



# Long-Acting Anti-Matriptase-2 Antibody As a Potentially Best-in-Class Therapy for Iron Overload Diseases



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## INTRODUCTION AND OBJECTIVE

**Iron overload** can lead to severe and life-threatening conditions. Many diseases and conditions are associated with iron overload, including polycythemia vera (PV), myelodysplastic syndrome (MDS) and beta-thalassemia (BT).

The **current standard of care** for iron overload diseases primarily revolves around reducing the excess iron accumulated in the body to prevent organ damage. These treatments carry risks like anemia and present some side effects.

### Therapeutic Mechanism:

Hepcidin, a key regulatory hormone in iron metabolism, is critical in maintaining iron homeostasis within the body. Matriptase 2 (MTP-2) is a serine protease that plays an essential role in hepcidin formation. Inhibition of MTP-2 to increase levels of hepcidin.

**RLYB332** is a fully-humanized MAb inhibitor of MTP-2. The mechanism of action supports the development for the treatment of iron overload and ineffective erythropoiesis-associated disorders such as PV, MSD, or BT.

### Objective:

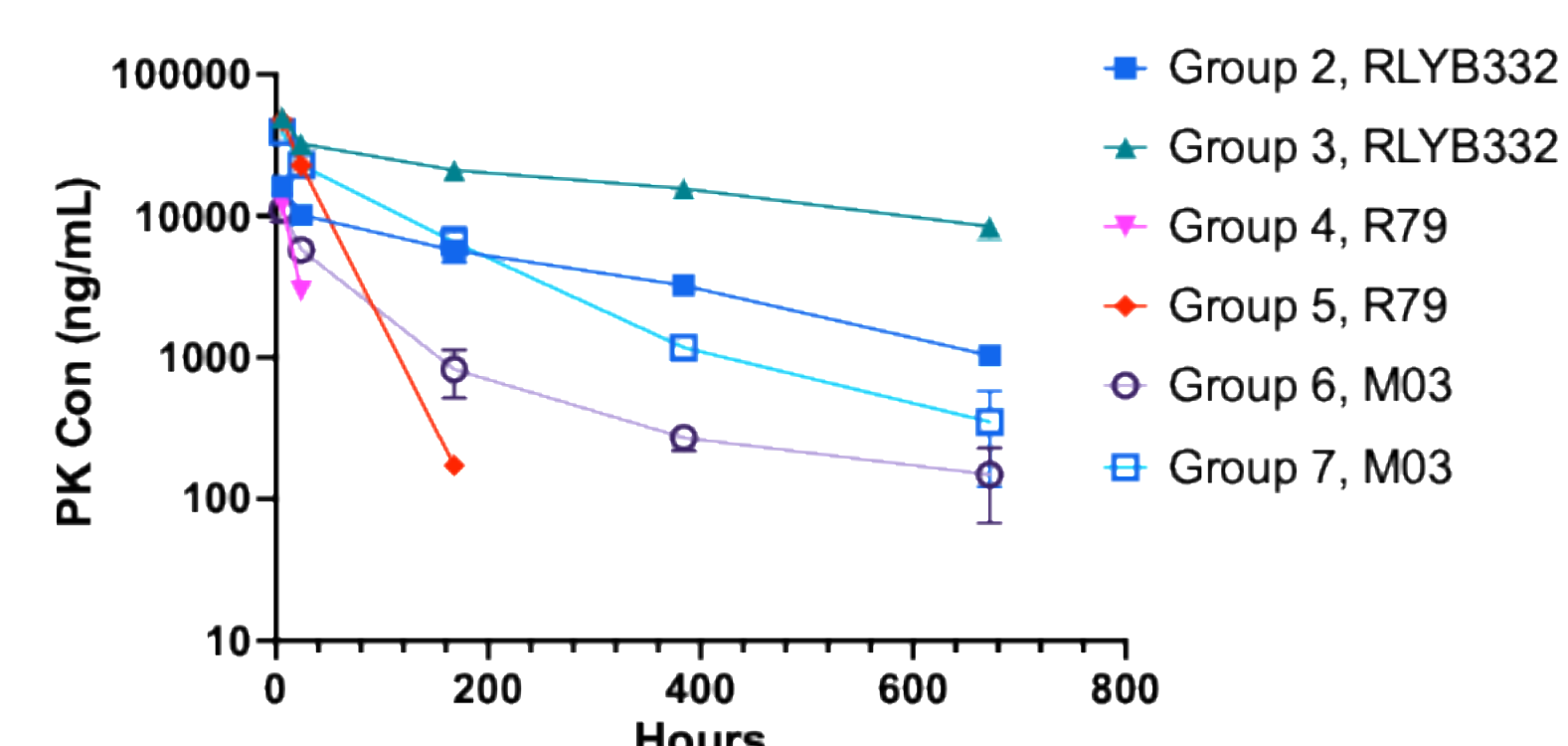
To evaluate the pharmacokinetic (PK), pharmacodynamic (PD), and safety profiles of the anti-MTP-2 antibody RLYB332 using a humanized FcRn (Tg32) mouse model.

## RESULTS

### • Safety:

- There was no unscheduled mortality and no test item-related clinical observations.
- There were no test item-related effects on body weights.
- Following macroscopic examination of gross lesions, no test item-related effects were found.

### • PK:

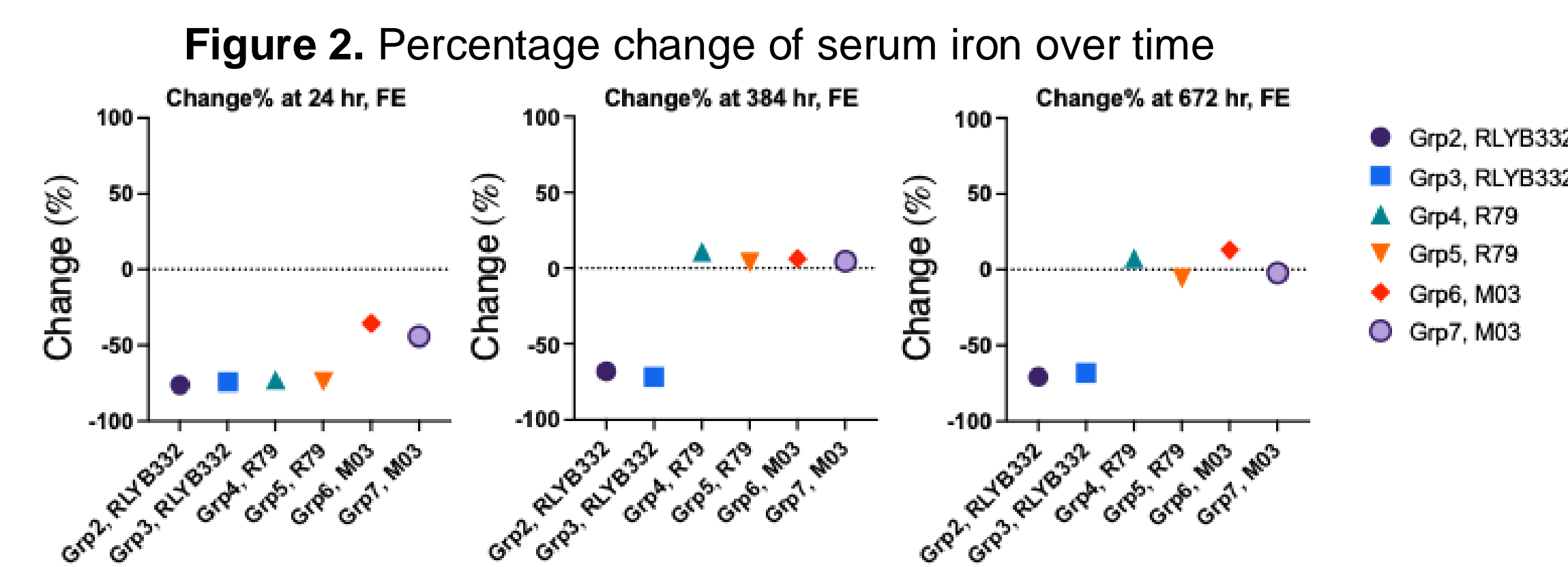


**Figure 1.** PK profiles of RYB332, R79, and M03 in Tg32 mice following intravenous administration at 1 and 3 mg/kg/day (N=3).

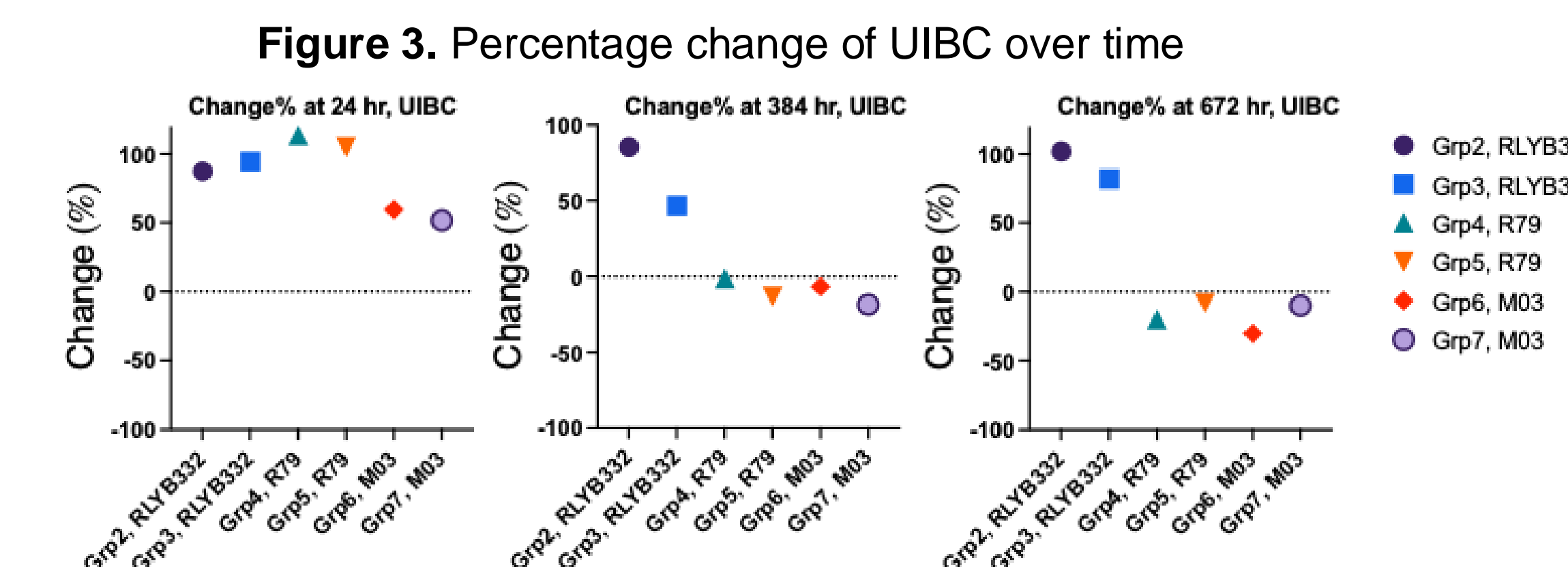
**Table 2.** The PK parameters of RYB332, R79, and M03 in Tg32 mice following intravenous administration at 1 and 3 mg/kg/day.

| Analytes | Group | Number of Time-points | Dose mg/kg/day | Rs <sub>q</sub> | T <sub>1/2</sub> hour | T <sub>max</sub> hour | C <sub>max</sub> ng/mL |
|----------|-------|-----------------------|----------------|-----------------|-----------------------|-----------------------|------------------------|
|          |       |                       |                |                 |                       |                       |                        |
| RLYB332  | 2     | 5                     | 1              | 0.99            | 204                   | 6                     | 16189.1                |
| RLYB332  | 3     | 5                     | 3              | 0.99            | 348                   | 6                     | 49598.1                |
| RG79     | 4     | 2                     | 1              | NC              | NC                    | 6                     | 12038.6                |
| RG79     | 5     | 3                     | 3              | 1.00            | 20                    | 6                     | 47330.6                |
| M03      | 6     | 5                     | 1              | 0.94            | 209                   | 6                     | 11036.2                |
| M03      | 7     | 5                     | 3              | 0.97            | 121                   | 6                     | 39057.2                |

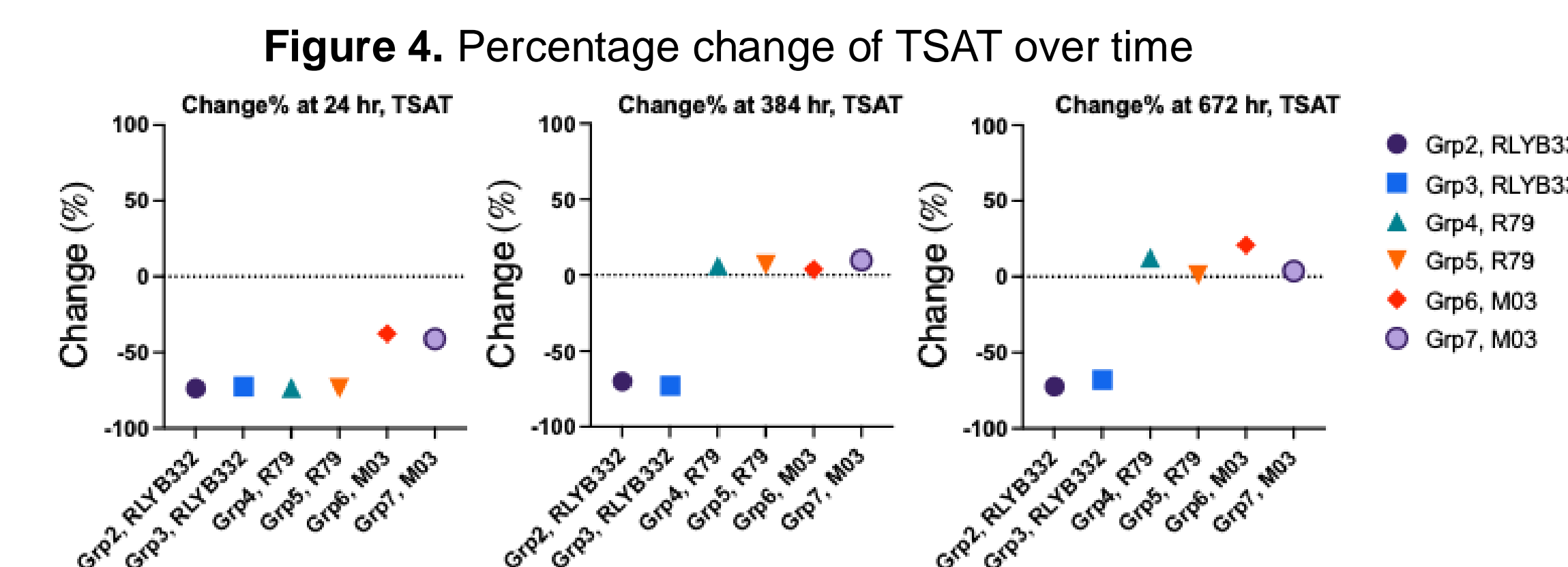
### • PD:



**Figure 2.** Percentage change of serum iron over time



**Figure 3.** Percentage change of UIBC over time



**Figure 4.** Percentage change of TSAT over time

**Table 3.** Summary of PD results observed on serum iron, UIBC, and TSAT levels.

|                         | Results (Mean) |        |        | % Change from the baseline |        |        |
|-------------------------|----------------|--------|--------|----------------------------|--------|--------|
|                         | 24 hr          | 384 hr | 672 hr | 24 hr                      | 384 hr | 672 hr |
| <b>Control</b>          |                |        |        |                            |        |        |
| FE (µg/dL)              | 173.0          | 154.7  | 159.0  | NC                         | NC     | NC     |
| UIBC (µg/dL)            | 115.0          | 139.3  | 129.3  | NC                         | NC     | NC     |
| TSAT (%)                | 60.7           | 52.9   | 55.1   | NC                         | NC     | NC     |
| <b>RLYB332 (1mg/kg)</b> |                |        |        |                            |        |        |
| FE (µg/dL)              | 41.0           | 49.3   | 46.3   | -76.3                      | -68.1  | -70.9  |
| UIBC (µg/dL)            | 215.3          | 258.3  | 261.0  | 87.2                       | 85.4   | 101.8  |
| TSAT (%)                | 16.0           | 15.9   | 15.2   | -73.7                      | -69.9  | -72.4  |
| <b>RLYB332 (3mg/kg)</b> |                |        |        |                            |        |        |
| FE (µg/dL)              | 44.7           | 43.3   | 50.3   | -74.2                      | -72.0  | -68.3  |
| UIBC (µg/dL)            | 223.7          | 260.3  | 235.0  | 94.5                       | 46.8   | 81.7   |
| TSAT (%)                | 16.7           | 14.4   | 17.7   | -72.5                      | -72.8  | -67.9  |
| <b>R79 (1mg/gk)</b>     |                |        |        |                            |        |        |
| FE (µg/dL)              | 47.0           | 171.7  | 171.0  | -72.8                      | 11.0   | 7.5    |
| UIBC (µg/dL)            | 245.3          | 136.3  | 103.3  | 113.3                      | -1.2   | -20.1  |
| TSAT (%)                | 16.1           | 56.2   | 62.0   | -73.5                      | 6.3    | 12.4   |
| <b>R79 (3mg/kg)</b>     |                |        |        |                            |        |        |
| FE (µg/dL)              | 45.0           | 160.3  | 149.7  | -74.0                      | 3.7    | -5.9   |
| UIBC (µg/dL)            | 235.7          | 121.7  | 118.7  | 104.9                      | -13.0  | -8.2   |
| TSAT (%)                | 16.0           | 56.7   | 55.7   | -73.6                      | 7.1    | 1.1    |
| <b>M03 (1mg/kg)</b>     |                |        |        |                            |        |        |
| FE (µg/dL)              | 111.3          | 164.3  | 179.7  | -35.6                      | 6.3    | 13.0   |
| UIBC (µg/dL)            | 183.3          | 131.3  | 90.3   | 59.4                       | -6.6   | -30.2  |
| TSAT (%)                | 37.8           | 55.0   | 66.6   | -37.7                      | 3.9    | 20.8   |
| <b>M03 (3mg/kg)</b>     |                |        |        |                            |        |        |
| FE (µg/dL)              | 96.7           | 161.7  | 155.7  | -44.1                      | 4.5    | -2.1   |
| UIBC (µg/dL)            | 174.3          | 115.0  | 116.3  | 51.6                       | -18.5  | -10.1  |
| TSAT (%)                | 35.7           | 58.1   | 57.2   | -41.1                      | 9.8    | 3.8    |

## METHOD

### Model

A humanized FcRn(Tg32) mouse was used to approximate human physiological responses.

### Administration

RYB332, R79, and M03 were administered via intravenous injection.

### Group settings:

- RLYB332: at dosages of 1 and 3 mg/kg/day;
- Comparable molecules: R79 (1 and 3 mg/kg/day) and M03 (1 and 3 mg/kg/day).

**Table 1.** The study design of PK and PD in Tg 32 mouse model

| Group No. | Test Material | Dose              |                | No. of Animals |    |
|-----------|---------------|-------------------|----------------|----------------|----|
|           |               | Level (mg/kg/day) | Volume (mL/kg) | PK             | PD |
| 1         | Control       | 0                 | 5              | 15             | 9  |
| 2         | RLYB332       | 1                 | 5              | 15             | 9  |
| 3         | RLYB332       | 3                 | 5              | 15             | 9  |
| 4         | R79           | 1                 | 5              | 15             | 9  |
| 5         | R79           | 3                 | 5              | 15             | 9  |
| 6         | M03           | 1                 | 5              | 15             | 9  |
| 7         | M03           | 3                 | 5              | 15             | 9  |

## CONCLUSIONS

RLYB332, the antibody targeting MTP-2, is a promising candidate for treatment of iron overload disorders.

In our study, single intravenous injections of the antibody were well tolerated in humanized FcRn mice at doses tested, whilst demonstrating greater effects on PD parameters than compared molecules.

Rapid and sustained pharmacodynamic effects were observed in both the 1 mg/kg and 3 mg/kg groups, highlighting the potential for self-administration in patients with iron overload disorders.

These findings support the continued preclinical and clinical development of this **anti-MTP-2 antibody as a potentially best-in-class therapeutic molecule** for managing iron overload diseases.

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