suite 301S           |
|       | Philadelphia, Pennsylvania 19104 United States |
| HE209 | USC Health Sciences Campus Institutional Review Board |
|       | General Hospital Suite 4700          |
|       | 1200 North State Street              |
|       | Los Angeles, California 90033 United States |
| HE209 | UT Southwestern Medical Center of Dallas |
|       | 5323 Harry Hines Boulevard Rm C1.206 |
|       | Dallas, Texas 75390 United States    |
| HE209 | VA Western New York Healthcare System IRB |
|       | 3495 Bailey Ave                      |
|       | Buffalo, New York 14215 United States |
| HE209 | Vanderbilt University Human Research Protection Program |
|       | 1313 21st Avenue South               |
|       | 504 Oxford House                    |
|       | Nashville, Tennessee 37232-4315 United States |
| HE209 | Western Institutional Review Board  |
|       | 1019 39th Avenue SE, Suite 120      |
|       | Puyallup, Washington 98347-2115 United States |
| HE209 | Winthrop-University, Institutional Review Board |
|       | 222 Station Plaza North, Suite 521  |
|       | Mineola, New York 11501 United States |
| HE209 | Yale University Human Investigation Committee |
|       | 25 Science Park-3rd Floor           |
|       | New Haven, Connecticut 06520 United States |

Review boards are listed in alphabetical order within each study.
Supplementary Table S2. Covariate test for PAA nonlinear models in healthy volunteers.

| Model # | Model description                                                                 | OFV    | ΔOFV   |
|---------|-----------------------------------------------------------------------------------|--------|--------|
| 1       | Add ethnicity to $V_{\text{max}}$ and $V$ (Caucasian, Japanese, Chinese ethnicity on $V_{\text{PAA}}$) in addition to weight and Sex | 3502.370 |        |
| 2       | Remove Sex from $V_{\text{max}}$                                                  | 3505.169 | 2.799  | Remove Sex on $V_{\text{max}}$ |
| 3       | Remove ethnicity from Model 2                                                       | 3509.097 | 3.928  | Remove ethnicity               |
| 4       | Remove Sex on $V_{\text{PAA}}$ from Model 3                                        | 3533.276 | 24.179 | Keep Sex on $V_{\text{PAA}}$   |

Additional tests on $V_{\text{max}}$ and $K_m$ start from Model 3:

|   |                                                                              | OFV         | ΔOFV   |
|---|--------------------------------------------------------------------------------|-------------|--------|
| 5 | Add ethnicity (Caucasian vs. Chinese and Japanese) to $V_{\text{max}}$ in Model 3 | 3504.519    | -4.578 | Discard                         |
| 6 | Separate Caucasian, Chinese, and Japanese in Model 5                          | 3498.309    | -6.21  | Discard                         |
| 7 | Add Age to $V_{\text{max}}$ in Model 6                                        | 3498.371    | 0.062  | Discard                         |
| 8 | Add Sex to $V_{\text{max}}$ in Model 6                                         | 3495.08     | -3.229 | Discard                         |

$k_m$, Michaelis constant; OFV, objective function value; $V$, volume of distribution; $V_{\text{max}}$, maximum velocity; $V_{\text{PAA}}$, volume of distribution of phenylacetic acid.