# Electronic Supplementary Material

**Article title:** HLX11, A Proposed Pertuzumab Biosimilar: Pharmacokinetics, Immunogenicity, and Safety Profiles Compared Among Three Reference Biologic Products (US-, EU-, and CN-approved Pertuzumab) Administered to Healthy Male Subjects

**Journal: BioDrugs**

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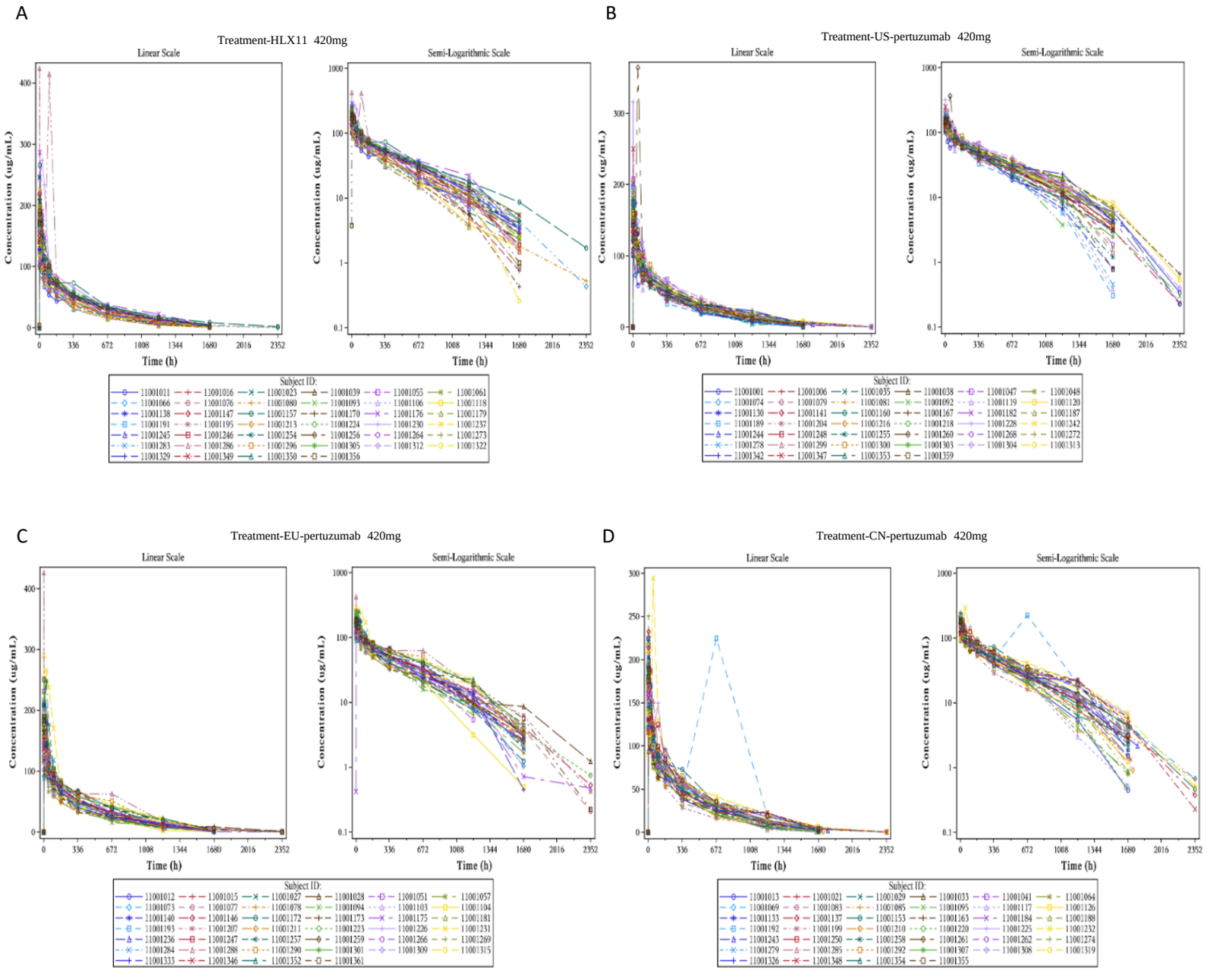
# ESM Figure S1 Mean serum concentration-time profiles for each subject after infusion of four study products



## ESM Table S1 Investigational Products

| | **HLX11** | **CN-pertuzumab** | **EU-pertuzumab** | **US-pertuzumab** |
|---|---|---|---|---|
| Study Drug Code | HLX11 | N/A | N/A | N/A |
| Generic Name | Pertuzumab Injection | | | |
| Trade Name | N/A | Perjeta® | Perjeta® | Perjeta® |
| Dosage Form | Injection | | | |
| Strength | 420 mg (14 mL)/vial | | | |
| Excipients | Histidine, Histidine Hydrochloride, Sorbitol, Polysorbate 20, Water for Injection | Glacial acetic acid<br>L-Histidine<br>Sucrose<br>Polysorbate 20<br>Water for injections | | |
| Packaging Site | Shanghai Henlius Biological Pharmaceutical Co., Ltd. | F. Hoffmann-La Roche Ltd. | Roche Pharma AG | Genentech, Inc. |
| Origin | No. 1289 Yishan Road, Shanghai, China 200233 | Sandhofer Straβe 116, 68305 Mannheim, Germany | Emil-Barell-Strasse 1<br>D-79639 Grenzach-Wyhlen<br>Germany | 1 DNA Way<br>South San Francisco, CA 94080-4990<br>U.S. License No. 1048 |
| Manufacturer | Shanghai Henlius Biological Pharmaceutical Co., Ltd. | Roche Diagnostics GmbH | Roche Pharma AG | Genentech, Inc. |

## ESM Table S2 Immunogenicity methodology validation results

### Anti-drug antibody (ADA) validation results

| | |
|---|---|
| Screening Cut Point Factor (95% percentile) | 1.06 (52 individual healthy serums, 6 replicates) |
| Confirmatory Cut Point (99% percentile) | 10.3% (52 individual healthy serums, 6 replicates |
| Titer Cut Point Factor | 1.59 |
| Conc. of Positive Control | HPC: 4000.00 ng/mL<br>LPC: 10.00 ng/mL<br>TPC: 40.00 ng/mL |
| Titer range | 1.0-5.3 |
| MRD | 1:80 |
| Sensitivity | Screening sensitivity: 4.29 ng/mL Confirmatory sensitivity: 7.38 ng/mL |
| Precision (ratio) | Intra-assay precision of HPC: 1.8% - 4.1%<br>Intra-assay precision of LPC: 1.9% - 4.0%<br>Inter-assay precision of HPC: 9.2 %<br>Inter-assay precision of LPC: 3.6% |
| Precision (%Inhibition) | Intra-assay precision of HPC: 0.0% - 0.1% Intra-assay precision of LPC: 9.2% - 19.6% Inter-assay precision of HPC: 0.1% Inter-assay precision of LPC: 15.3% |
| Selectivity | No matrix effect influence were concluded in healthy human serum, lipemic serum and hemolytic serum |
| Hook Effect | No hook effect observed at the concentration of 40000 ng/mL |
| Drug Interference | No drug interference observed with Her2-Fc at 200 ng/mL (4000 ng/mL of ADA samples) No drug interference observed with Her2-Fc at 200 ng/mL (10 ng/mL of ADA samples) |
| Drug Tolerance | 1000 ng/mL of ADA can tolerate 200 μg/mL of drug;<br>250 ng/mL of ADA can tolerate 200 μg/mL of drug;<br>100 ng/mL of ADA can tolerate 200 μg/mL of drug;<br>50 ng/mL of ADA can tolerate 200 μg/mL of drug;<br>10 ng/mL of ADA can tolerate 14 μg/mL of drug. |
| Short-term Stability | Room temperature Stability: 72 hours<br>2-8°C Stability: 72 hours<br>-20°C Freeze-Thaw Stability: 9 cycles<br>-70°C Freeze-Thaw Stability: 9 cycles |
| Long-term Stability | -20 °C Stability: 1 month（31days）<br>-70 °C Stability: 1 month（31days）<br>Stability for 6、12 months will be reported with Amendment |

## ESM Table S2 Immunogenicity methodology validation results

### Neutralizing antibody (Nab) validation results

| | |
|---|---|
| Method ID | 20BASM244V1 |
| Analyte | Anti-HLX11 Neutralizing antibody |
| Matrix | Human serum |
| Cut point factor | 0.87 |
| Positive control | HPC:1 μg/mL, LPC: 0.3 μg/ml |
| Sensitivity | 172.01 ng/mL |
| Drug tolerance | HPC (1.0 μg/mL) can tolerate more than 802 μg/mL HLX11 PC(0.5 μg/mL) can tolerate 317 μg/mL HLX11 LPC (0.3 μg/mL) can tolerate 124 μg/mL HLX11 |
| Sensitivity | No matrix effect was observed in normal human serum, lipemic serum and hemolytic serum. |
| Robustness | The method is robust under the validation parameter |
| Hook effect | No hook effect was observed. |
| Target Interference | Up to 500 ng/mL Her2 no target interference |
| Precision(ratio) | HPC: Intra-precision 3%~8% , Inter- precision :13% LPC: Intra-precision 3%~17% , Inter- precision: 20% |
| Bench top stability1 | 72hours |
| 2-8°C stability1 | 72hours |
| 8 cycle freeze-thaw stability1 | 8 cycles |
| Long-term stability | One month Other long-term stability is still ongoing and will be reported in the report amendment. |

# ESM Table S3 Laboratory Evaluation: Myocardial Enzymes(Safety Set)

**Laboratory Parameter: N-Terminal ProB-type Natriuretic Peptide (pmol/L)**

| | HLX11 (N=40) | | US-pertuzumab (N=40) | | EU-pertuzumab (N=40) | | CN-pertuzumab (N=40) | | Total (N=160) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Value | CFB | Value | CFB | Value | CFB | Value | CFB | Value | CFB |
| Baseline, N | 40 | | 40 | | 40 | | 40 | | 160 | |
| Mean | 2.7996 | | 3.1388 | | 2.5842 | | 3.3866 | | 2.9773 | |
| SD | 2.0213 | | 2.4336 | | 2.1920 | | 2.5922 | | 2.3188 | |
| Median | 2.1240 | | 2.2420 | | 2.0650 | | 3.0680 | | 2.2420 | |
| Day 02, N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 160 | 160 |
| Mean | 11.6319 | 8.8323 | 2.3807 | -0.7582 | 2.2184 | -0.3658 | 3.5666 | 0.1800 | 4.9494 | 1.9721 |
| SD | 60.4060 | 59.4948 | 1.8575 | 3.0650 | 2.1584 | 2.5554 | 5.9171 | 5.9875 | 30.3453 | 29.9468 |
| Median | 1.2980 | -0.5900 | 1.7110 | -0.4130 | 1.5340 | -0.3540 | 1.7110 | -0.5900 | 1.5930 | -0.5310 |
| Day 05, N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 160 | 160 |
| Mean | 2.6550 | -0.1446 | 3.2686 | 0.1298 | 2.5016 | -0.0826 | 2.8645 | -0.5222 | 2.8224 | -0.1549 |
| SD | 2.2948 | 2.7945 | 3.0423 | 3.9114 | 2.1136 | 2.7563 | 1.9107 | 2.2069 | 2.3742 | 2.9634 |
| Median | 1.8880 | -0.2360 | 2.3600 | 0.0000 | 1.8880 | -0.1770 | 2.5960 | -0.3540 | 2.0060 | -0.2360 |
| Day 08, N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 160 | 160 |
| Mean | 2.2066 | -0.5929 | 2.3276 | -0.8112 | 1.8821 | -0.7021 | 1.7376 | -1.6491 | 2.0384 | -0.9388 |
| SD | 2.0526 | 3.0804 | 2.1024 | 3.1007 | 1.6737 | 2.5134 | 1.4175 | 2.2399 | 1.8315 | 2.7642 |
| Median | 1.5930 | -0.6490 | 1.6520 | -0.6490 | 1.5340 | -0.3540 | 1.2980 | -1.0620 | 1.5340 | -0.7080 |
| Day 15, N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 160 | 160 |
| Mean | 2.3689 | -0.4307 | 1.9116 | -1.2272 | 2.1535 | -0.4307 | 2.0414 | -1.3452 | 2.1188 | -0.8584 |
| SD | 2.9484 | 3.5178 | 1.4568 | 2.2999 | 2.1774 | 2.4422 | 1.7874 | 2.0622 | 2.1512 | 2.6504 |
| Median | 1.4160 | -0.6490 | 1.3570 | -0.7080 | 1.2980 | -0.2950 | 1.4750 | -0.8850 | 1.2980 | -0.7080 |
| Day 29, N | 40 | 40 | 40 | 40 | 40 | 40 | 39 | 39 | 159 | 159 |
| Mean | 2.1063 | -0.6933 | 1.4099 | -1.6913 | 1.7199 | -0.8643 | 1.6402 | -1.7464 | 1.7210 | -1.2461 |
| SD | 2.6298 | 2.7456 | 0.9946 | 2.4823 | 1.8074 | 2.7202 | 1.3419 | 2.3181 | 1.8053 | 2.5927 |
| Median | 1.1210 | -0.7080 | 1.0620 | -1.1800 | 1.0030 | -0.6490 | 1.1800 | -1.2980 | 1.0620 | -0.9440 |
| Day 50, N | 40 | 40 | 40 | 40 | 40 | 40 | 39 | 39 | 159 | 159 |
| Mean | 1.4249 | -1.3747 | 1.4662 | -1.6727 | 1.3836 | -1.2007 | 1.8245 | -1.5340 | 1.5229 | -1.4449 |
| SD | 1.1093 | 1.8847 | 1.3448 | 2.3199 | 1.6762 | 2.5856 | 2.1633 | 2.4454 | 1.6124 | 2.3076 |
| Median | 1.0620 | -0.9440 | 0.8260 | -1.2390 | 0.5900 | -1.1210 | 0.9440 | -1.6520 | 0.8260 | -0.9440 |
| Day 71, N | 38 | 38 | 40 | 40 | 40 | 40 | 39 | 39 | 157 | 157 |
| Mean | 1.9781 | -0.8508 | 2.1742 | -0.9647 | 1.5399 | -1.0443 | 2.4175 | -0.9410 | 2.0255 | -0.9515 |
| SD | 1.9562 | 2.7110 | 2.5235 | 2.0206 | 1.1362 | 2.4053 | 3.8862 | 2.8222 | 2.5703 | 2.4810 |
| Median | 1.2390 | -0.4720 | 1.1800 | -0.7080 | 1.1800 | -0.7080 | 1.4160 | -0.9440 | 1.1800 | -0.5900 |
| D99/Early Termination, N | 40 | 40 | 40 | 40 | 40 | 40 | 39 | 39 | 159 | 159 |
| Mean | 1.8320 | -0.9676 | 2.6668 | -0.4720 | 2.8615 | 0.2773 | 2.4841 | -0.8744 | 2.4609 | -0.5069 |
| SD | 1.0373 | 1.8019 | 3.5432 | 3.8645 | 3.5970 | 3.9786 | 1.8466 | 2.4079 | 2.7441 | 3.1674 |
| Median | 1.1800 | -0.4720 | 1.5340 | -0.3540 | 1.4160 | -0.1770 | 1.7700 | -0.4720 | 1.4160 | -0.3540 |

Note: Baseline is defined as the last available assessment prior to the first dose of study drug; CFB=change from baseline,Change from baseline is defined as the difference between the measured value at the planned time point and the baseline value;
SD=standard deviation;

# ESM Table S3 Laboratory Evaluation: Myocardial Enzymes(Safety Set)

**Laboratory Parameter: Troponin I (ug/L)**

| | HLX11 (N=40) | | US-pertuzumab (N=40) | | EU-pertuzumab (N=40) | | CN-pertuzumab (N=40) | | Total (N=160) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Value | CFB | Value | CFB | Value | CFB | Value | CFB | Value | CFB |
| Baseline, N | 40 | | 40 | | 40 | | 40 | | 160 | |
| Mean | 0.003 | | 0.003 | | 0.005 | | 0.005 | | 0.004 | |
| SD | 0.0045 | | 0.0047 | | 0.0055 | | 0.0075 | | 0.0057 | |
| Median | 0.000 | | 0.000 | | 0.000 | | 0.000 | | 0.000 | |
| Day 02, N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 160 | 160 |
| Mean | 0.006 | 0.003 | 0.003 | -0.000 | 0.002 | -0.003 | 0.004 | -0.001 | 0.004 | -0.000 |
| SD | 0.0193 | 0.0202 | 0.0052 | 0.0070 | 0.0038 | 0.0073 | 0.0074 | 0.0078 | 0.0109 | 0.0120 |
| Median | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Day 05, N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 160 | 160 |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 160 | 160 |
| Mean | 0.003 | 0.000 | 0.003 | -0.000 | 0.003 | -0.002 | 0.004 | -0.001 | 0.003 | -0.001 |
| SD | 0.0051 | 0.0055 | 0.0066 | 0.0075 | 0.0045 | 0.0070 | 0.0075 | 0.0080 | 0.0060 | 0.0071 |
| Median | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Day 08, N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 160 | 160 |
| Mean | 0.002 | -0.001 | 0.002 | -0.002 | 0.003 | -0.002 | 0.004 | -0.001 | 0.003 | -0.001 |
| SD | 0.0041 | 0.0062 | 0.0045 | 0.0066 | 0.0047 | 0.0078 | 0.0078 | 0.0078 | 0.0055 | 0.0071 |
| Median | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Day 15, N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 160 | 160 |
| Mean | 0.002 | -0.001 | 0.002 | -0.001 | 0.002 | -0.003 | 0.003 | -0.002 | 0.002 | -0.002 |
| SD | 0.0042 | 0.0060 | 0.0042 | 0.0059 | 0.0041 | 0.0069 | 0.0076 | 0.0056 | 0.0052 | 0.0061 |
| Median | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Day 29, N | 40 | 40 | 39 | 39 | 40 | 40 | 40 | 40 | 159 | 159 |
| Mean | 0.002 | -0.001 | 0.002 | -0.002 | 0.001 | -0.005 | 0.003 | -0.003 | 0.002 | -0.002 |
| SD | 0.0055 | 0.0071 | 0.0037 | 0.0060 | 0.0022 | 0.0064 | 0.0071 | 0.0059 | 0.0050 | 0.0064 |
| Median | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Day 50, N | 40 | 40 | 40 | 40 | 40 | 40 | 39 | 39 | 159 | 159 |
| Mean | 0.005 | 0.002 | 0.005 | 0.001 | 0.004 | -0.001 | 0.006 | 0.001 | 0.005 | 0.001 |
| SD | 0.0078 | 0.0100 | 0.0050 | 0.0072 | 0.0055 | 0.0084 | 0.0125 | 0.0120 | 0.0082 | 0.0095 |
| Median | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Day 71, N | 38 | 38 | 40 | 40 | 40 | 40 | 39 | 39 | 157 | 157 |
| Mean | 0.005 | 0.002 | 0.005 | 0.002 | 0.005 | 0.000 | 0.007 | 0.002 | 0.005 | 0.001 |
| SD | 0.0056 | 0.0069 | 0.0055 | 0.0058 | 0.0055 | 0.0072 | 0.0091 | 0.0090 | 0.0066 | 0.0073 |
| Median | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.010 | 0.000 | 0.000 | 0.000 |
| D99/Early Termination, N | 40 | 40 | 40 | 40 | 40 | 40 | 39 | 39 | 159 | 159 |
| Mean | 0.004 | 0.001 | 0.008 | 0.004 | 0.006 | 0.001 | 0.006 | 0.001 | 0.006 | 0.002 |
| SD | 0.0059 | 0.0074 | 0.0103 | 0.0117 | 0.0068 | 0.0078 | 0.0085 | 0.0075 | 0.0081 | 0.0089 |
| Median | 0.000 | 0.000 | 0.010 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

Note: Baseline is defined as the last available assessment prior to the first dose of study drug; CFB=Change from baseline, Change from baseline is defined as the difference between the measured value at the planned time point and the baseline value;
SD=standard deviation;

## ESM Table S4 Summary of Echocardiogram (Safety Set)

| | HLX11 (N=40) | US-pertuzumab (N=40) | EU-pertuzumab (N=40) | CN-pertuzumab (N=40) | Total (N=160) |
|---|---|---|---|---|---|
| Echocardiogram during screening period | 40 (100) | 40 (100) | 40 (100) | 40 (100) | 160 (100) |
| LVEF, % | | | | | |
| n | 40 | 40 | 40 | 40 | 160 |
| Mean (SD) | 70.5 (4.64) | 69.8 (4.29) | 70.4 (4.40) | 69.2 (4.31) | 70.0 (4.40) |
| Median (Min, Max) | 70.0 (61, 79) | 70.0 (61, 78) | 71.0 (59, 78) | 69.0 (62, 77) | 70.0 (59, 79) |
| Assessment, n (%) | | | | | |
| Normal | 25 ( 62.5) | 13 ( 32.5) | 21 ( 52.5) | 23 ( 57.5) | 82 ( 51.3) |
| ACS | 0 | 0 | 0 | 0 | 0 |
| ANCS | 15 ( 37.5) | 27 ( 67.5) | 19 ( 47.5) | 17 ( 42.5) | 78 ( 48.8) |
| Echocardiogram in Day 8, n (%) | 40 (100) | 40 (100) | 40 (100) | 40 (100) | 160 (100) |
| LVEF, % | | | | | |
| n | 40 | 40 | 40 | 40 | 160 |
| Mean (SD) | 70.0 (4.20) | 68.7 (4.45) | 68.6 (3.71) | 68.4 (4.62) | 68.9 (4.27) |
| Median (Min, Max) | 70.0 (63, 79) | 68.5 (60, 77) | 68.5 (63, 79) | 68.0 (58, 78) | 68.5 (58, 79) |
| Assessment, n (%) | | | | | |
| Normal | 22 (55.0) | 16 ( 40.0) | 19 ( 47.5) | 20 ( 50.0) | 77 ( 48.1) |
| ACS | 0 | 0 | 0 | 0 | 0 |
| ANCS | 18 ( 45.0) | 24 ( 60.0) | 21 ( 52.5) | 20 ( 50.0) | 83 ( 51.9) |
| Echocardiogram in Day 99, n (%) | 40 (100) | 40 (100) | 40 (100) | 39 ( 97.5) | 159 ( 99.4) |
| LVEF, % | | | | | |
| n | 40 | 40 | 40 | 39 | 159 |
| Mean (SD) | 67.9 (4.40) | 68.2 (3.89) | 67.7 (4.57) | 67.0 (4.00) | 67.7 (4.21) |
| Median (Min, Max) | 67.0 (62, 78) | 66.5 (62, 76) | 66.0 (60, 78) | 66.0 (60, 77) | 66.0 (60, 78) |
| Assessment, n (%) | | | | | |
| Normal | 26 ( 65.0) | 21 ( 52.5) | 19 ( 47.5) | 25 ( 62.5) | 91 ( 56.9) |
| ACS | 0 | 0 | 0 | 0 | 0 |
| ANCS | 14 ( 35.0) | 19 ( 47.5) | 21 ( 52.5) | 14 ( 35.0) | 68 ( 42.5) |

Note : ACS = abnormal – clinically significant; ANCS = abnormal – not clinically significant; LVEF:left ventricular ejection fraction; N = number of subjects in the analysis population; n = number of subjects in the specified category; Percentage (%) = (n/N) * 100. SD=standard deviation.

# ESM Table S5 Summary of 12-Lead Electrocardiograms (ECG) (Safety Set)

**12-lead ECG Parameter: ECG Mean Heart Rate (beats/min)**

| | HLX11 (N=40) | | US-pertuzumab (N=40) | | EU-pertuzumab (N=40) | | CN-pertuzumab (N=40) | |
|---|---|---|---|---|---|---|---|---|
| | Value | CFB | Value | CFB | Value | CFB | Value | CFB |
| Baseline | | | | | | | | |
| N | 40 | | 40 | | 40 | | 40 | |
| Mean±SD | 68.0±8.69 | | 67.9±10.10 | | 67.0±8.34 | | 68.4±8.10 | |
| Median | 67.0 | | 65.5 | | 67.0 | | 68.5 | |
| Day 01, post-dose 3h | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 66.7±10.25 | -1.3±7.15 | 66.8±12.79 | -1.1±6.83 | 65.2±9.38 | -1.8±6.35 | 63.3±6.18 | -5.1±8.70 |
| Median | 64.5 | -2.0 | 63.0 | -1.0 | 65.0 | -3.0 | 63.5 | -5.5 |
| Day 01, post-dose 6h | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 73.3±10.44 | 5.3±7.31 | 71.1±13.59 | 3.2±7.78 | 71.3±9.94 | 4.3±8.48 | 70.4±8.30 | 2.0±10.84 |
| Median | 72.5 | 5.0 | 69.0 | 2.0 | 68.5 | 2.0 | 71.5 | 1.0 |
| Day 01, post-dose 12h | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 66.9±9.95 | -1.0±8.33 | 66.6±11.19 | -1.4±6.88 | 65.0±9.43 | -2.0±7.14 | 66.2±9.67 | -2.2±11.52 |
| Median | 66.5 | -2.0 | 65.0 | -1.5 | 61.0 | -2.5 | 64.5 | -2.0 |
| Day 02 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 60.4±5.55 | -7.6±5.87 | 60.1±10.51 | -7.8±8.17 | 60.2±7.39 | -6.9±6.85 | 60.9±6.71 | -7.5±6.79 |
| Median | 61.0 | -7.0 | 57.0 | -9.0 | 59.0 | -6.0 | 59.5 | -7.0 |
| Day 05 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 64.3±7.75 | -3.6±6.93 | 62.5±9.01 | -5.4±5.58 | 61.6±6.10 | -5.4±6.95 | 63.4±6.25 | -5.0±8.11 |
| Median | 65.0 | -4.0 | 59.5 | -6.0 | 61.0 | -6.0 | 62.0 | -4.5 |
| Day 08 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 64.7±7.55 | -3.3±8.80 | 65.3±8.77 | -2.6±9.22 | 64.4±8.06 | -2.6±7.59 | 64.7±7.07 | -3.7±9.17 |
| Median | 65.0 | -4.0 | 65.0 | -5.5 | 64.0 | -5.0 | 65.5 | -4.0 |
| Day 99 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 39 | 39 |
| Mean±SD | 66.4±8.40 | -1.6±10.48 | 68.1±12.09 | 0.2±11.35 | 66.0±8.56 | -1.0±8.95 | 68.9±8.77 | 0.6±10.76 |
| Median | 65.0 | -1.5 | 68.0 | -0.5 | 66.0 | -2.0 | 67.0 | 2.0 |

Note: Baseline is defined as the last available assessment prior to the first dose of study drug; CFB=Change from baseline, Change from baseline is defined as the difference between the measured value at the planned time point and the baseline value; SD=standard deviation.

# ESM Table S5 Summary of 12-Lead Electrocardiograms (ECG) (Safety Set)

**12-lead ECG Parameter: QT Interval, Aggregate (msec)**

| | HLX11(N=40) | | US-Perjeta®(N=40) | | EU-Perjeta®(N=40) | | CN-Perjeta®(N=40) | |
|---|---|---|---|---|---|---|---|---|
| | Value | CFB | Value | CFB | Value | CFB | Value | CFB |
| Baseline | | | | | | | | |
| N | 40 | | 40 | | 40 | | 40 | |
| Mean±SD | 362.7±23.52 | | 364.5±26.21 | | 366.7±25.61 | | 362.0±24.08 | |
| Median | 367.0 | | 364.0 | | 367.0 | | 362.0 | |
| Day 01, post-dose 3hours | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 368.1±23.59 | 5.4±14.35 | 365.7±29.29 | 1.2±13.56 | 369.2±23.36 | 2.5±20.26 | 370.0±22.79 | 8.0±21.81 |
| Median | 370.0 | 3.0 | 367.0 | 6.0 | 368.0 | 2.0 | 372.0 | 10.0 |
| Day 01, post-dose 6 hours | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 354.5±23.28 | -8.2±16.64 | 358.6±27.46 | -5.9±13.96 | 355.4±24.65 | -11.4±19.25 | 354.8±19.06 | -7.2±21.55 |
| Median | 352.0 | -7.0 | 363.0 | -6.0 | 353.0 | -12.0 | 354.0 | -9.0 |
| Day 01, post-dose 12 hours | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 360.6±23.31 | -2.1±20.73 | 365.5±31.02 | 1.1±15.59 | 369.0±23.85 | 2.3±17.67 | 362.8±23.92 | 0.9±25.65 |
| Median | 360.0 | -4.0 | 363.0 | 2.0 | 365.0 | 4.0 | 368.0 | 8.0 |
| Day 02 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 376.1±18.91 | 13.4±16.29 | 376.2±27.80 | 11.8±16.22 | 380.0±21.88 | 13.3±21.17 | 370.0±22.62 | 8.1±19.35 |
| Median | 379.0 | 12.0 | 380.0 | 15.0 | 376.0 | 12.0 | 371.0 | 10.0 |
| Day 05 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 366.9±20.20 | 4.2±22.97 | 368.0±27.33 | 3.5±14.47 | 373.3±20.78 | 6.6±19.75 | 362.2±22.26 | 0.3±21.73 |
| Median | 362.0 | 11.0 | 374.0 | 3.0 | 372.0 | 6.0 | 364.0 | 0.0 |
| Day 08 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 366.1±22.82 | 3.4±22.08 | 364.0±23.40 | -0.5±19.17 | 367.2±21.85 | 0.5±16.99 | 361.3±20.07 | -0.7±21.91 |
| Median | 366.0 | 3.0 | 363.0 | 2.0 | 368.0 | 4.0 | 358.0 | -2.0 |
| Day 99 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 39 | 39 |
| Mean±SD | 359.2±20.28 | -3.5±23.42 | 360.0±29.44 | -4.5±24.33 | 366.6±25.53 | -0.1±27.57 | 358.4±26.58 | -4.3±29.56 |
| Median | 360.0 | -4.0 | 363.0 | -6.0 | 365.0 | 4.0 | 360.0 | -10.0 |

Note: Baseline is defined as the last available assessment prior to the first dose of study drug; CFB=Change from baseline, Change from baseline is defined as the difference between the measured value at the planned time point and the baseline value;
SD=standard deviation;

# ESM Table S5 Summary of 12-Lead Electrocardiograms (ECG) (Safety Set)

**12-lead ECG Parameter: PR Interval, Aggregate (msec)**

| | HLX11(N=40) | | US-Perjeta®(N=40) | | EU-Perjeta®(N=40) | | CN-Perjeta®(N=40) | |
|---|---|---|---|---|---|---|---|---|
| | Value | CFB | Value | CFB | Value | CFB | Value | CFB |
| Baseline | | | | | | | | |
| N | 40 | | 40 | | 40 | | 40 | |
| Mean±SD | 150.6±19.04 | | 155.1±21.84 | | 147.9±18.42 | | 155.3±16.88 | |
| Median | 150.0 | | 158.0 | | 146.0 | | 153.0 | |
| Day 01, post-dose 3hours | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 141.8±16.22 | -8.8±11.36 | 142.0±16.53 | -13.2±22.61 | 141.7±15.91 | -6.2±14.05 | 141.7±15.64 | -13.6±11.32 |
| Median | 138.0 | -10.0 | 141.0 | -15.0 | 136.0 | -7.0 | 139.0 | -12.0 |
| Day 01, post-dose 6hours | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 143.8±16.72 | -6.9±12.39 | 142.4±18.86 | -12.8±16.65 | 140.3±14.94 | -7.6±14.86 | 145.1±14.88 | -10.2±11.80 |
| Median | 141.0 | -8.0 | 138.0 | -10.0 | 137.0 | -6.0 | 144.0 | -12.0 |
| Day 01, post-dose 12hours | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 149.6±15.93 | -1.0±15.88 | 148.0±17.54 | -7.1±14.36 | 147.3±15.42 | -0.6±14.44 | 151.5±18.43 | -3.8±13.41 |
| Median | 147.0 | -1.0 | 148.0 | -4.0 | 146.0 | -3.0 | 152.0 | -2.0 |
| Day 02 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 152.1±17.44 | 1.5±13.72 | 156.2±20.27 | 1.1±14.45 | 153.4±18.34 | 5.5±12.50 | 158.9±18.11 | 3.7±13.12 |
| Median | 150.0 | 3.0 | 155.0 | 0.0 | 152.0 | 4.0 | 157.0 | 4.0 |
| Day 05 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 151.7±16.82 | 1.1±16.65 | 155.9±20.12 | 0.8±14.35 | 151.7±17.34 | 3.8±14.24 | 155.3±18.56 | 0.0±11.38 |
| Median | 149.0 | 0.0 | 158.0 | 3.0 | 149.0 | 2.0 | 152.0 | -1.0 |
| Day 08 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 150.0±17.33 | -0.7±13.25 | 153.6±20.30 | -1.6±14.04 | 150.9±18.05 | 3.0±12.33 | 156.5±18.18 | 1.2±14.19 |
| Median | 150.0 | -2.0 | 156.0 | -1.0 | 148.0 | 1.0 | 158.0 | 1.0 |
| Day 99 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 39 | 39 |
| Mean±SD | 147.9±16.64 | -2.8±14.26 | 146.5±18.90 | -8.6±11.25 | 145.1±16.55 | -2.9±17.32 | 148.2±17.65 | -7.8±14.65 |
| Median | 146.0 | -2.0 | 149.0 | -8.0 | 142.0 | -2.0 | 142.0 | -8.0 |

Note: Baseline is defined as the last available assessment prior to the first dose of study drug; CFB=Change from baseline, Change from baseline is defined as the difference between the measured value at the planned time point and the baseline value;
SD=standard deviation;

# ESM Table S5 Summary of 12-Lead Electrocardiograms (ECG) (Safety Set)

**12-lead ECG Parameter: QRS Duration, Aggregate (msec)**

| | HLX11(N=40) | | US-Perjeta®(N=40) | | EU-Perjeta®(N=40) | | CN-Perjeta®(N=40) | |
|---|---|---|---|---|---|---|---|---|
| | Value | CFB | Value | CFB | Value | CFB | Value | CFB |
| Baseline | | | | | | | | |
| N | 40 | | 40 | | 40 | | 40 | |
| Mean±SD | 93.7±7.60 | | 93.8±7.29 | | 93.5±7.24 | | 91.0±8.84 | |
| Median | 94.0 | | 94.0 | | 94.0 | | 90.0 | |
| Day 01, post-dose 3hours | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 90.6±7.96 | -3.1±9.50 | 89.9±8.11 | -3.9±6.91 | 88.4±9.15 | -5.1±9.58 | 87.0±6.41 | -4.0±9.93 |
| Median | 92.0 | -2.0 | 90.0 | -4.0 | 91.0 | -3.0 | 87.0 | -3.0 |
| Day 01, post-dose 6hours | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 89.9±9.68 | -3.8±8.63 | 91.3±7.34 | -2.5±7.61 | 91.7±8.23 | -1.8±8.04 | 89.8±7.23 | -1.2±9.53 |
| Median | 90.0 | -3.0 | 92.0 | -2.0 | 94.0 | -2.0 | 90.0 | -1.0 |
| Day 01, post-dose 12hours | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 91.1±8.03 | -2.6±9.64 | 92.3±6.42 | -1.5±7.31 | 92.2±8.00 | -1.4±9.65 | 90.5±7.13 | -0.5±9.61 |
| Median | 92.0 | -2.0 | 92.0 | -2.0 | 94.0 | -1.0 | 90.0 | 0.0 |
| Day 02 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 91.8±8.04 | -1.9±8.37 | 92.7±6.48 | -1.1±8.98 | 89.1±8.81 | -4.5±10.61 | 89.4±7.03 | -1.6±11.32 |
| Median | 94.0 | -2.0 | 92.0 | -2.0 | 91.0 | -2.0 | 88.0 | 0.0 |
| Day 05 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 90.7±8.36 | -3.0±8.58 | 91.4±7.60 | -2.4±9.22 | 91.7±7.27 | -1.8±8.69 | 89.5±6.86 | -1.5±10.04 |
| Median | 93.0 | -2.0 | 92.0 | -2.0 | 93.0 | -1.0 | 90.0 | 0.0 |
| Day 08 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Mean±SD | 92.0±7.57 | -1.7±7.19 | 94.8±6.68 | 1.0±8.11 | 93.7±7.81 | 0.2±9.09 | 92.5±6.20 | 1.5±9.35 |
| Median | 94.0 | -1.0 | 94.0 | -1.0 | 94.0 | 0.0 | 92.0 | 0.0 |
| Day 99 | | | | | | | | |
| N | 40 | 40 | 40 | 40 | 40 | 40 | 39 | 39 |
| Mean±SD | 91.0±8.10 | -2.7±8.88 | 92.3±6.20 | -1.5±7.85 | 91.1±7.43 | -2.5±8.65 | 90.5±8.53 | -0.7±11.13 |
| Median | 91.0 | -2.0 | 92.0 | -2.0 | 93.0 | -2.0 | 92.0 | 0.0 |

Note: Baseline is defined as the last available assessment prior to the first dose of study drug; CFB=Change from baseline, Change from baseline is defined as the difference between the measured value at the planned time point and the baseline value; SD=standard deviation;

## Inclusion and Exclusion criteria:

**Inclusion Criteria:**

1. Willing to provide signed informed consent
2. Healthy Chinese male (healthy defined as no clinically significant abnormalities in medical history, physical examination, vital signs, chest X-ray, 12-lead ECG and laboratory tests)
3. Age ≥ 18 years and ≤ 45 years
4. Body mass index (BMI) ≥ 19 and ≤ 26 kg/m2
5. Left ventricular ejection fraction (LVEF) within the normal range (≥ 55%) measured by echocardiography within 14 days before randomization.
6. The male subject and his spouse or partner agreed to the use of reliable contraception within 7 months after the study treatment. or that the subject is not of reproductive potential

**Exclusion criteria:**

1. Have a history of any serious clinical disease such as haematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, mental, neurological diseases, and tumour, or allergic diseases
2. Use of a monoclonal antibody or any biological product within 6 months before study drug administration
3. Have a history of allergic reactions or anaphylaxis, including such reactions to any drug or excipient in the clinical study
4. Use of prescription drugs, over-the-counter drugs (OTC), or traditional Chinese medicine (TCM) (excluding vitamins, mineral supplements, and dietary supplements) within 28 days before study drug administration.
5. A history of blood donation within 3 months before study drug administration
6. Participation in other clinical studies and use of the investigational product/comparator within 3 months before study drug administration
7. Positive for hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody, or Treponema pallidum antibody
8. Have a history of drug abuse
9. Failure to comply with protocol requirements, instructions, and study limitations, such as uncooperative attitude, failure to return to the study site for follow-up visits, or failure to complete the entire clinical study, as judged by investigators

**Clinical and Laboratory Assessments:**

- Screening:The demographic characteristics (Age, Height, Weight, Sex, BMI), Medical history, ECG monitoring, Chest X-ray, Laboratory tests (including Haematology, Blood chemistry, Urinalysis and Myocardial damage markers (NT-proBNP , Myocardial Enzymes and Troponin I).
- 12-lead electrocardiography: Day1, From the beginning of the administration to 1 hour after the end of the administration, at 0 hours (immediately after the end of dosing), 1.5 hours, 3 hours, 6 hours, and 12 hours, D2, D5, D8, D99.
- Vital signs: Including blood pressure, heart rate, blood oxygen saturation, temperature, pulse, were performed on Day1:From the beginning of the administration to 1 hour after the end of the administration, at 0 hours (immediately after the end of dosing), 1.5 hours, 3 hours,24h, 48hours,96hours, D8, D15, D29, D50, D71, D99.
- Physical examinations:Performed on D2, D5, D8, D15, D29, D50, D71, D99.
- Echocardiography:on D8, D99.
- Laboratory tests: Including Haematology, Blood chemistry, Urinalysis and Myocardial damage markers (NT-proBNP, Myocardial Enzymes and Troponin I). performed : On Days 2, 5, 8, 15, 29, 50, 71,99
- During the 99-day follow-up period, the subjects were questioned about any symptoms, adverse events and concomitant medications information were collected.